Impact of Long-Term Tenofovir-Based Treatment on Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis B Using the reREACH-B Score

WED-296

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Conclusions

- In a cohort of >1600 patients with hepatitis B e antigen (HBeAg)-positive and HBeAg-negative chronic hepatitis B (CHB) enrolled in 2 large Phase 3 studies, antiviral treatment for up to 8 years demonstrated low rates of hepatocellular carcinoma (HCC) with tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) followed by TAF treatment (1.3% and 2.2%, respectively)
- Using Revised Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (reREACH-B) scoring, long-term treatment with tenofovir-based therapies showed few patients at low risk at baseline shifted to higher risk, whereas many patients at higher risk shifted to lower risk on long-term tenofovir-based treatment
- These data highlight the importance of antiviral treatment to the attenuation of HCC risk in both low-risk and high-risk patients

Plain Language Summary

- We used a risk-assessment tool to predict liver cancer risk in patients treated with tenofovir-based treatments in clinical trials
- Over 8 years, few patients (26 of 1632, or 1.6%) developed hepatocellular carcinoma; many patients (52%) with higher risk at the start of the study shifted to lower risk with long-term antiviral treatment. Importantly, few patients (8%) at lower risk shifted to high risk by year 8

References: **1.** Maucort-Boulch D, et al. *Int J Cancer.* 2018;142:2471-7. **2.** Kim WR, et al. *Cancer.* 2015;121:3631-8. **3.** Kumada T, et al. *J Hepatol.* 2013;58:427-33. **4.** Yang H-I, et al. *Lancet Oncol.* 2011;12:568-74. **5.** Choi W-M, et al. *Gut.* 2024;73:649-58. **6.** Kim G-A, et al. *Ann Intern Med.* 2024;177:1308-18. **7.** Toy M, et al. *PLoS One.* 2025;20(1):e0313898.

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Introduction

- CHB is a leading cause of HCC, accounting for over 50% of all HCC cases globally[1]
- Oral antivirals can reduce but do not eliminate HCC risk[2,3]
- Various scoring systems incorporating disease-specific factors, such as hepatitis B virus (HBV) DNA level and HBeAg status, have been developed to predict HCC risk in patients with CHB. These include nomograms, such as the REACH-B score[4]
- Recent reports indicate that the relationship between HBV DNA level and HCC risk follows a nonlinear, parabolic pattern[5]; thus, the REACH-B score was updated to incorporate age, sex, platelet count, HBV DNA level, alanine aminotransferase (ALT) level, and HBeAg status
- The reREACH-B model showed improved overall performance and offered greater clinical utility vs the REACH-B model[6]

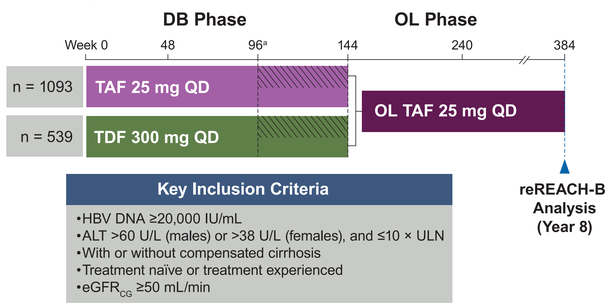
Objective

- To evaluate HCC incidence and risk based on the updated reREACH-B score in patients with HBeAg-positive and HBeAg-negative CHB enrolled in 2 Phase 3 studies evaluating tenofovir-based treatments

Methods

- This analysis used pooled data from 2 global Phase 3, randomised, double-blind, active-controlled trials
  - Study 108 (N = 579): HBeAg-negative patients (global and China cohorts: NCT01940341 and NCT02836236, respectively)
  - Study 110 (N = 1053): HBeAg-positive patients (global and China cohorts: NCT01940471 and NCT02836249, respectively)
- Patients were randomised 2:1, stratified by HBV DNA level and treatment status (naïve/experienced), and treated with one of the following:
  - TAF 25 mg once daily (QD) for up to 144 weeks (3 years) followed by open-label (OL) TAF 25 mg QD
  - TDF 300 mg QD for up to 144 weeks (3 years) followed by OL TAF 25 mg QD
- Patients were assessed through 384 weeks (8 years)

Study Design



[a]Amended to extend the DB period to week 144 and OL period to week 384 (year 8); shaded areas represent patients in the global cohort who rolled over to OL TAF at week 96 (TAF, n = 360; TDF, n = 180).
ALT, alanine aminotransferase; DB, double blind; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBV, hepatitis B virus; OL, open label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

- HCC was a predefined adverse event
- Screening, diagnosis, and treatment were per local standards of care
  - Hepatic ultrasonography (every 6 months) was added at week 96
- Predicted HCC risk was assessed at baseline and during treatment through year 8 (384 weeks) using reREACH-B scores
- Patients were stratified into low (<0.01) and high (≥0.01) HCC risk categories based on reREACH-B scores (minimum, 0; maximum, 1), reflecting an annual incidence rate of 0.2%, the cost-effectiveness threshold for HCC surveillance[7]
- Using the reREACH-B model, the standardised incidence ratios (SIRs) for HCC (observed cases vs model-predicted rates) with 95% CIs (calculated by Poisson regression) were determined

Results

Baseline Characteristics by HCC Risk

	Low Risk n = 547	High Risk n = 1084	Total n = 1631
Age, years, mean (SD)	33 (9.7)	44 (11.2)	40 (11.8)
Treatment group, n (%)			
TAF	384 (70)	708 (65)	1092 (67)
TDF→TAF	163 (30)	376 (35)	539 (33)
Male sex, n (%)	259 (47)	803 (74)	1062 (65)
Asian, n (%)	436 (80)	917 (85)	1353 (83)
Cirrhosis, n (%)	5 (1)	150 (14)	155 (10)
HBV DNA, log$_{10}$ IU/mL, mean (SD)	7.4 (1.91)	6.6 (1.47)	6.9 (1.67)
Genotype, n (%)			
A	29 (5)	56 (5)	85 (5)
B	120 (22)	251 (23)	371 (23)
C	245 (45)	578 (53)	823 (50)
D	146 (27)	184 (17)	330 (20)
Other	6 (1)	13 (1)	19 (1)
Unknown	1 (<1)	2 (<1)	3 (<1)
Platelets, 10^3/µL, mean (SD)	235 (54.8)	172 (46.2)	193 (57.4)
ALT, U/L, mean (SD)	81 (50.5)	134 (138.8)	116 (119.5)
HBeAg positive, n (%)	421 (77)	617 (57)	1038 (64)
Albumin, g/dL, mean (SD)	43 (3.4)	43 (3.9)	43 (3.7)
reREACH-B score, mean (SD)	0.00 (0.003)	0.11 (0.131)	0.07 (0.118)
FibroTest score, mean (SD)	0.23 (0.153)	0.46 (0.229)	0.38 (0.232)

reREACH-B score could not be calculated for 1 patient. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; reREACH-B, Revised Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Compared with patients at low risk, those at high risk were more likely to be older and male; were less likely to be HBeAg positive; had lower platelet counts, lower HBV DNA levels, and higher baseline ALT levels; and were more likely to have cirrhosis

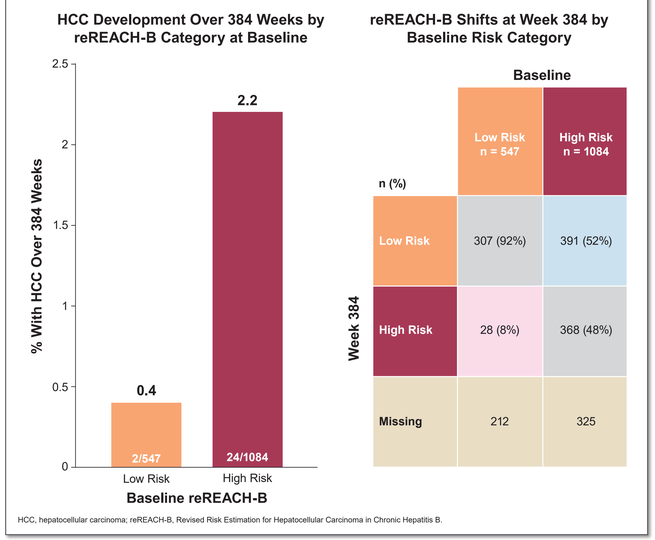
Baseline Characteristics by HCC Development

	HCC n = 26	No HCC n = 1606	*P*-value for HCC vs No HCC
Age, years, mean (SD)	52 (8.8)	40 (11.7)	**<.0001**
Treatment group, n (%)			
TAF	14 (54)	1079 (67)	.1515
TDF→TAF	12 (46)	527 (33)	
Male sex, n (%)	23 (88)	1040 (65)	**.0119**
Asian, n (%)	25 (96)	1329 (83)	.5135
Cirrhosis, n (%)	9 (35)	146 (9)	**<.0001**
HBV DNA, log$_{10}$ IU/mL, mean (SD)	6.6 (1.10)	6.9 (1.68)	.1385
Genotype, n (%)			
A	0	85 (5)	.0705
B	2 (8)	369 (23)	
C	21 (81)	802 (50)	
D	3 (12)	328 (20)	
Other	0	19 (1)	
Unknown	0	3 (0)	
ALT, U/L, mean (SD)	84 (57.8)	117 (120.1)	.1272
HBeAg positive, n (%)	13 (50)	1026 (64)	.1443
Albumin, g/dL, mean (SD)	40.1 (4.26)	43.0 (3.67)	**.0003**
reREACH-B score, median (Q1, Q3)	0.21 (0.11, 0.36)	0.02 (0.01, 0.08)	**<.0001**
FibroTest score, mean (SD)	0.61 (0.219)	0.38 (0.230)	**<.0001**

Cirrhosis was defined as a FibroTest score ≥0.75 in Studies 108/110. *P*-values are from the CMH test and the 2-sided Wilcoxon rank sum test for categorical data and continuous data, respectively. Bold text indicates significant *P*-values.
ALT, alanine aminotransferase; CMH, Cochran-Mantel-Haenszel; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; Q, quartile; reREACH-B, Revised Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Through 8 years of follow-up, HCC occurred in 26 of 1632 (1.6%) patients (TAF, 14 of 1093 [1.3%]; TDF, 12 of 539 [2.2%])
  - Of the 26 patients with HCC, 9 (35%) had cirrhosis at baseline
- Patients who developed HCC were significantly older, more likely to be male, had lower mean albumin, and more likely to have cirrhosis at baseline

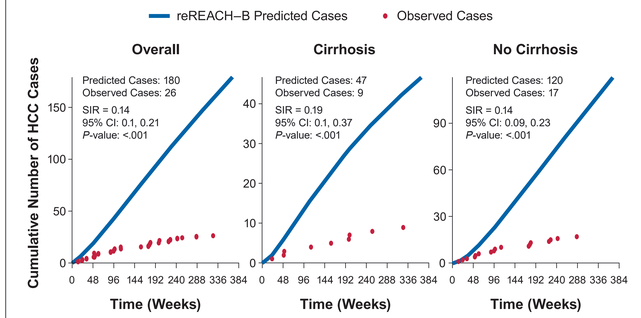
Year 8 Findings by Baseline reREACH-B Score



HCC, hepatocellular carcinoma; reREACH-B, Revised Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B.

- Among individuals characterised as high or low risk at baseline, 24 of 1084 (2.2%) and 2 of 547 (0.4%), respectively, developed HCC over 8 years
- At year 8, the mean (range) change from baseline in reREACH-B score was −0.1 (−1.0 to 0.1)
- Notably, 52% of patients deemed high risk at baseline with available data at year 8 shifted to low risk; only 8% of patients shifted from low to high risk at year 8

Observed vs Predicted HCC Cases by reREACH-B: Overall and by Baseline Cirrhosis Status



HCC, hepatocellular carcinoma; reREACH-B, Revised Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardised incidence ratio.

- Based on the SIR, the HCC incidence seen with treatment overall was 86% lower compared with the incidence predicted by the reREACH-B model
- Similar significant reductions in HCC incidence were observed with long-term antiviral treatment in patients with and without cirrhosis at baseline

European Association for the Study of the Liver; 7–10 May 2025; Amsterdam, the Netherlands