GILEAD | Medical Information

Vemlidy® (tenofovir alafenamide) Bone Safety

This document is in response to your request for information regarding the bone safety profile of Vemlidy® (tenofovir alafenamide [TAF]) and its use in patients with chronic hepatitis B (CHB) infection.

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Summary

Clinical Data on the Use of TAF in Patients With CHB

In a network meta-analysis of 16 Asian RCTs that compared the efficacy and safety of TAF, TDF, and ETV, TAF showed less worsening of BMD compared with TDF, with no notable difference compared with ETV. The SUCRA values indicated that TAF had the lowest chance of BMD reduction, while ETV had the lowest chance of decreasing serum phosphorus levels, followed by TAF.[1]

In phase 3 Studies 108 and 110, a Year 8 analysis showed improved hip and spine BMD after switching from TDF to TAF at Year 2 or Year 3. In participants who initiated treatment with TAF, changes from baseline to Year 8 in hip and spine BMD were <2% and <1%, respectively.[2]

- A subanalysis of bone and renal safety outcomes according to the presence or absence of risk factors for TDF-related toxicities demonstrated stable renal and bone safety findings after treatment with TAF through Week 384.[3]
- A Week 96 subanalysis showed that TAF had less impact than TDF on BMD in participants with osteoporosis and osteopenia, independent of the number of risk factors for osteoporosis. TAF had less impact than TDF in participants with risk factors for bone and renal toxicity.[4,5]

In the phase 3 Study 4018, participants who switched from TDF to TAF experienced improvements in hip and spine BMD through Week 96. Improvements from osteoporosis to osteopenia occurred in 38% and 21% of hip and spine BMD measurements, respectively.[6]

In the phase 2 Study 4035, hip and spine BMD measurements through Week 96 were relatively stable among participants with renal or hepatic impairment who switched from TDF or other OAVs to TAF.[7,8]

A phase 2 OL study compared TAF and TDF-containing regimens in post-OLT participants with CKD. In both groups, switching to TAF resulted in improvements in hip and spine BMD at Week 192, and improvements were observed regardless of baseline $eGFR_{CKD\text{-}EPI}$.[9,10]

Real-World Data on TAF Use in Patients With CHB

Patients receiving TAF treatment had a significantly lower risk of developing osteoporotic fractures than those receiving TDF.[11] Significant improvements in BMD were observed in participants who initiated or switched to TAF from TDF or another NA. Similar improvements in BMD while receiving TAF treatment were seen in patients with baseline osteoporosis or osteopenia.[12-16]

Clinical Data on TAF Use in Patients With CHB

Network Meta-Analysis of Asian RCTs[1]

Study design

A total of 4278 participants treated with ETV, TDF, or TAF were included in a network meta-analysis of 16 RCTs from China, South Korea, and Japan to evaluate bone and kidney safety of long-term use. Changes in lumbar BMD and serum phosphorus levels were analyzed before and after the treatment for various durations (24 weeks to 5 years) in 1419 participants from 4 studies and 926 participants from 8 studies to identify potential effects on bone tissue.

Bone safety

TAF showed a significantly smaller decrease in BMD compared with TDF (SMD=-0.02; 95% CI: -0.01 to -0.02), while no notable difference in BMD was found between ETV and TAF (SMD=0.01; 95% CI: -0.07 to 0.09). There were no statistically significant differences among TAF, TDF, and ETV in serum phosphorus levels. The SUCRA values for reducing BMD were 19.6% for TAF, 50.6% for ETV, and 79.7% for TDF, indicating that TAF had the lowest chance of BMD reduction. Conversely, SUCRA values for lowering serum phosphorus levels were 9.7% for ETV, 49.8% for TAF, and 90.6% for TDF, demonstrating that ETV had the least probability to lower serum phosphorus level, followed by TAF.

Studies 108 and 110

Studies 108 and 110 were phase 3 clinical trials that compared outcomes in predominantly NA-naive participants with CHB who were randomly assigned (2:1) to receive once-daily TAF 25 mg or TDF 300 mg. A total of 1298 HBeAg- and HBeAg+ adult participants with an HBV DNA level ≥20,000 IU/mL, both with and without compensated cirrhosis, and an $eGFR_{CG}$ ≥50 mL/min received double-blind treatment for 3 years in Studies 108 (HBeAg-; n=425) and 110 (HBeAg+; n=873). The study allowed participants in both treatment groups to switch to OL TAF at Year 2 or Year 3, and the OL TAF phase was extended to Year 8.[17]

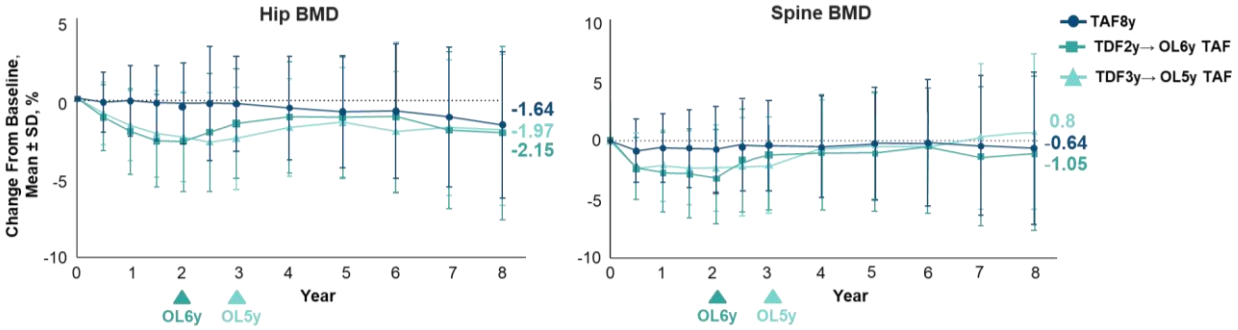
In addition to the primary endpoint of the proportion of participants with HBV DNA <29 IU/mL at Week 48 with a non-inferiority margin of 10%, bone-related secondary endpoints included percent changes in hip and spine BMD.[18,19] A total of 647 participants of the original 866 in the TAF group and 327 participants of the original 432 in the TDF to OL TAF groups completed the OL TAF phase.[17]

Bone safety through 8 years (Week 384)[17]

At Year 8 (Week 384), changes in BMD from baseline in the TAF8y group were minimal; mean percentage decreases from baseline in hip and spine BMD were <2% (Figure 1),

which is consistent with the rates of BMD decline seen with advanced age. Among participants in the TDF group, early decreases in hip and spine BMD that occurred during TDF treatment improved over time after participants switched to TAF at 2 or 3 years.

Figure 1. Studies 108 and 110: Changes in BMD From Baseline to Year 8[17]



In the TAF8y group, the mean percentage decrease from baseline to Year 8 was 2.7% for CTX (bone resorption) and 9.03% for P1NP (bone formation). The median change from baseline during the blinded phase in CTX resorption and P1NP formation was much greater in the TDF groups than that observed in the TAF8y group; however, those values increased after participants switched to TAF at 2 or 3 years. This reduction from baseline was maintained through Year 8 (CTX resorption: OL6y TAF, -4.2%; OL5y TAF, -7.7%; P1NP formation: OL6y TAF, -14.96%; OL5y TAF, -5.66%).

Bone safety subanalysis according to risk factors[3]

Study design and demographics

A pooled subanalysis of Studies 108 and 110 evaluated the long-term renal and bone safety of TAF in participants with ≥1 risk factor for TDF-associated renal and bone toxicities (eg, age >60 years, T-score <-2.5 on DXA of hip and/or spine, $eGFR_{CG}$ <60 mL/min, UA:Cr >30 mg/g, and serum phosphorus level <2.5 mg/dL). Hip and spine DXA scans, serum bone biomarkers, $eGFR_{CG}$, and biomarkers of renal tubular function through Year 8 of treatment were compared between those with and without risk factors. In the subanalysis population, 1059 participants did not have risk factors, and 239 (18%) had ≥1 risk factor (Table 1).

Table 1. Subanalysis of Studies 108 and 110: Baseline Demographics and Disease Characteristics Among Participants With ≥1 Risk Factor for Renal and Bone Toxicities[3]

Key Demographics and Characteristics		Participants With ≥1 Risk Factor	
		TAF (n=151)	TDF→TAF (n=88)
Male, n (%)		91 (60)	53 (60)
Race, Asian/White/Native Hawaiian or Pacific Islander/ Black or African American, %		81/17/1/1	80/20/0/0
HBeAg-, n (%)		73 (48)	40 (46)
FibroTest score ≥0.75, n/N (%)		26/145 (18)	14/87 (16)
Risk factors for TDF-associated renal and bone toxicities, n or n (%)	Number of risk factors, 1/2/≥3	133/17/1	75/12/1
	Osteoporosis of hip/spine	60 (40)	30 (34)
	UA:Cr >30 mg/g	44 (29)	28 (32)
	Age >60 years	42 (28)	28 (32)
	Serum phosphorus level <2.5 mg/dL	19 (13)	12 (14)
	$eGFR_{CG}$ <60 mL/min	5 (3)	4 (5)

Results

Among those who received TAF for 8 years, and regardless of the presence or absence of risk factors, mean percent changes from baseline in hip and spine BMD were small. Serum levels of markers of bone turnover were stable among those with ≥1 risk factor. Recovery in hip and spine BMD measurements occurred after participants switched from TDF to TAF in both those with and those without risk factors; serum markers of bone turnover decreased after switching and eventually stabilized in participants with and without risk factors.

Among those with ≥1 TDF risk factor, 68% and 74% of participants in the TAF and TDF→TAF groups experienced any AE. No participants in either group experienced a study drug-related Grade 3 or 4 AE or a study drug-related serious AE.

Week 96 bone safety subanalyses

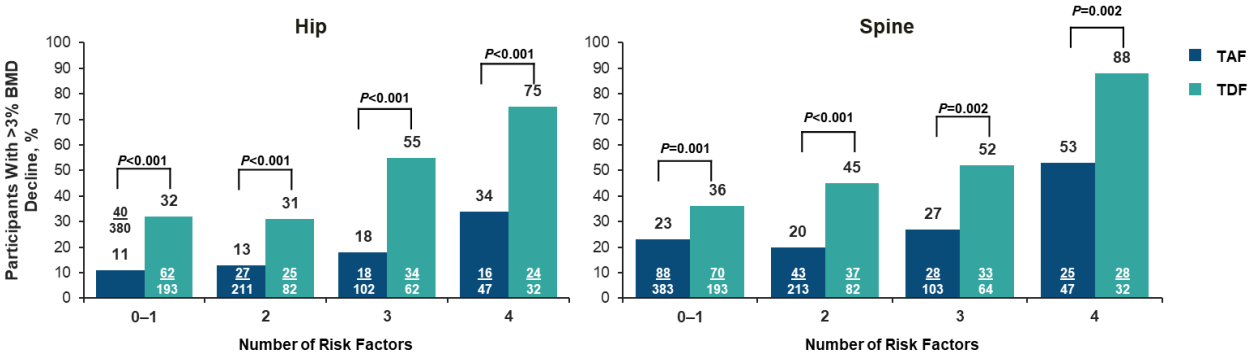
Participants were stratified by baseline diagnosis of osteopenia and osteoporosis and were evaluated for shifts in T-scores through Week 96. A lower percentage of participants in the TAF group than participants in the TDF→TAF groups had worsening of spine and hip BMD categories at Week 96 (Table 2).[4]

Table 2. Studies 108 and 110: Participants Who Exhibited Worsened Spine and Hip BMD Categories From Baseline at Week 96[4]

Change in BMD Category, %		TAF	TDF
Spine	Normal to osteopenia	9	11
	Osteopenia to osteoporosis	7	10
Hip	Normal to osteopenia	6	16
	Osteopenia to osteoporosis	1	4

The decline in BMD was also stratified by the number of risk factors for osteoporosis present at baseline: female sex, age ≥50 years, Asian race, and baseline eGFR <90 mL/min. As shown in Figure 2, a significantly smaller percentage of participants on TAF than on TDF had >3% declines in hip and spine BMD, independent of the number of risk factors.[4]

Figure 2. Studies 108 and 110: Hip and Spine BMD Decline by Number of Baseline Risk Factors[4]



A separate subanalysis at 96 weeks was conducted to evaluate the safety and efficacy of TAF compared to TDF in participants who were considered at risk for TDF-associated renal and/or bone-related toxicities, defined as the presence of ≥1 of the following baseline characteristics: age >60 years, eGFR <60 mL/min, serum phosphorus level <2.5 mg/dL, albuminuria (UA:Cr >30 mg/g), and osteoporosis (T-score <-2.5 based on DXA scan at the hip and/or spine). Participants with ≥1 risk factor who were treated with TAF had similar efficacy, higher ALT level normalization rates, and less impact on bone and renal

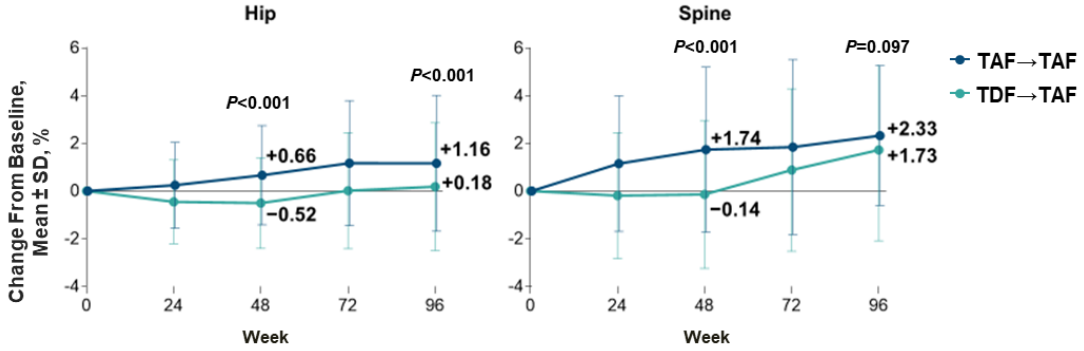
parameters than participants ≥1 risk factor who were treated with TDF. Results were similar to those in the overall study population.[5]

Study 4018

Study 4018 was a double-blind, randomized, phase 3 study that evaluated the safety and efficacy of switching from TDF to TAF (n=243) vs continuing TDF (n=245) in virologically suppressed participants with CHB. Participants had been treated with TDF for ≥48 weeks prior to screening and had an $eGFR_{CG}$ ≥50 mL/min at screening. At the end of the 48-week double-blind study period, participants who were randomly assigned to receive TDF or who were switched to TAF at baseline were switched to OL TAF through Week 96.[20]

Participants who switched to TAF experienced improvements in hip and spine BMD that increased through Week 96 (Figure 3).[6,21] Improvements from osteoporosis to osteopenia were observed in 21% of participants' spine BMD measurements and in 38% of participants' hip BMD measurements. Less than 3% of participants had BMD measurements that declined to a worse category (normal BMD to osteopenia or osteopenia to osteoporosis).[6]

Figure 3. Study 4018: Changes in Hip and Spine BMD From Baseline to Week 96[6,21]



Study 4035

Study design and demographics[7]

Study 4035 was a phase 2, open-label, multicohort switch study that evaluated the efficacy and safety of switching from TDF and/or other OAVs to TAF 25 mg daily in virologically suppressed participants with CHB in the following groups: Part A/Cohort 1, moderate to severe RI ($eGFR_{CG}$ 15 to <60 mL/min; n=78); Part A/Cohort 2, ESRD maintained on hemodialysis ($eGFR_{CG}$ <15 mL/min; n=15); or Part B/Cohort 3, moderate to severe hepatic impairment (moderate hepatic impairment, CPT 7–9; severe hepatic impairment, CPT 10–12; n=31; median [range] CPT score, 6 [5–10]).

Table 3. Study 4035: Baseline Demographics and Disease Characteristics[7,8]

Key Demographics and Characteristics	Moderate to Severe RI (n=78)	ESRD (n=15)	Hepatic Impairment (n=31)
Age, mean ± SD, years	66±10.1	54±12.8	55±10.8
Male, n (%)	57 (73)	12 (80)	21 (68)
Race, Asian/White/Black/other, %	76/19/4/1	87/0/0/13	81/13/3/3
HBeAg-, n (%)	65 (83)	12 (80)	28 (90)
History of cirrhosis, n (%)	27 (35)	5 (33)	30 (97)
FibroTest ≥0.75,[b] n (%)	11 (14)	0	19 (61)

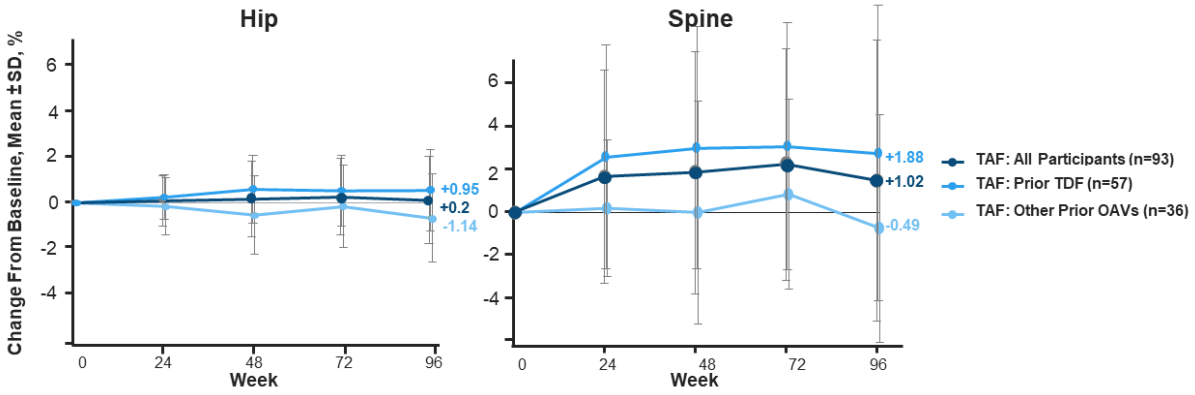
Key Demographics and Characteristics	Moderate to Severe RI (n=78)	ESRD (n=15)	Hepatic Impairment (n=31)
$eGFR_{CG}$, median (IQR), mL/min	45.7 (36.3–54.9)	7.3 (5.5–9.7)	98.5 (72.5–129.8)
T-score <-2.5, spine/hip, n (%)	19 (24)/7 (9)	3 (20)/7 (47)	6 (19)/1 (3)
Select comorbid conditions, HTN/hyperlipidemia/DM/CVD, %	58/33/27/18	73/20/13/40	23/13/23/13
Most common (>5% in any group) prior OAVs, TDF/ADV/LAM/ETV/IFN or PEG-IFN/LdT,[c] %	73/55/54/41/9/6	7/7/27/73/0/7	68/32/45/45/0/6

Abbreviations: CVD=cardiovascular disease; IFN=interferon; PEG=pegylated.
[a]FibroTest scores were not available for 1 participant in Cohort 1.
[b]Participants could have received >1 agent previously. Other agents included CLV or a combination of OAVs.

Bone safety[7,8]

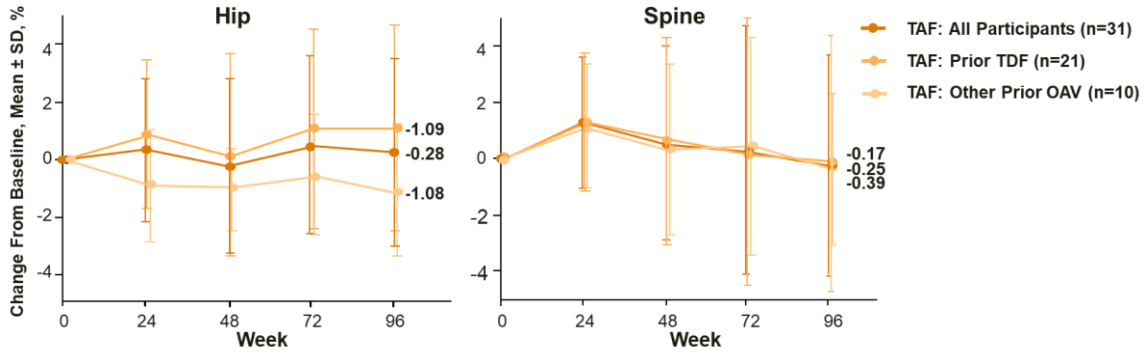
Within the overall RI subgroup, switching to TAF from TDF or other OAVs resulted in stable hip (mean ± SD, +0.2±3.25%) and spine (mean ± SD, +1.02±4.44%) BMD measurements through Week 96 (Figure 4), and percent increases in BMD were observed among those previously treated with TDF relative to those treated with other OAVs. Switching to TAF resulted in median percent decreases from baseline to Week 96 of 18.9% overall in CTX (Cohort 1, -18.9%; Cohort 2, -9.9%) and of 13.89% overall in P1NP (Cohort 1, -13.76%; Cohort 2, -20.81%). Two fractures occurred within Cohort 1(traumatic rib and ankle), though neither were treatment related or serious.

Figure 4. Study 4035 RI Subgroup: Changes in BMD Overall and by Prior Use of TDF or Other OAVs Through Week 96[7]



Within the hepatic impairment subgroup, following the switch to TAF, hip and spine BMDs were stable through Week 96 (Figure 5). Small median decreases from baseline to Week 96 in CTX (-6.3%) and P1NP (-3.84%) were observed, and no fractures were reported in this subgroup.

Figure 5. Study 4035 Hepatic Impairment Subgroup: Bone Parameters at Week 96 Overall and by Prior Use of TDF or Other OAVs[7,22]



Study GS-320-3912

Study design and demographics[9,10]

A phase 2 OL study was conducted to evaluate the safety and efficacy of TAF (n=26) and TDF-containing regimens (n=25) as HBV prophylaxis in participants with recurrent HBV and CKD who were post OLT. Participants were also required to have HBV DNA below the lower limit of quantitation, ALT levels ≤10 × ULN, and $eGFR_{CKD\text{-}EPI}$ <90 mL/min/1.73 m^2 at screening. Eligible participants were randomly assigned (1:1) to begin TAF or to continue a TDF-containing regimen for 48 weeks. After the randomization phase, all participants received TAF during the OLE phase; the final analysis occurred at Week 192. OLT was performed ≥12 weeks prior to screening. The study included participants with compensated cirrhosis, and randomization was stratified by renal function at screening ($eGFR_{CKD\text{-}EPI}$ <50 mL/min/1.73 m^2 or ≥50 mL/min/1.73 m^2).

Table 4. Study GS-320-3912: Baseline Demographics and Disease Characteristics[9,10]

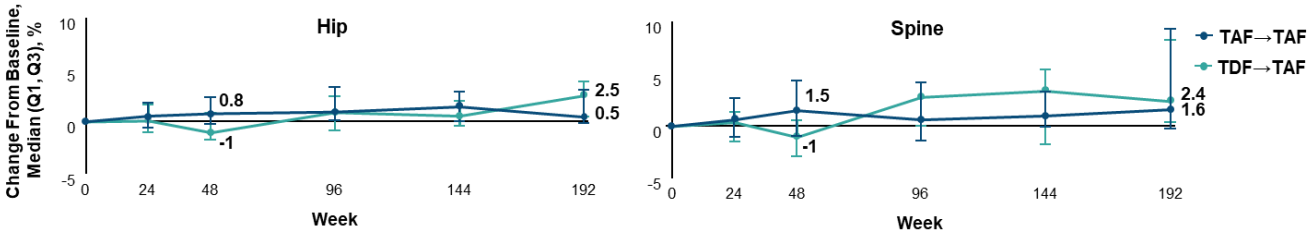
Key Demographics and Characteristics	TAF (n=26)	TDF-Containing Regimen (n=25)
Age, mean (range), years	58 (26–76)	62 (45–77)
Male, n (%)	16 (62)	22 (88)
Race/ethnicity, Pacific Islander/Asian, n (%)	15 (58)/7 (27)	12 (48)/10 (40)
ALT level, mean ± SD, U/L	28±12.6	38±43.7
$eGFR_{CKD\text{-}EPI}$, median (Q1, Q3), mL/min/1.73 m^2	48.8 (44.8, 59.2)	52.2 (45, 60.3)
<50 mL/min/1.73 m^2, n (%)	15 (58)	12 (48)
Current calcineurin inhibitor use, n (%)	21 (81)	19 (76)
Years since OLT, median (Q1, Q3)	9 (3, 14)	9 (4, 12)
History of rejection, n (%)	0	2 (8)
Multiple organ transplant, n (%)	1 (4)[a]	0
HBsAg+, n (%)	2 (8)	1 (4)
HBeAg+, n (%)	1 (4)	0

[a]Renal transplant.

Bone safety

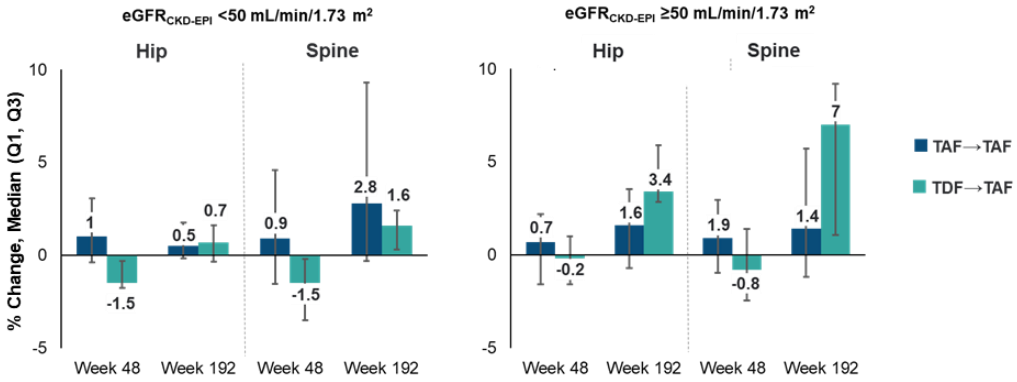
During the randomized phase (up to Week 48), improvements from baseline in hip and spine BMD measurements were observed in participants treated with TAF; in comparison, declines were observed in participants treated with a TDF-containing regimen. During the OLE phase, improvements in hip and spine BMD were observed at Week 192 in participants who switched from TDF to TAF after Week 48 (Figure 6).

Figure 6. Study GS-320-3912: BMD Changes From Baseline at Weeks 48 and 192[9,10]



In an analysis of bone safety according to baseline $eGFR_{CKD-EPI}$, greater decreases from baseline in hip and spine BMD measurements at Week 48 were observed in participants in the TDF-containing regimen group who had a baseline $eGFR_{CKD-EPI}$ <50 mL/min/1.73 m^2 than in those who had a baseline $eGFR_{CKD-EPI}$ ≥50 mL/min/1.73 m^2 (Figure 7). After the switch from TDF to TAF in the OLE phase, improvements from baseline in hip and spine BMD measurements were observed in both $eGFR_{CKD-EPI}$ subgroups. Improvements in BMD measurements were observed among participants in the TAF group at Weeks 48 and 192, regardless of baseline $eGFR_{CKD-EPI}$ (Figure 7).[9,10]

Figure 7. Study GS-320-3912: Changes at Weeks 48 and 192 in BMD by Baseline $eGFR_{CKD-EPI}$[9,10]



Observed changes in bone biomarkers (C-type collagen sequence and P1NP) were similar in both groups at Week 192.

Real-World Data on TAF Use in Patients With CHB

Korean Nationwide Claims Study[11]

Study design and demographics

A retrospective study compared the impact of TAF vs TDF treatment on the risk of developing osteoporotic fractures in adult patients with CHB. Patient data were extracted from the Korean Health Insurance Review and Assessment (HIRA) claims database and included all adult patients with CHB who had received ≥6 months of prescribed treatment with TAF or TDF and did not have a history of fractures or osteoporosis. Data from both before and after IPTW are presented. A subanalysis was conducted to compare impact based on sex (male or female), age (18–49 or 50–99 years), and presence or absence of cirrhosis.

Table 5. Baseline Demographics and Disease Characteristics (Kim et al)[11]

Key Demographics and Characteristics		Before IPTW Adjustment			After IPTW Adjustment		
		TAF[a] (n=11,705)	TDF[a] (n=20,877)	*P*-Value	TAF	TDF	*P*-Value
Age, mean ± SD, years		46.5±10.7	48.6±11.5	<0.001	47.7±11	47.8±11.3	0.199
Male,[b] n (%)		7287 (62.3)	13,726 (65.7)	<0.001	64.1	64.4	0.552
Comorbidity,[b,c] n (%)	Liver cirrhosis	3408 (29.1)	6167 (29.5)	0.425	29.3	29.3	0.978
	DM	2168 (18.5)	4666 (22.3)	<0.001	21.1	21	0.758
	Corticosteroid use	1082 (9.2)	2867 (13.7)	<0.001	12.1	12.1	0.872

[a]The mean ± SD duration of follow-up was as follows: TAF, 23.3±10.7; TDF, 25±12 (*P*<0.001).
[b]Presented as n (%) before IPTW adjustment and % after IPTW adjustment.
[c]Includes comorbidities present in >10% of patients in either treatment group.

Bone safety

Treatment with TAF was associated with a lower risk of osteoporotic fracture development than treatment with TDF; this was true before and after IPTW. The fracture incidence was 0.49/100 PY in the TAF group and 0.78/100 PY in the TDF group (HR, 0.68; 95% CI: 0.55–0.85; *P*=0.001). Across all variables in the subgroup analysis, the fracture incidence was lower in the TAF group than in the TDF group, though the difference was not always statistically significant (Table 6).

Table 6. Subgroup Analysis of Fracture Incidence (Kim et al)[11]

Variable		TAF (n=11,705)	TDF (n=20,877)	HR (95% CI)[a]	*P*-Value
Sex	Male	0.43 (0.33–0.55)	0.75 (0.65–0.86)	0.62 (0.46–0.84)	0.002
	Female	0.59 (0.44–0.77)	0.83 (0.69–0.99)	0.78 (0.56–1.09)	0.149
Age	18–49 years	0.29 (0.21–0.39)	0.37 (0.30–0.46)	0.74 (0.51–1.08)	0.12
	50–99 years	0.82 (0.64–1.03)	1.27 (1.12–1.44)	0.64 (0.49–0.84)	0.001
Cirrhosis	Yes	0.67 (0.49–0.9)	1.06 (0.89–1.26)	0.66 (0.47–0.93)	0.018
	No	0.41 (0.32–0.52)	0.67 (0.58–0.76)	0.69 (0.52–0.92)	0.013

[a]Data calculated after IPTW.

Korean Study: Switch From TDF to TAF

Study design and demographics[12]

A retrospective, multicenter, observational study (N=309) in Korea evaluated efficacy and safety of switching from TDF to TAF in participants with CHB who were virologically suppressed (HBV DNA <20 IU/mL) after treatment with TDF for ≥12 months. Patients were eligible to switch to TAF based on specific clinical conditions: diagnosis with osteoporosis (BMD T-score ≤-2.5); decrease in eGFR to <60 mL/min/1.73 m^2; or serum phosphate levels <2.5 mg/dL). Overall, 182 patients (58.9%) switched from TDF to TAF due to osteoporosis.

Table 7. Baseline Demographics and Disease Characteristics (Nam et al)[12]

Key Demographics and Characteristics		TAF (N=309)
Age, median (IQR), years		59 (54–66)
Male sex, n (%)		130 (42.1)
Cirrhosis, n (%)		73 (23.6)
HBeAg+, n (%)		108 (35)
Duration of prior TDF treatment, mean ± SD, months		52.9±21.5
Comorbidities, HTN/dyslipidemia/DM, n (%)		92 (29.8)/85 (27.5)/72 (23.3)
eGFR, mL/min/1.73 m^2	Mean ± SD	77.8±21.9
	≥90, n (%)	114 (36.9)
	60–89, n (%)	109 (35.3)
	30–59, n (%)	84 (27.2)
	15–29, n (%)	2 (0.6)
Osteoporosis[a] (n=182), treated[b]/untreated,[c] n (%)		73 (40.1)/109 (59.9)

[a]Defined as BMD T-score ≤-2.5 at the lumbar spine, total hip, or femoral neck.
[b]Treated refers to patients who received bisphosphonates (29.7%; n=54), denosumab (7.7%; n=14), or SERMs (2.7%; n=5).
[c]Untreated refers to patients who received calcium ± vitamin D supplementation.

Bone safety

Lumbar spine and hip BMD values improved significantly from baseline to Months 12 and 24 (*P*<0.001 for each; Table 8). BMD values increased in the lumbar spine and hip by a mean of 9.9% and 10.3%, respectively, from baseline to Month 12 and by 13% and 15.2%, respectively, from baseline to Month 24.[12]

Table 8. BMD Values at Baseline, Month 12, and Month 24 (Nam et al)[12]

BMD, Mean ± SD	Baseline	Month 12	*P*-Value[a]	Month 24	*P*-Value[a]
Lumbar spine	-2.55±0.89	-2.3±0.93	<0.001	-2.11±0.8	<0.001
Hip	-2.5±0.72	-2.24±0.66	<0.001	-2.24±0.55	<0.001

[a]Comparison vs baseline values.

As some patients did not experience an improvement in BMD values after switching from TDF to TAF, an analysis was performed to identify characteristics associated with decreases in BMD. Patients who were considered untreated for osteoporosis (ie, those who only received calcium ± vitamin D supplementation) were more likely to have a decrease in spine BMD (*P*=0.028); age >60 years (*P*=0.015) and untreated osteoporosis status (*P*=0.048) were factors associated with decreased hip BMD. [12]

Relative to patients who were untreated, patients who were treated for osteoporosis (ie, those who received bisphosphonates, denosumab, or SERMs) during treatment with TAF had a significantly lower risk of worsened BMD values at the spine (RR, 0.349; 95% CI:

0.134–0.905) and hip (RR, 0.359; 95% CI: 0.142–0.927). No significant changes during the study were observed for serum calcium and phosphorus levels.[12,23]

Switch From Other NAs to TAF[13]

Study design and demographics

A prospective, multinational, real-world study was conducted to assess virologic, biochemical, renal, and bone outcomes in participants with CHB who switched to TAF after treatment for ≥1 year with other NAs (N=270). This cohort was composed of participants from Japan, Korea, Taiwan, and the US. BMD was assessed with DXA at the time of the switch and at the end of the study. All participants were monitored for 24 months after they switched to TAF.

The primary outcome was the percentage of participants with complete virologic suppression (HBV DNA level <20 IU/mL) at Month 24 after switch to TAF. Key secondary outcomes included changes in BMD (T-scores), biochemical response (defined as ALT level <35 U/L for men and <25 U/L for women) rate, and renal function changes (eGFR) through Month 24 after participants switched to TAF.

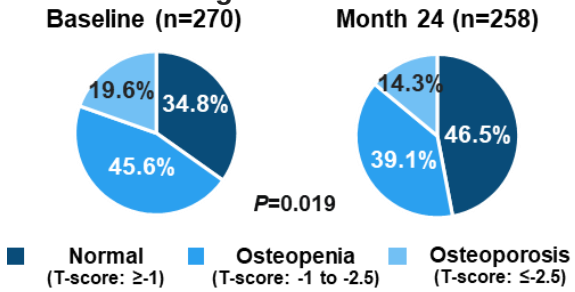
Table 9. Baseline Demographics and Disease Characteristics (Ogawa et al)[13]

Key Demographics and Characteristics		TAF (N=270)
Age, mean ± SD, years		58.1±10.6
Male, n (%)		157 (58.2)
Race, Asian/non-Asian, n (%)		269 (99.6)/1 (0.4)
Comorbid conditions, HTN/DM, n (%)		63 (23.3)/47 (17.4)
eGFR, mean ± SD, mL/min		88.4±16.9
Spine BMD, T-score, n (%)	Normal, ≥-1	94 (34.8)
	Osteopenia, -1 to -2.5	123 (45.6)
	Osteoporosis, ≤-2.5	53 (19.6)
Prior NA, n (%)	ETV	199 (73.7)
	TDF- or ADV-based regimen	62 (23)
	Other (LAM, LdT, or CLV)	9 (3.4)
Duration of prior NA treatment, n ± SD, years		7.5±4

Bone safety through Month 24

Twelve participants did not complete the Month 24 follow-up (n=258). After the switch to TAF, the mean ± SD T-score significantly improved from -1.43±1.36 at baseline to at -1.17±1.38 Month 24 (*P*<0.0001). Additionally, the proportion of participants with normal BMD increased, while the proportion with osteoporosis/osteopenia decreased (*P*=0.019; Figure 8).

Figure 8. Proportions of BMD Categories at Baseline and Month 24 (Ogawa et al)[13]



In multivariable logistic regression analyses, male sex was the only independent factor significantly associated with a lower risk of worsening spine BMD (aOR, 0.29; 95% CI: 0.1–0.82; *P*=0.02). Independent factors associated with improved spine BMD were male sex (aOR, 2.26; 95% CI: 1.12–4.65; *P*=0.022) and baseline spine T-score (aOR, 0.56; 95% CI: 0.41–0.75; *P*<0.0001).

None of the 15 severe AEs reported were related to TAF, and none of the patients developed fragility fractures during the study.

HERACLIS-TAF Study[14]

Study design and demographics

A prospective, multicenter cohort study was conducted in Greece to assess the efficacy and safety of TAF in participants with CHB. Adult participants (aged >16 years) with or without cirrhosis who were NA naive or experienced before initiating TAF between February 2018 and October 2019 were included. Outcomes included BMD changes at 12 and 24 months, and participants were followed for 24 months according to standard clinical practice.

Table 10. HERACLIS-TAF: Baseline Demographics and Disease Characteristics[14]

Key Demographics and Characteristics	TAF (N=176)
Age, mean ± SD, years	64±12
>60 years, n (%)	113 (64.2)
Male, n (%)	124 (70.5)
Osteoporosis (T-score <-2.5), n (%)	54 (30.7)
CHB ± cirrhosis, n (%)	165 (93.8)
Undetectable HBV DNA, n (%)	150 (85.2)
HBeAg+, n (%)	2 (1.1)
NA therapy prior to TAF, n (%)	166 (94.3)
TDF, n/N (%)	141/160 (88.1)
ETV, n/N (%)	15/160 (9.4)

Bone safety

At 12 months, BMD measurements were available in 64 participants. The median (Q3-Q1) BMD (hip T-score) did not change significantly from baseline (-2.2 [1.3]) to 12 months (-2.1 [1.3]; *P*=0.157). The median (Q3-Q1) change in BMD at 12 months was 2% (33%) of the baseline BMD value.

At 24 months, among those with baseline and 12-month BMD measurements (n=68), the median (Q3-Q1) BMD (hip T-score) was improved on TAF treatment compared with baseline (-1.9 [1.1]; *P*=0.001) and 12-month scores (*P*=0.032). The median (Q3-Q1) change in BMD at 24 months of TAF treatment was 9% (48%).

Among participants with premorbid osteoporosis, the median BMDs at 0, 12, and 24 months of TAF treatment were -2.6, -2.3, and -2.1, respectively.

Chinese Study: Switch From ETV or TDF to TAF[15]

Study design and demographics

A prospective, multicenter, open-label study was conducted in China to assess the bone safety and efficacy of TAF in adult participants with suppressed CHB who were diagnosed with osteopenia or osteoporosis. Participants who had been treated with ETV or TDF for >48 weeks and had HBV DNA <20 IU/mL for >6 months underwent an osteoporosis risk test. At-risk participants who were diagnosed with osteopenia or osteoporosis and switched from ETV or TDF to TAF (n=138) were included in the analysis.

The primary safety endpoint was changes in BMD values as measured by the mean percent change from baseline and shifts from baseline in T-score. Other secondary safety endpoints were biomarkers of bone turnover (CTX for bone resorption and P1NP for bone formation). Participants were followed up for 48 weeks.

Bone safety

Participants showed improved lumber spine BMD after switching from TDF to TAF at Week 24 compared to baseline (*P*=0.001) and remained stable up to Week 48. There were no notable changes in total hip BMD after switching from ETV or TDF to TAF from baseline through Week 24 and Week 48 (Table 11).

Participants who switched from ETV to TAF had stable P1NP and β-CTX levels from baseline through Week 48. Those who switched from TDF to TAF showed a significant decrease in P1NP and β-CTX at Week 24 compared to baseline (*P*=0.016 and *P*=0.017, respectively), but no further significant change at Week 48 (Table 11).

Table 11. Bone Parameters at Baseline, Week 24, and Week 48 (Li et al)[15]

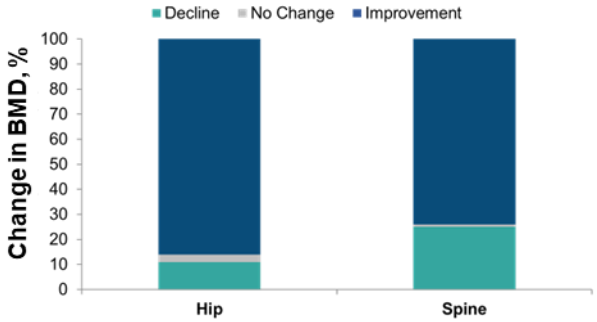
Bone Parameters[a]	Switch ETV to TAF (n=40)			Switch TDF to TAF (n=98)		
	Baseline	Week 24	Week 48	Baseline	Week 24	Week 48
BMD						
Lumbar spine, g/cm^2	0.99±0.1	0.98±0.11	1.01±0.12	0.97±0.12	1.03±0.11[b]	1.01±0.13
Lumbar spine T-score	-1.47±0.91	-1.19±0.97	-1.20±1.1	-1.71±0.83	-1.04±0.95[b]	-1.23±0.89
Change from baseline, %	–	1.9	1.8	–	3.9	3
Total hip, g/cm^2	0.85±0.14	0.87±0.12	0.9±0.11	0.87±0.11	0.88±0.12	0.89±0.14
Total hip T-score	-1.08±0.76	-1.06±0.75	-1.05±0.78	-1.69±0.62	-1.62±0.57	-1.64±0.61
Change from baseline, %	–	1.8	2.7	–	1.15	2.29
Bone biomarkers						
P1NP, mcg/L	67.07±22.09	55.19±18.89	48.84±17.1	63.65±19.17	50.35±18.9[c]	55.03±16.51
β-CTX, ng/L	0.32±0.13	0.26±0.1	0.23±0.29	0.32±0.1	0.21±0.13[c]	0.24±0.1

[a]Bone parameters were described as either mean ± SD or %.
[b]*P*<0.01, compared with baseline.
[c]*P*<0.05, compared with baseline.

Switch From TDF to TAF: Asian Pacific Liver Center, Los Angeles[16]

A real-world study that evaluated efficacy and renal and bone safety in 75 patients who switched from TDF to TAF showed significant increases in hip and spine BMD from baseline to Week 12 (+12.9% and +2.4%, respectively) that remained stable at Week 24. There were also significantly more improvements in hip and spine BMD than declines (Figure 9).

Figure 9. Proportion of BMD Changes by Week 24 (Fong et al)[16]



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Abbreviations

β-CTX=β-C-terminal telopeptide of type 1 collagen
ADV=adefovir
AE=adverse event
aOR=adjusted odds ratio
BMD=bone mineral density
CG=Cockcroft Gault equation
CHB=chronic hepatitis B
CKD=chronic kidney disease
CKD-EPI=CKD Epidemiology Collaboration equation
CLV=clevudine
CPT=Child-Pugh-Turcotte
CTX=C-terminal telopeptide of type 1 collagen
DM=diabetes mellitus
DXA=dual-energy x-ray absorptiometry
ESRD=end-stage renal disease
ETV=entecavir
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HR=hazard ratio
HTN=hypertension
IPTW=inverse probability of treatment weighting
LAM=lamivudine
LdT=telbivudine
NA=nucleos(t)ide analogue
OAV=oral antiviral
OL=open-label
OLE=open-label extension
OLT=orthotopic liver transplant
P1NP=N-terminal propeptide of type 1 procollagen
PY=patient years
Q=quartile
RCT=randomized controlled trial
RI=renal impairment
RR=relative risk
SERM=selective estrogen receptor modulator
SMD=standardized mean difference
SUCRA=surface under the cumulative ranking curve
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
UA=urine albumin
ULN=upper limit of normal

Product Label

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