GILEAD | Medical Information

Vemlidy® (tenofovir alafenamide) Resistance Profile

The document provides available resistance data regarding Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of chronic hepatitis B (CHB).

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Summary

Product Labeling[1]

In a pooled analysis of treatment-naive and treatment-experienced subjects receiving TAF in Studies 108 and 110 and in pediatric Study 1092, no specific substitutions occurred at a sufficient frequency to be associated with resistance to TAF.

Clinical Data on Resistance to TAF in Participants With CHB

In Studies 108 and 110, all participants who had HBV DNA ≥69 IU/mL during the study had direct sequencing of HBV pol/RT for resistance assessment.[2]

- At Year 8, 2% of participants (29/1298) had HBV DNA ≥69 IU/mL and qualified for sequence analysis. All identified amino acid substitutions at Year 8 remained susceptible to TAF in vitro.

In Study 4018, participants with HBV DNA ≥69 IU/mL at any study visit from baseline through the end of Week 48 underwent sequence analysis of HBV pol/RT to scan for potential resistance mutations. Viral resistance was not detected in the 1% of participants who qualified for viral sequencing and received treatment with either TAF or TDF. According to sequence analysis, no pre-existing resistance mutations associated with adefovir dipivoxil, entecavir, or lamivudine were present in any of these participants.[3]

Product Labeling[1]

Microbiology

Resistance in clinical trials

Genotypic resistance analysis was performed on paired baseline and on-treatment HBV isolates for subjects who either experienced virologic breakthrough (2 consecutive visits with HBV DNA ≥69 IU/mL [400 copies/mL] after having been <69 IU/mL, or ≥1-$\log_{10}$ increase in

HBV DNA from nadir) through Week 48, or had HBV DNA ≥69 IU/mL at early discontinuation at or after Week 24.

In a pooled analysis of treatment-naïve and treatment-experienced subjects receiving TAF in Trials 108 and 110, treatment-emergent amino acid substitutions in the HBV reverse transcriptase domain, all occurring at polymorphic positions, were observed in some HBV isolates evaluated (5/20); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to TAF.

In virologically suppressed subjects receiving TAF in Trial 4018, no subjects qualified for resistance analysis through 48 weeks of TAF treatment.

In pediatric Trial 1092, 17/70 subjects in Cohort 1 (aged 12 to <18 years) and 7/18 subjects in Cohort 2, Group 1 (aged 6 to <12 years) receiving TAF qualified for resistance analysis at Week 96. Results were obtained from 19/24 qualified subjects. No HBV amino acid substitutions known to be associated with resistance to TAF were detected through 96 weeks of treatment.

Cross resistance

The antiviral activity of TAF was evaluated against a panel of isolates containing substitutions associated with HBV nucleoside reverse transcriptase inhibitor resistance in a transient transfection assay using HepG2 cells. HBV isolates expressing the lamivudine resistance-associated substitutions rtM204V/I (±rtL180M±rtV173L) and expressing the entecavir resistance-associated substitutions rtT184G, rtS202G, or rtM250V in the presence of rtL180M and rtM204V showed <2-fold reduced susceptibility (within the inter-assay variability) to TAF. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir also had <2-fold changes in EC_{50} values; however, the HBV isolate expressing the rtA181V plus rtN236T double substitutions exhibited reduced susceptibility (3.7-fold) to TAF. The clinical relevance of these substitutions is not known.

Clinical Data on Resistance to TAF in Participants With CHB

Studies 108 and 110

Study designs and demographics

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 1298 adult participants with an HBV DNA level ≥20,000 IU/mL, both with and without compensated cirrhosis, were randomly assigned to receive either double-blind TAF 25 mg or TDF 300 mg for 3 years in Studies 108 (HBeAg-; n=425) and 110 (HBeAg+; n=873).[2] 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.[2,4]

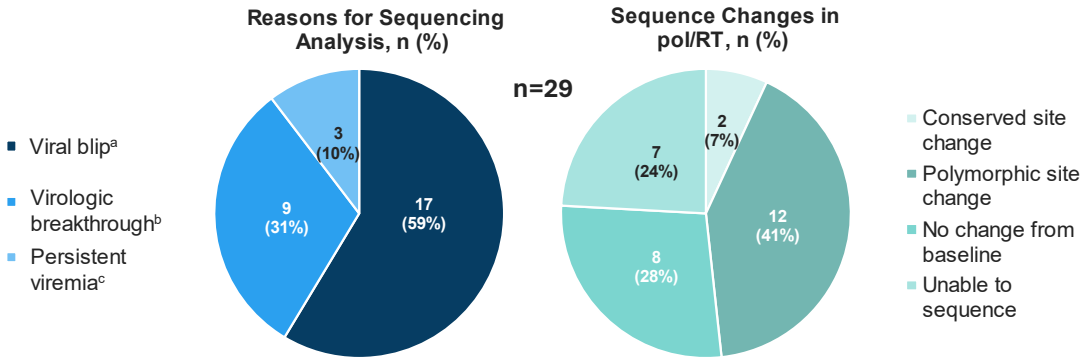
The primary endpoint was a noninferiority margin of 10% in the proportion of participants with undetectable HBV DNA (HBV DNA <29 IU/mL) at Week 48. Prespecified secondary endpoints included changes in hip and spine bone mineral density, changes in SCr, dipstick

proteinuria, biochemical response (ie, ALT normalization), serologic response (ie, HBsAg seroconversion), and change in fibrosis as measured by FibroTest.[5,6]

Year 8 resistance analysis

At Year 8, in the integrated analysis, a total of 29/1298 participants (2%) qualified for resistance testing (if HBV DNA was ≥69 IU/mL, sequencing was performed annually).[2] From Year 6 to Year 8, the proportion of participants with virologic breakthrough and persistent viremia declined (Year 6: 16/36 participants [44%] and 9/36 participants [25%], respectively), and the proportion of participants with a viral blip increased (Year 6: 11/36 participants [31%]); Year 8 data are shown in Figure 1.[4]

Figure 1: Studies 108 and 110: Integrated Analysis of Sequencing at Year 8[2,4]



[a]Met 1 virologic breakthrough criterion at only 1 visit.
[b]HBV DNA increase ≥1 $\log_{10}$ IU/mL from nadir or confirmed HBV DNA ≥69 IU/mL if previously <69 IU/mL at 2 consecutive visits.
[c]Persistent HBV DNA ≥69 IU/mL over the course of treatment.

Of the 29 participants who had HBV sequencing at Year 8, 8 (28%) qualified for phenotyping (if there were observed changes at conserved sites in the HBV pol/RT or >1 participant had changes at polymorphic sites or the participant had virologic breakthrough while on TAF, with amino acid change substitution in pol/RT). Among these 8 participants, 2 had conserved site substitutions, while 6 had polymorphic site substitutions observed in ≥2 participants. The fold change from baseline in the EC_{50} of isolates from these 8 participants ranged from 0.43 to 1.8 at Year 8. All identified amino acid substitutions at Year 8 remained susceptible to TAF in vitro (<2-fold change from baseline in EC_{50}).[2,4]

Safety at Year 8[2]

The incidence of AEs was similar between the TAF and TDF→OL TAF groups in the OL safety analysis, and most AEs were Grade 1 or 2 (Table 1).

Table 1. Studies 108 and 110 OL Safety Analysis: AEs Through Year 8[2]

Safety Outcomes, n (%) or n/N (%)	TAF (n=775)	TDF→OL TAF[a] (n=382)
Any AE	525 (68)	271 (71)
Treatment-related AEs	43 (6)	18 (5)
Grade 3 or 4 AE	60 (8)	27 (7)
Grade 3 or 4 treatment-related AE	2 (<1)[b]	0
Serious AEs	97 (13)	49 (13)
Serious treatment-related AE	4 (1)[c]	0
Discontinuation due to AE	9 (1)[d]	3 (<1)[e]

Safety Outcomes, n (%) or n/N (%)		TAF (n=775)	TDF→OL TAF[a] (n=382)
Death		1 (<1)[f]	1 (<1)[g]
HCC[h]		7 (<1)	3 (<1)
AEs that occurred in ≥5% of participants	Headache	59 (8)	30 (8)
	URTI	55 (7)	27 (7)
	Nasopharyngitis	52 (7)	23 (6)
	Hypertension	37 (5)	26 (7)
	Arthralgia	41 (5)	23 (6)
	Cough	28 (4)	27 (7)
	Back pain	34 (4)	23 (6)
Grade 3 or 4 laboratory abnormalities that occurred in ≥2% of participants	Fasting LDL-C increased[i]	45/760 (6)	30/373 (8)
	Urine glucose[i]	40/772 (5)	10/377 (3)
	Urine occult blood[i]	26/772 (3)	12/377 (3)
	Amylase increased	15/772 (2)	10/377 (3)
	Creatine kinase increased	11/772 (1)	8/377 (2)
	Fasting cholesterol increased[i]	11/767 (1)	11/373 (3)

Abbreviations: HCC=hepatocellular carcinoma; LDL-C=LDL-cholesterol; URTI=upper respiratory tract infection.
[a]Included participants who switched to OL TAF at Year 2 and at Year 3.
[b]Cerebrovascular accident, renal neoplasm (each, n=1).
[c]Cerebrovascular accident, renal neoplasm, ALT increase, osteonecrosis (each, n=1).
[d]Cardiopulmonary failure, myelodysplastic syndrome, HCC, pancreatic carcinoma, cerebrovascular accident, γ-glutamyltransferase increased, osteonecrosis, osteoporosis, proteinuria (each, n=1).
[e]Tuberculosis, ascites, pemphigoid (each, n=1).
[f]Pancreatic cancer.
[g]Bilateral pneumonia.
[h]Over the course of the entire study, 21 participants developed HCC (12/866 in TAF vs 9/432 in TDF→TAF; *P*=0.33).[4]
[i]Grade 3 only.

Study 4018[3]

Study design and demographics

Study 4018 was a double-blind, randomized, phase 3 study that evaluated the safety and efficacy of switching from TDF to TAF (n=243) versus continuing treatment with TDF (n=245) in virologically suppressed (HBV DNA < lower limit of quantification for ≥12 weeks before screening) adult participants with CHB. Eligible participants had been treated with TDF for ≥48 weeks prior to screening and had eGFR (according to Cockcroft-Gault) ≥50 mL/min at screening.

Participants were randomly assigned in a 1:1 ratio either to receive TAF 25 mg with a matching TDF placebo or to continue treatment with TDF 300 mg with a matching TAF placebo for 48 weeks. Randomization was stratified by age (<50 years or ≥50 years) and HBeAg (positive or negative) status. Upon completion of the double-blind phase, eligible participants from both arms were enrolled into an OL phase to receive TAF for an additional 48 weeks.

The primary efficacy endpoint was the proportion of participants who had HBV DNA levels ≥20 IU/mL at Week 48. Secondary efficacy endpoints included the proportion of participants with HBV DNA <20 IU/mL, the proportions of participants with HBeAg loss and seroconversion to HBe antibodies, and the proportion of participants with HBsAg loss and seroconversion to HBs antibodies. The primary safety endpoint was the tolerability of TAF in participants who switched from TDF compared with participants who continued treatment with TDF at Week 48.

Resistance analysis

Participants with HBV DNA ≥69 IU/mL at any study visit from baseline through the end of Week 48 underwent sequence analysis of HBV pol/RT to scan for potential resistance mutations.

Viral resistance was not detected in the 1% of participants who qualified for viral sequencing and received treatment with either TAF (n/N=3/243) or TDF (n/N=2/245). One participant who received TDF had HBV DNA ≥69 IU/mL while receiving study treatment; the other 4 participants had HBV DNA ≥69 IU/mL at the baseline visit only. Of the 3 participants who received TAF treatment and underwent resistance testing, 2 were virologically suppressed (HBV DNA <20 IU/mL) at Week 48, and 1 discontinued the study at Week 24 with HBV DNA <20 IU/mL. No viral resistance developed in either treatment group. Of the 2 participants who received TDF and underwent resistance testing, 1 discontinued the study on Day 46 with HBV DNA ≥69 IU/mL, and 1 experienced a viral blip at Week 12. According to sequence analysis, no pre-existing resistance mutations associated with adefovir dipivoxil, entecavir, or lamivudine were present in any participant who underwent resistance testing.

At Week 48, 96% of participants in each treatment group were virally suppressed (TAF, n/N=234/243; TDF, n/N=236/245).

References

1. Enclosed. Gilead Sciences Inc, VEMLIDY® (tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. Buti M, Lim YS, Chan HLY, et al. Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: Final results from two randomised phase 3 trials. *Aliment Pharmacol Ther.* 2024;60(11-12):1573-1586.
3. Lampertico P, Buti M, Fung S, et al. Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Virologically Suppressed Patients with Chronic Hepatitis B: A Randomised, Double-Blind, Phase 3, Multicentre Non-Inferiority Study. *Lancet Gastroenterol Hepatol.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32087795
4. Buti M, Lim YS, Chan HLY, et al. Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: Final results from two randomised phase 3 trials [Supplemental material]. *Aliment Pharmacol Ther.* 2024;60(11-12):1573-1586. https://www.ncbi.nlm.nih.gov/pubmed/39327857
5. 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.
6. 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

AE=adverse event
CHB=chronic hepatitis B
EC_{50}=half maximal effective concentration
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
OL=open-label
pol/RT=polymerase/reverse transcriptase
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate

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

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

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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