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Vemlidy® (tenofovir alafenamide) Fibrosis Improvement

This document is in response to your request for information regarding the use of Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of chronic hepatitis B (CHB) and available data regarding fibrosis improvement.

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Summary

Clinical Data: TAF Use and Fibrosis Improvement

- In a pooled analysis of phase 3 Studies 108 and 110, participants who received TAF had a greater reduction in FibroTest scores at Week 48 (HBeAg+, *P*=0.005; HBeAg-, *P*=0.033) and a similar improvement in fibrosis stage by Ishak score compared with participants who received TDF. The strongest predictors of fibrosis improvement were higher baseline ALT and lower baseline HBsAg.[1] In another pooled analysis (N=1632), all participants with available baseline and Year 8 data had improved FibroTest, APRI, and FIB-4 scores from baseline to Week 48, and these improvements were maintained at Year 8.[2]
- In an ongoing prospective study, significant declines from baseline to Week 96 in APRI score, FIB-4 score, and LSM (each, *P*<0.001) were achieved in treatment-naïve participants with CHB, and noninvasive indicators demonstrated that TAF was effective in reversing liver fibrosis.[3]

Real-World Data: TAF Use and Fibrosis Improvement

Prospective and retrospective studies showed that treatment with TAF resulted in fibrosis improvement, as measured by FIB-4, APRI, transient elastography, and SWE.[4,5]

Clinical Data: TAF Use and Fibrosis Improvement

Studies 108 and 110

Study design

Studies 108 and 110 were phase 3 clinical trials that compared once-daily oral administration of TAF 25 mg with TDF 300 mg in predominantly nucleos(t)ide-naïve participants with CHB. A total of 1632 (1298 from a global cohort and 334 from a Chinese cohort) adult monoinfected participants with CHB and compensated liver function were

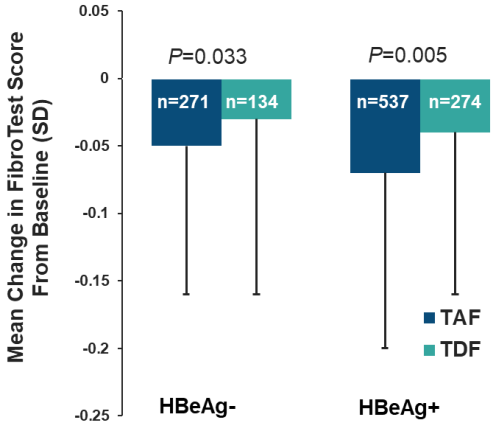
randomly assigned in a ratio of 2:1 to receive either double-blind TAF 25 mg (n=1093) for 3 years or TDF 300 mg for 2 years (TDF2y→TAF6y; n=207) or 3 years (TDF3y→TAF5y; n=332). Upon completion of the blinded phase, eligible participants from both arms enrolled in an open-label phase, in which they received TAF through Week 384. Participants who were initially randomly assigned to receive TAF remained on TAF, and participants who were initially randomly assigned to receive TDF were switched to TAF during the open-label phase.[2,6,7]

The primary endpoint was the proportion of participants with HBV DNA <29 IU/mL at Week 48 with a noninferiority margin of 10%. A secondary endpoint included the change from baseline in fibrosis, as assessed by FibroTest. Liver biopsies were not performed.[6,7]

FibroTest results through Week 48[1]

In a pooled analysis of Studies 108 and 110, participants who received TAF 25 mg experienced a greater reduction in FibroTest scores at Week 48 than did those who received TDF 300 mg. FibroTest scores declined similarly in HBeAg+ and HBeAg- participants (Figure 1).

Figure 1. Studies 108 and 110: Mean Changes in FibroTest Scores From Baseline to Week 48 by HBeAg Status[1]



When the sample was stratified by FibroTest score category at baseline, TAF resulted in a greater mean reduction than TDF at Week 48; this difference was significant for FibroTest scores 0 to 0.48 (corresponding to Ishak F1–F2) and 0.49 to 0.74 (Ishak F3–F4), as shown in Table 1.

Table 1. Studies 108 and 110: Changes in FibroTest Scores at Week 48 by Category[1]

Baseline FibroTest Category		TAF	TDF	*P*-Value
0–0.48	n Mean (SD)	579 -0.04 (0.09)	289 -0.01 (0.1)	<0.01
0.49–0.74	n Mean (SD)	162 -0.11 (0.15)	78 -0.08 (0.15)	0.04
0.75–1	n Mean (SD)	67 -0.15 (0.17)	41 -0.12 (0.16)	0.46

As shown in Table 2, the strongest predictors of fibrosis improvement were higher baseline ALT (>5 × ULN, by AASLD) and lower HBsAg.

Table 2. Studies 108 and 110: Predictors of Fibrosis Improvement via a Multivariate Analysis[1]

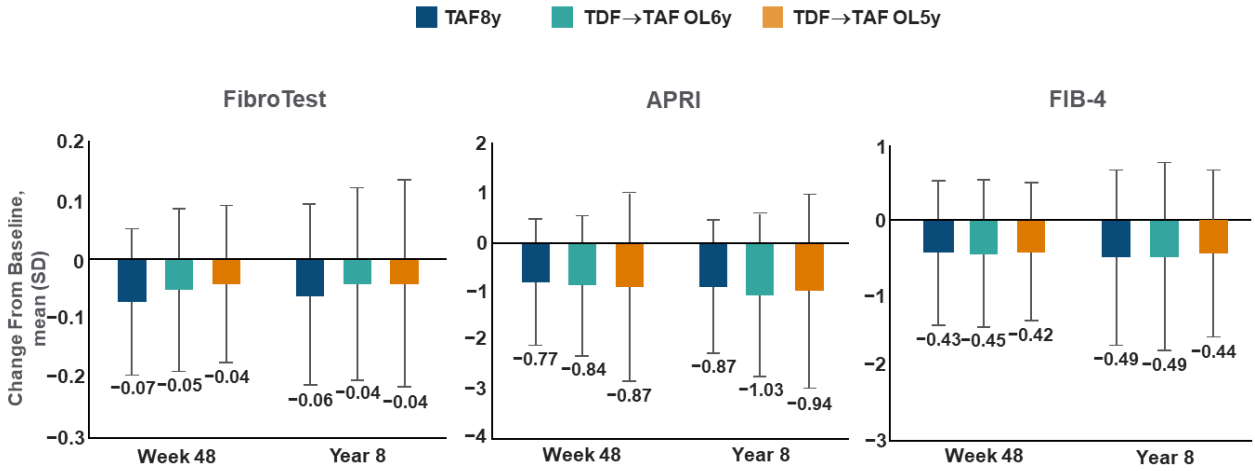
Predictor	Odds Ratio	95% CI	*P*-Value
Baseline ALT >5 × ULN by AASLD	3.76	2.45–5.77	<0.0001
Age	1.04	1.02–1.06	0.0001
Baseline HBsAg	0.57	0.44–0.74	<0.0001
No cirrhosis	0.37	0.21–0.63	0.0003

Overall, a similar proportion of participants who received TAF (15% [119/808]) and TDF (13% [54/408]) had improvements in fibrosis stage by Ishak score. In participants with baseline Ishak scores of F3 to F4, 51% (83/162) of participants in the TAF group and 41% (32/78) of participants in the TDF group experienced a ≥1 category improvement. Among participants with baseline Ishak scores of F5 or F6, 54% (36/67) of participants in the TAF group and 54% (22/41) of participants in the TDF group presented a ≥1 category improvement.

Pooled analysis of fibrosis status at Year 8[2]

In a pooled analysis of all participants in Studies 108 and 110 (N=1632), all participants with available baseline and Year 8 data had improved FibroTest, APRI, and FIB-4 scores from baseline to Week 48; these improvements were maintained at Year 8 (Figure 2).

Figure 2. Studies 108 and 110: Pooled Analysis of Noninvasive Fibrosis Indicators at Week 48 and Year 8[2]



Most participants across all treatment groups with no to mild fibrosis per noninvasive test scores at baseline had no change in fibrosis category at Year 8 (FibroTest, 87–95%; APRI, 93–96%; FIB-4, 71–80%). Of all participants with cirrhosis at baseline (FibroTest score ≥0.75), there was no change in fibrosis category in 38%, 21%, and 9% of participants in the TDF3y→TAF5y, TAF8y, and TDF2y→TAF6y groups, respectively; 21% of participants (14/66) in the TAF8y group and 30% of participants (12/40) in the combined TDF→TAF groups with cirrhosis at baseline had no cirrhosis (FibroTest score <0.75) at Year 8.
Of all participants with advanced fibrosis or cirrhosis at BL, 99% per APRI score and 83% per FIB-4 score had an improvement in fibrosis category at Year 8.

Single-Arm, Prospective Study[3]

Study design and demographics

An ongoing, single-arm, prospective study (NCT04939441) in treatment-naïve participants with CHB and histologically confirmed liver fibrosis (N=100) from 10 hospitals in China evaluated the effects of TAF treatment for 96 weeks. Liver fibrosis was noninvasively assessed using LSM, APRI, and FIB-4.

At baseline, 59% were male, the mean age was 42.2±10.3 years, 23% had cirrhosis, 61% were HBeAg+, and the median (Q1, Q3) ALT level was 45.2 (29.7, 79.1) IU/L. Before receiving treatment, 47% of participants at baseline were staged at F2, 30% at F3, and 23% at F4 according to the METAVIR scoring system.

Results

Among the 93/100 participants who completed 96 weeks of follow-up, the rate of HBV DNA <20 IU/mL achieved was 74% at Week 48 and 87% at Week 96, and the ALT normalization (<40 IU/mL) rate was 79% at Week 96. At Week 96, liver fibrosis was significantly reversed, as evaluated by noninvasive tests (Table 3).

Table 3. Noninvasive Indicators of Liver Fibrosis at Baseline and Week 96 (Zhou et al)[3]

Indicator	Baseline (N=100)	Week 96 (N=93)	*P*-Value
APRI score, median (Q1, Q3)	0.73 (0.41, 1.15)	0.31 (0.22, 0.44)	<0.001
FIB-4 score, median (Q1, Q3)	1.24 (0.8, 2.26)	1.03 (0.74, 1.43)	<0.001
LSM, median (Q1, Q3), kPa	9.6 (6.8, 15)	6.3 (5.4, 8.9)	<0.001

From baseline to Week 96, the LSM declined >30% in 45 participants (51%). In participants staged at F2, F3, and F4 at baseline, the median LSM decreased from 7.5, 10, and 15.5 kPa to 6, 6.7, and 9.9 kPa at Week 96, respectively (P<0.001).

Nine serious adverse events were reported over 96 weeks of treatment; none were considered to be related to TAF treatment.

Real-World Data: TAF Use and Fibrosis Improvement

Prospective Cohort Study[4]

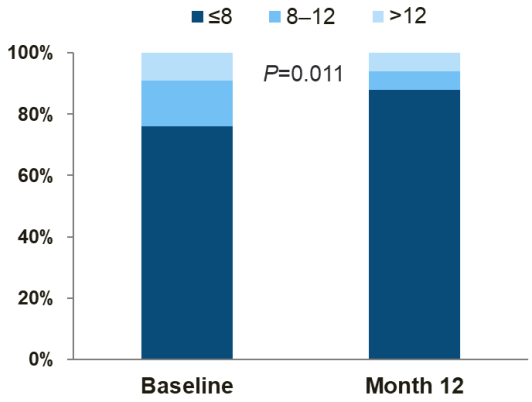
Study design

A prospective cohort study in treatment-experienced participants with CHB evaluated changes in LSM in those who received TAF treatment for >12 months (N=67). Transient elastography was performed at baseline (ie, the start of TAF therapy) and at Month 12.

Results

In participants who received treatment with TAF for >12 months, significant improvements from baseline in LSM were observed (P=0.011; Figure 3).

Figure 3. LSM Categories at Baseline and Month 12 (Liang et al)[4]



Retrospective Study[5]

Study design and demographics

A single-center, retrospective study in patients with CHB (N=53) evaluated the effects of switching from TDF to TAF treatment on hepatic fibrosis. Changes in ALT, AST, APRI score, FIB-4 score, and SWE through Week 144 postswitch were analyzed, as were factors associated with changes in SWE.

Table 4. Baseline Demographics and Characteristics (Hyuhn et al)[5]

Key Baseline Demographics and Characteristics	TAF (N=53)
Age, mean (range), years	55 (28–80)
Male, n (%)	24 (45.3)
Clinical evidence of cirrhosis, n (%)	8 (15.1)
Spleen >12 cm, n (%)	4 (7.7)
ALT, mean (range), IU/L	24.8 (7–108)
AST, mean (range), IU/L	25.7 (15–89)
Platelets ≤120 × 10^9/L, n (%)	6 (11.3)
APRI score, mean (range)	0.37 (0.13–0.92)
FIB-4 score, mean (range)	1.66 (0.49–5.33)

Results

After switching to TAF treatment, mean ALT and AST levels and APRI and FIB-4 scores improved, and these changes persisted through Week 144. The mean SWE reading also improved after switching, from 7.05 to 6.3 kPa. In multivariate analyses, larger spleen size (>12 cm) prior to switching treatments had a statistically significant negative association with SWE improvement (*P*=0.016; Table 5). After a mean (range) of 108 (4–240) weeks of TAF treatment post switch, the proportion of patients with fibrosis stage 0 to 1 increased from 64% (32/50) to 86% (43/50).

Table 5. Univariate and Multivariate Analyses of Factors Associated With SWE Improvement (Hyuhn et al)[5]

Variable	Univariate *P*-Value	Multivariate *P*-Value
Preswitch spleen size >12 cm	0.031	0.016
Platelets <120 × 10^9/L	0.018	0.25
APRI score <0.5 at Week 24 post switch	0.047	0.448
FIB-4 score <1.45 at Week 24 post switch	0.055	0.244
ALT <40 IU/L at Week 24 post switch	0.46	–
ALT <30 (males)/19 (females) IU/L at Week 24 post switch	0.155	–
AST <40 IU/L at Week 24 post switch	0.46	–
AST <30 (males)/19 (females) IU/L at Week 24 post switch	0.242	–

References

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2. Castera L, Yu M-L, Buti M, et al. Characterization of Changes in Noninvasive Fibrosis Markers Over 8 Years of Tenofovir-Based Treatment in Patients With Chronic Hepatitis B Enrolled in Two Phase 3 Trials. [poster #1337]. Paper presented at: AASLD - The Liver Meeting; November 15-19, 2024; San Diego, California.
3. Zhou J, Wu X, Zhu C, et al. Tenofovir Alafenamide Fumarate in Treatment-Naïve Chronic Hepatitis B Patients With Liver Fibrosis: A Preliminary Non-Invasive Results of 96 Weeks. [Poster #1347] Paper presented at: AASLD - The Liver Meeting; November 15-19 2024; San Diego, California.
4. Liang L, Wong V, Yip T, Tse Y, K., Hui V, Wong G. Changes of liver fibrosis and steatosis in patients with chronic hepatitis B receiving tenofovir alafenamide [Poster 773]. Paper presented at: American Association for the Study of Liver Diseases (AASLD) The Liver Meeting Virtual; 12-15 November, 2021.
5. Huynh T, Hu K. Tenofovir Disoproxil Fumarate Switching to Tenofovir Alafenamide for Three Years Resulted in Improvement of Hepatic Fibrosis by APRI and FIB-4 Score as well as Shear Wave Elastography (SWE) in Patients with Chronic Hepatitis B [Poster]. 2022.
6. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.
7. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:185-195.

Abbreviations

AASLD=American Association for the Study of Liver Disease
APRI=AST to Platelet Ratio Index
CHB=chronic hepatitis B
FIB-4=Fibrosis-4
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
LSM=liver stiffness measurement
METAVIR=Meta-analysis of Histological Data in Viral Hepatitis
Q=quartile
SWE=shear wave elastography
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
ULN=upper limit of normal

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Follow-Up

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