No Resistance to Tenofovir Alafenamide (TAF) in Adult, HBeAg-positive and HBeAg-negative Participants With Chronic Hepatitis B Infection Treated With TAF for up to 8 Years

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Key Findings

- **Through a rigorous annual surveillance approach, no resistance to TAF was detected in treatment-naïve or -experienced, HBeAg-positive or -negative CHB adults treated with TAF for up to 8 years**

Conclusions

These results, and particularly the documented lack of resistance through 8 years of treatment, provide additional support for TAF as a preferred, first-line treatment for CHB

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Introduction

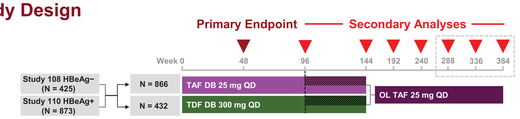
- Hepatitis B virus (HBV) infection affects >300 million people globally and is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma if not properly treated[1,2]
- Approximately 820,000 people die every year from HBV, despite the availability of effective vaccines and antivirals[3]
- International guidelines recommend the use of nucleot(s)ide analogues (NA; tenofovir alafenamide [TAF], tenofovir disoproxil fumarate [TDF], or entecavir) as the preferred monotherapy regimens[4,5]
- TAF, a novel prodrug of tenofovir, is approved in the United States for the treatment of chronic hepatitis B (CHB) in adult and pediatric patients aged 12 years or older with compensated liver disease
- In 2 randomized, Phase 3 studies (108 and 110), TAF showed noninferior efficacy with improved renal and bone safety vs TDF at weeks 48 and 96[6–8]
- No resistance was detected after 5 years of TAF treatment[9]

Objective

- To assess development of drug resistance during long-term treatment (year 6 [week 288] to year 8 [week 384]) of CHB with TAF in 2 Phase 3 clinical trials (GS-US-320-0108, hepatitis B e antigen [HBeAg]-negative participants; GS-US-320-0110, HBeAg-positive participants)

Methods

Study Design



Amendment 3 enacted to extend DB to week 144 and OL to week 384 (year 8); shaded areas represent participants who rolled over to OL TAF at week 96 (OL3y) or week 144 (OL2y); missing = failure (M=F) analysis for efficacy using OL full analysis set; missing = excluded using observed data. DB, double-blind; HBeAg, hepatitis B e antigen; OL, open-label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Key Inclusion Criteria

- HBV DNA ≥20,000 IU/mL
- Alanine aminotransferase >60 U/L (males) and >38 U/L (females)
- With/without compensated cirrhosis
- Treatment-naïve or treatment-experienced (12 weeks or more of prior nucleos[t]ide use)
- Estimated glomerular filtration rate with Cockcroft-Gault ≥50 mL/min

Sequencing and Phenotyping Criteria

Sequencing* (direct sequencing of HBV pol/RT)

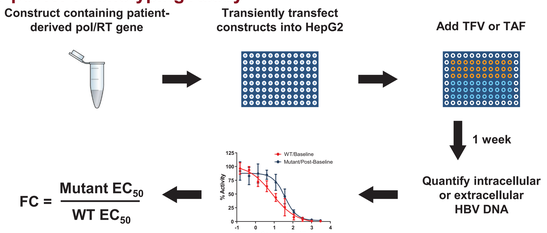
All participants
- At baseline
- Yearly if HBV DNA ≥69 IU/mL
- At premature study discontinuation if HBV DNA ≥69 IU/mL

Phenotyping in vitro analysis

In vitro phenotyping performed for participants with
- Changes at conserved sites in the HBV pol/RT
- Changes at polymorphic sites if seen in >1 participant
- Virologic breakthrough† while on study drug with amino acid change substitution in pol/RT

*Limit of sequencing assay HBV DNA = 69 IU/mL, consensus-level results are reported (15% cutoff). †Virologic breakthrough: HBV DNA increase 1 $\log_{10}$ IU/mL above nadir or ≥69 IU/mL after being <69 IU/mL for 2 consecutive visits. HBV, hepatitis B virus; pol/RT, polymerase reverse transcriptase.

HBV pol/RT Phenotyping Assay



EC_{50}, half-maximal effective concentration; FC, fold-change; HBV, hepatitis B virus; pol/RT, polymerase reverse transcriptase; TAF, tenofovir alafenamide; TFV, tenofovir; WT, wildtype.

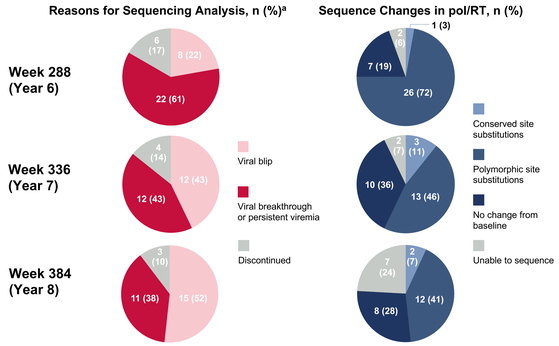
Results

Participants Who Qualified for Sequencing After Week 240

	Study 108			Study 110			Integrated 108/110
	TAF	TDF→TAF	Total	TAF	TDF→TAF	Total	Overall
Week 288 (Year 6)							
Participants in FAS on OL treatment, n	213	104	317	398	197	595	912
Sequenced, n (%)	4 (1.9)	1 (1.0)	5 (1.6)	23 (5.8)	8 (4.1)	31 (5.2)	36 (3.9)
Week 336 (Year 7)							
Participants in FAS on OL treatment, n	221	106	327	401	198	599	926
Sequenced, n (%)	8 (3.6)	1 (0.9)	9 (2.8)	12 (3.0)	7 (3.6)	19 (3.2)	28 (3.0)
Week 384 (Year 8)							
Participants in FAS on OL treatment, n	208	102	310	392	193	585	895
Sequenced, n (%)	6 (2.9)	1 (1.0)	7 (2.3)	15 (3.8)	7 (3.6)	22 (3.8)	29 (3.2)

FAS, full analysis set; OL, open-label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Integrated Analysis of Sequencing Data After Week 240



[a]Virologic breakthrough: HBV DNA ≥1 $\log_{10}$ IU/mL increase from nadir or confirmed ≥69 IU/mL if previously <69 IU/mL for 2 consecutive visits; viral blip: met 1 virologic breakthrough criterion at only 1 visit; viremia: persistent HBV DNA ≥69 IU/mL over treatment course. pol/RT, polymerase reverse transcriptase.

- The proportion of participants that qualified for sequencing analysis was low (range 1.6%–2.8%) for Study 108 and declined in Study 110 (from 5.2% at week 288 to 3.8% at week 384)
- The proportion of participants that experienced a viral blip increased with time

Integrated Analysis of Phenotyping Data After Week 240

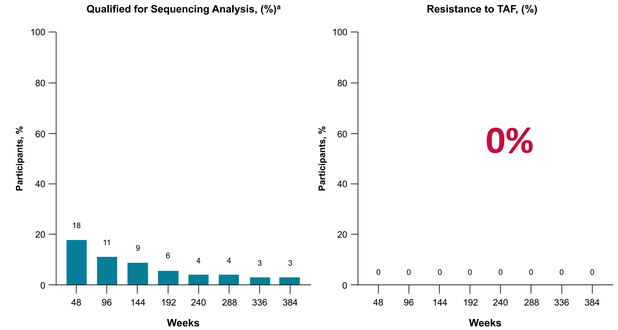
	Number of Participants Sequenced	Participant Disposition[a]			Number of Participants Phenotyped	TAF EC_{50} FC Range
		VB/PV	Blip	DC		
Week 288 (Year 6)	36	22	8	6	19	0.21–1.51
Week 336 (Year 7)	28	12	12	4	11	0.67–1.85
Week 384 (Year 8)	29	11	15	3	8	0.43–1.80

[a]Virologic breakthrough: HBV DNA ≥1 $\log_{10}$ IU/mL increase from nadir or confirmed ≥69 IU/mL if previously <69 IU/mL for 2 consecutive visits; viral blip: met 1 virologic breakthrough criterion at only 1 visit; viremia: persistent HBV DNA ≥69 IU/mL over treatment course. Blip, viral blip; DC, discontinued; EC_{50}, half-maximal effective concentration; FC, fold-change; HBV, hepatitis B virus; PV, persistent viremia; TAF, tenofovir alafenamide; VB, virologic breakthrough.

Fold Change for HBV pol/RT Phenotyping Assay

Dotted line represents assay cut-off. Hashed bars indicate the original isolate and 3 cloned individual substitutions derived from a unique participant.
HBV, hepatitis B virus; pol/RT, polymerase reverse transcriptase; TAF, tenofovir alafenamide.

Overall Integrated Data From Studies 108 and 110



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Summary of Key Takeaways

- At week 384, 29 of 895 (3%) participants entering year 8 of the study qualified for sequencing
  - Viral blip was the most common reason for sequence analysis
  - Polymorphic site substitutions were the most common sequence changes in the polymerase reverse transcriptase (pol/RT) assay
- 8 of 29 (28%) sequenced participants qualified for phenotyping at week 384
- Week 384 isolates remained sensitive to TAF in vitro (fold change in EC_{50} <2 from baseline)
- During the study, the number of participants with persistent viremia declined over time
- No amino acid substitutions in HBV pol/RT conferring reduced susceptibility to TAF were identified throughout 8 years of treatment

AASLD: The Liver Meeting; November 10–14, 2023; Boston, MA, USA