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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 a retrospective, multicenter study in TN patients with indeterminate phase CHB and normal ALT levels (N=265), median APRI scores improved significantly from baseline to Week 48 (0.25 and 0.26, respectively; *P*=0.002), and there were numerical improvements in median FIB-4 scores (1 and 0.95; *P*=0.228) and median GPR levels (0.16 and 0.14; *P*=0.146).[3]

In a prospective study, significant declines from baseline to Week 96 in APRI score, FIB-4 score, and LSM (each, *P*<0.001) were achieved in TN participants with CHB.[4]

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.[5,6]

Clinical Data: TAF Use and Fibrosis Improvement

Studies 108 and 110

Study design

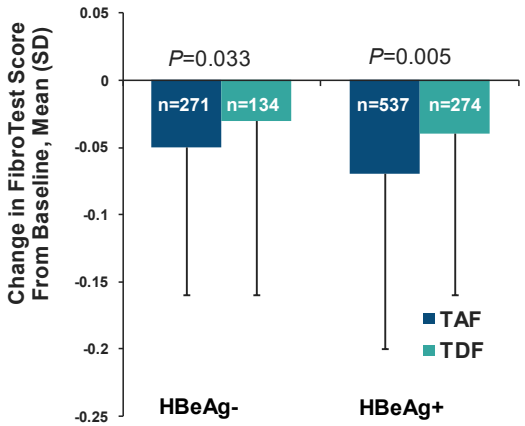
Studies 108 and 110 were phase 3 clinical trials that compared once-daily oral administration of TAF 25 mg with TDF 300 mg in predominantly nucleos(t)ide-naïve participants with CHB. A total of 1632 (1298 from a global cohort and 334 from a Chinese cohort) adult monoinfected participants with CHB and 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.[2,7,8]

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.[7,8]

FibroTest results through Week 48[1]

In a pooled analysis of Studies 108 and 110, participants who received TAF experienced a greater reduction in FibroTest scores at Week 48 than did those who received TDF. 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 data 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]

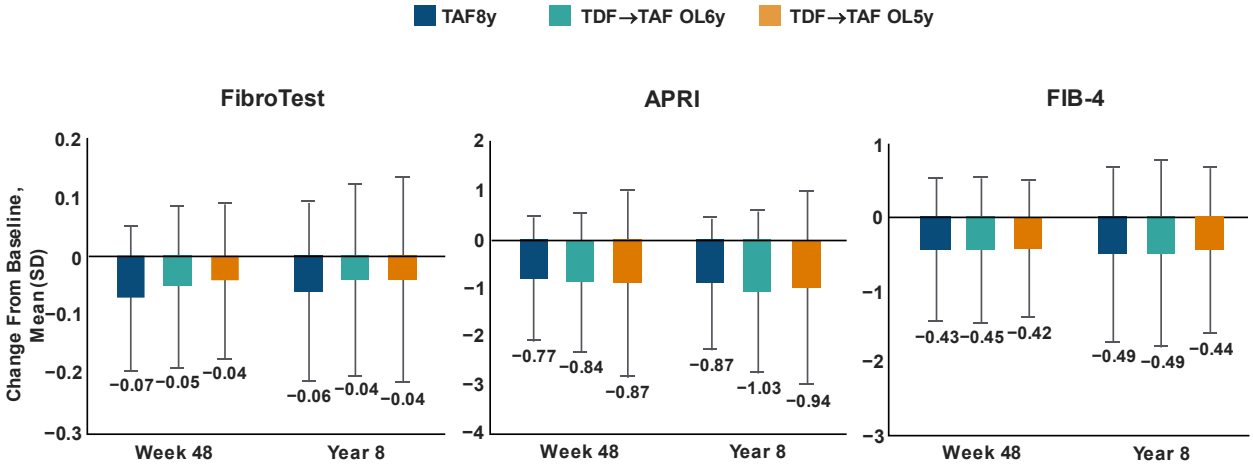
Predictor	Odds Ratio	95% CI	*P*-Value
Baseline ALT >5 × ULN by AASLD	3.76	2.45–5.77	<0.0001
Age	1.04	1.02–1.06	0.0001
Baseline HBsAg	0.57	0.44–0.74	<0.0001
No cirrhosis	0.37	0.21–0.63	0.0003

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% of participants (83/162) in the TAF group and 41% of participants (32/78) in the TDF group experienced a ≥1 category improvement. Among participants with baseline Ishak scores of F5 or F6, 54% of participants (36/67) in the TAF group and 54% of participants (22/41) 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]



Abbreviation: OL=open label.

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 baseline, 99% per APRI score and 83% per FIB-4 score had an improvement in fibrosis category at Year 8.

Retrospective, Multicenter Study[3]

A retrospective, multicenter study in TN patients with indeterminate phase CHB and normal ALT levels evaluated the early efficacy and impact on inflammatory liver fibrosis of 48 weeks of TAF treatment (N=265). The primary endpoint was CVR (HBV DNA <20 IU/mL), and secondary endpoints included improvements in APRI, FIB-4, and GPR.

At Week 48, 86% of patients (228/265) achieved CVR. There was a significant decline in median ALT levels from baseline to Week 48 (27 U/L and 22 U/L, respectively; *P*<0.001), as well as in AST levels (24 U/L and 21 U/L; *P*<0.001) and GGT levels (20 U/L and 18 U/L; *P*=0.046). Median APRI scores improved significantly from baseline to Week 48 (0.25 and 0.26, respectively; *P*=0.002), and there were numerical improvements in median FIB-4 scores (1 and 0.95; *P*=0.228) and median GPR levels (0.16 and 0.14; *P*=0.146).

Safety data were not reported.

Single-Arm, Prospective Study[4]

Study design and demographics

A single-arm, prospective study in TN participants with CHB and histologically confirmed liver fibrosis (N=100) from 10 hospitals in China evaluated the effects of TAF treatment for 96 weeks. The primary endpoint was the rate of fibrosis regression, defined as either a decrease of ≥1 stage in fibrosis in the Ishak score or a classification of predominant regression per the P-I-R criteria. Liver fibrosis was noninvasively assessed using LSM, APRI, and FIB-4.

At baseline, 58% of the participants with available paired liver biopsies (n=80) were male, the mean age was 41.3±10.5 years, 17 had cirrhosis, 61% were HBeAg+, and the median (Q1, Q3) ALT level was 43.7 (29.3, 79.1) U/L. Baseline Ishak scores were as follows: 1, n=1 (1%); 2, n=8 (10%); 3, n=30 (38%); 4, n=24 (30%); 5, n=12 (15%); and 6, n=5 (6%). Based on P-I-R criteria, 65/71 participants (92%) were considered predominantly progressive, 5 (7%) were indeterminate, and 1 (1%) was predominantly regressive.

Results

In total, 93 participants completed 96 weeks of TAF treatment. Of the 80 participants with available paired liver sections, 56 participants (70%) showed fibrosis regression, and 23 (29%) had no change in Ishak score. All 17 participants (100%) with cirrhosis achieved fibrosis regression; 15 of those participants had a ≥1 stage decrease in Ishak score, and 2 participants improved to the classification of predominant regression according to the P-I-R criteria. The rate of fibrosis regression was significantly higher among participants with cirrhosis (17/17) than among those without cirrhosis (39/63; *P*<0.009).

Of the 52 participants with available P-I-R data at Week 96, 17 (33%) were classified as predominantly progressive, 16 (31%) as indeterminate, and 19 (36%) as predominantly regressive. APRI, FIB-4, and LSM scores improved significantly from baseline to Week 96 (Table 3).

Table 3. Noninvasive Indicators of Liver Fibrosis at Baseline and Week 96 (Zhou et al)[4]

Indicator	Baseline (N=100)	Week 96 (n=93)	*P*-Value
APRI score, median (Q1, Q3)	0.55 (0.37, 0.9)	0.31 (0.22, 0.44)	<0.001
FIB-4 score, median (Q1, Q3)	1.14 (0.8, 2.14)	1 (0.73, 1.39)	<0.001
LSM, median (Q1, Q3), kPa	9.7 (7.2, 15.1)	6.4 (5.5, 9.1)	<0.001

Safety data were not reported.

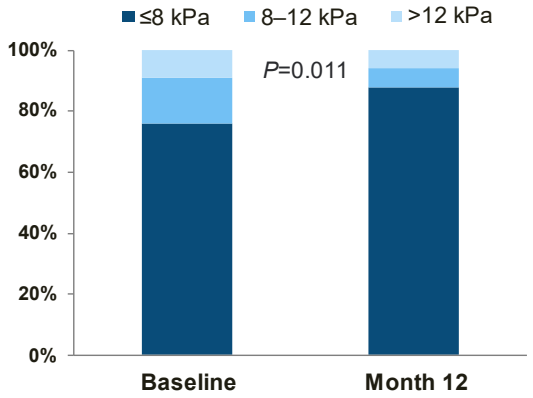
Real-World Data: TAF Use and Fibrosis Improvement

Prospective Cohort Study[5]

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.

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)[5]



Retrospective Study[6]

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 post switch were analyzed, as were factors associated with changes in SWE.

Table 4. Baseline Demographics and Characteristics (Hyuhn et al)[6]

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)[6]

Variable	Univariate *P*-Value	Multivariate *P*-Value
Pre-switch 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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4. 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 #1165] Paper presented at: AASLD - The Liver Meeting; November 7-11, 2025; Washington, DC.

5. 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.
6. 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.
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8. Chan HL, 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(3):185-195.

Abbreviations

AASLD=American Association for the Study of Liver Disease
APRI=AST to Platelet Ratio Index
CHB=chronic hepatitis B
CVR=complete virologic response
FIB-4=Fibrosis-4
GGT=γ-glutamyltransferase
GPR=γ-glutamyl transpeptidase to platelet ratio
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
LSM=liver stiffness measurement
P-I-R=Progressive-Indeterminate-Regressive
Q=quartile
SWE=shear wave elastography
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TN=treatment-naive
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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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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