Impact of Long-term Treatment With Continuous Tenofovir Alafenamide or After Switching From Tenofovir Disoproxil Fumarate on Hepatocellular Carcinoma Incidence in Patients With Chronic Hepatitis B

1422-C

Young-Suk Lim[1], Grace Wong[2], Sang Hoon Ahn[3], Wai-Kay Seto[4], Kosh Agarwal[5], Harry LA Janssen[6,7], Calvin Q Pan[8], Wan-Long Chuang[9], Scott K Fung[10], Dr Shalimar[11], Maurizia R Brunetto[12], Aric Josun Hui[13], Ting-Tsung Chang[14], Seng Gee Lim[15], Frida Abramov[16], John F Flaherty[16], Hongyuan Wang[16], Leland J Yee[16], Jia-Horng Kao[17], Patrick Marcellin[18], Edward J Gane[19], Maria Buti[20,21]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Medical Data Analytics Centre (MDAC), The Chinese University of Hong Kong, Hong Kong; [3]Department of Internal Medicine, Institute for Gastroenterology, Yonsei University College of Medicine, Seoul, South Korea; [4]Department of Medicine and School of Clinical Medicine, The University of Hong Kong, Hong Kong; [5]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom; [6]Toronto Centre for Liver Disease, University Health Network, Toronto, Canada; [7]Erasmus Medical Center, Rotterdam, Netherlands; [8]NYU Langone Health, New York University Grossman School of Medicine, New York, NY, USA; [9]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan; [10]Department of Medicine, University of Toronto, Toronto, Canada; [11]All India Institute of Medical Sciences, New Delhi, India; [12]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [13]Alice Ho Miu Ling Nethersole Hospital, Tai Po, Hong Kong; [14]National Cheng Kung University Hospital, Tainan City, Taiwan; [15]National University Health System, Singapore; [16]Gilead Sciences, Inc., Foster City, CA, USA; [17]National Taiwan University College of Medicine, Taipei City, Taiwan; [18]Hepatology Department, Hôpital Beaujon, APHP, INSERM, University of Paris, Clichy, France; [19]Auckland Clinical Studies, Auckland, New Zealand; [20]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [21]CIBEREHD del Instituto Carlos III, Madrid, Spain

Key Findings

- **Over 8 years (384 weeks), 21 of 1298 (1.6%) patients with CHB, enrolled in 2 Phase 3 studies, developed HCC; the incidence was lower and time to HCC onset more prolonged in patients randomized to TAF compared with those who received TDF treatment for 2 to 3 years followed by TAF (TDF→TAF)**
- **Older age, male sex, lower baseline platelet count, and lack of early (week 24) ALT normalization were predictors of HCC development by multivariate logistic regression analysis**
- **Using the REACH-B model, the standard incidence ratio for HCC development (observed cases under TAF or TDF→TAF treatment vs predicted cases based on the model) was significantly reduced at year 8, supporting a positive impact of antiviral treatment on HCC risk**
- **Results from 2 validated predictor models (aMAP and mPAGE-B) showed nearly all patients predicted to be low risk for HCC at baseline remained low risk at year 8 (98% and 97%, respectively), while the majority of patients at high risk shifted to a lower category of risk by year 8 (72% and 51%, respectively)**

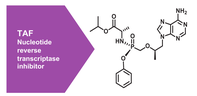
Conclusions

These findings from a large, well-characterized cohort of patients with CHB provide additional evidence that long-term treatment with TAF, or TDF followed by a switch to TAF, can reduce HCC risk

Introduction

- With an estimated all-age prevalence of 4.1%, representing approximately 316 million people living with chronic hepatitis B (CHB) worldwide, infection with the hepatitis B virus (HBV) resulted in over 550,000 deaths in 2019, primarily from cirrhosis and hepatocellular carcinoma (HCC)[1]
- CHB is a leading risk factor for development of HCC[2]; studies have shown anti-HBV nucleos(t)ide analogues, such as tenofovir disoproxil fumarate (TDF) and entecavir, reduce but do not eliminate the risk of HCC[3,4]
- Tenofovir alafenamide (TAF), a novel tenofovir prodrug with enhanced plasma stability and more efficient hepatic delivery, has ~90% lower circulating levels of tenofovir relative to TDF when given at a lower daily dose than TDF[5,6]
- In 2 randomized, Phase 3 studies (Studies 108 and 110), TAF showed noninferior efficacy with improved renal and bone safety vs TDF at weeks 48 and 96[7-9]
  - At 5 years, patients who received TAF had a lower incidence of HCC compared with patients randomized to TDF followed by open-label TAF (1.0% vs 2.0%; $P = .08$)[10]

TAF
Nucleotide reverse transcriptase inhibitor



References: **1.** GBD 2019 Hepatitis B Collaborators. *Lancet Gastroenterol Hepatol*. 2022;7:796-829. **2.** McGlynn KA, et al. *Hepatology*. 2021;73:4-13. **3.** Kim WR, et al. *Cancer*. 2015;121:3631-8. **4.** Kumada T, et al. *J Hepatol*. 2013;58:427-33. **5.** Agarwal K, et al. *J Hepatol*. 2015;62:533-40. **6.** Murakami E, et al. *Antimicrob Agents Chemother*. 2015;59:3563-9. **7.** Buti M, et al. *Lancet Gastroenterol Hepatol*. 2016;1:196-206. **8.** Agarwal K, et al. *J Hepatol*. 2018;68:672-81. **9.** Chan HL, et al. *Lancet Gastroenterol Hepatol*. 2016;1:185-95. **10.** Lim YS, et al. *JHEP Reports*. 2023;5(10):100847. **11.** Yang HI, et al. *Lancet Oncol*. 2011;12:568-74. **12.** Fan R, et al. *J Hepatol*. 2020;73:1368-78. **13.** Kim JH, et al. *J Hepatol*. 2018;69:1066-73.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Medical writing support was provided by Charlotte Bayley, PhD, of AlphaScientia, a Red Nucleus company, and was funded by Gilead Sciences, Inc.

Disclosures: **GW** reports research support, consulting fees, speaker fees, and support for attending meetings from Gilead Sciences, Inc. **WKS** served as an advisor for Abbot, AbbVie, and Gilead Sciences, Inc., and reports speaker fees from AbbVie; AstraZeneca; Gilead Sciences, Inc.; and Mylan. **KA** served as a speaker, consultant, and/or advisory board member for Aligos Therapeutics; Arbutus Biopharma; Assembly Biosciences; Boehringer Ingelheim; Bristol Myers Squibb; Drug Farm; Gilead Sciences, Inc.; GSK; Janssen; Roche; Saigmet; and Swedish Orphan Biovitrum, and his institution received research support from Gilead Sciences, Inc. **HLAJ** received research grants from Gilead Sciences, Inc.; GSK; Janssen; Roche; and Vir Biotechnology, and served as a consultant for Aligos Therapeutics; Antios Therapeutics; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; GSK; Janssen; Roche; and Vir Biotechnology. **CQP** received research support from Gilead Sciences, Inc. **SKF** served as an advisor for AbbVie; Gilead Sciences, Inc.; Novo Nordisk; and Pfizer; reports speaker fees from AbbVie; Gilead Sciences, Inc.; and Lupin; and received research support from Gilead Sciences, Inc. **MRB** reports speaker and consultancy fees from AbbVie; Eisai-MSD; Gilead Sciences, Inc.; Janssen; and Roche. **SGL** reports research support from Abbott; Fibronostics; Gilead Sciences, Inc.; and Sysmex; and served as a speaker bureau member for Gilead Sciences, Inc.; GSK; Janssen; Roche; and Sysmex; and an advisory board member for Abbott; Arbutus Biopharma; Assembly Biosciences; Gilead Sciences, Inc.; Grifols; GSK; Janssen; Roche; and Sysmex. **FA, JFF, HW,** and **LJY** are employees and stockholders of Gilead Sciences, Inc. **PM** received grants from AbbVie; Aligos Therapeutics; Assembly Biosciences; Bristol Myers Squibb; Gilead Sciences, Inc.; Humedics; Intercept; Madrigal; Novo Nordisk; Pfizer; and Roche. **EJG** served as an advisor for AbbVie; Aligos Therapeutics; Arbutus Biopharma; Gilead Sciences, Inc.; Janssen; Roche; Vir Biotechnology; and Virion Therapeutics. **MB** reports speaker fees, research support, and consulting fees from AbbVie; Gilead Sciences, Inc.; and Janssen. **YSL, SHA, WLC, DrS, AJH, TTC,** and **JHK** report no conflicts of interest.

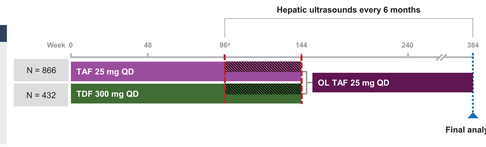
Objective

- To evaluate HCC incidence and risk for HCC development over 8 years among patients with CHB treated with TAF or treated with TDF followed by TAF

Methods

Study Design

Key Inclusion Criteria
- HBV DNA ≥20,000 IU/mL
- ALT >60 U/L (males) or >38 U/L (females) and ≤10 × ULN
- With/without compensated cirrhosis
- Treatment-naïve or treatment-experienced
- $eGFR_{CG}$ ≥50 mL/min

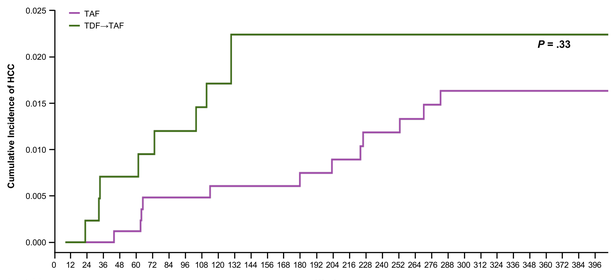


[a]Amendment 3 enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded/slashed areas represent patients who rolled over to OL TAF at week 96.
ALT, alanine aminotransferase; DB, double-blind; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBV, hepatitis B virus; OL, open-label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

- Two Phase 3, randomized, double-blind studies were conducted in patients with CHB who were hepatitis B e antigen (HBeAg)-negative (Study 108, NCT01940341)[7,8] or HBeAg-positive (Study 110, NCT01940471)[8,9]
  - **Double-blind phase:** randomized 2:1 (TAF 25 mg:TDF 300 mg once daily) and stratified by HBV DNA level and treatment status (naïve/experienced)
  - **Open-label phase:** TAF 25 mg once daily in patients who received TAF or who received TDF for 2 or 3 years
- The presence of HCC was assessed by local standards of care; beginning at week 96, hepatic ultrasonography was introduced via Protocol Amendment 3 to be performed on all patients every 6 months to enrich HCC surveillance
- Cumulative HCC incidence curves by treatment group were plotted by the Kaplan-Meier method and compared via the log-rank test
- Baseline and on-treatment factors associated with HCC development were assessed by multivariate analysis using a Cox proportional hazards model; stepwise selection was used to determine factors to be included in the final model
- Three validated models (REACH-B,[11] aMAP,[12] and modified PAGE-B[13] [mPAGE-B]) were used to assess the predicted risk for HCC development
  - Using the REACH-B model, the standard incidence ratios for HCC (observed cases vs model-predicted rates) with 95% CIs (calculated by Poisson regression) were determined overall, by treatment group (TAF and TDF→TAF), and by cirrhosis status
  - Using the aMAP and mPAGE-B prediction tools, scores were calculated at baseline and by visit with shifts from baseline HCC risk categories (low, medium, high) determined over 8 years (384 weeks)

Results

Cumulative Incidence of HCC Over 8 Years (384 Weeks) by Treatment Group



HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Over 8+ years of follow-up, a total of 21/1298 (1.6%) patients developed HCC

HCC Cases Over 8 Years (384 Weeks) by Treatment Group and Study Period

	TAF (n = 866)	TDF→TAF (n = 432)	Total (N = 1298)
HCC cases, n (%)*	12 (1.4)	9 (2.1)	21 (1.6)
Double-blind phase	5 (0.6)	6 (1.4)	11 (0.7)
Open-label TAF phase	7 (0.8)	3 (0.7)	10 (0.8)
Median time to HCC onset, days (Q1, Q3)**	1291 (397, 1629)	460 (180, 729)	729 (388, 1373)

*$P = .357$ (TAF vs TDF→TAF by 2-sided Fisher's exact test); **$P = .030$ (TAF vs TDF→TAF by 2-sided Wilcoxon rank sum test).
HCC, hepatocellular carcinoma; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- In the TAF group, the overall incidence of HCC was lower and the median time to HCC onset was more prolonged compared with the TDF→TAF group

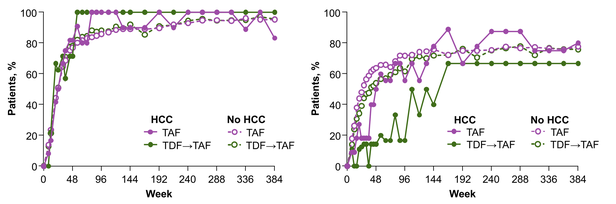
Baseline Characteristics by HCC Status

	HCC (n = 21)	No HCC (n = 1277)	*P*-value
Median age, years (Q1, Q3)	54 (51, 59)	39 (31, 49)	<.0001
Male, n (%)	18 (86)	801 (63)	.030
Race, n (%)			
Asian	20 (95)	1000 (78)	.472
White	1 (5)	253 (20)	
Black/African American	0	13 (1)	
Native Hawaiian/Pacific Islander/Other	0	11 (1)	
HBeAg positive, n (%)	10 (48)	849 (67)	.070
Mean HBV DNA, $\log_{10}$ IU/mL (SD)	6.6 (1.00)	7.0 (1.61)	.072
HBV DNA ≤7 $\log_{10}$ IU/mL, n (%)	13 (62)	561 (44)	
Median ALT, U/L (Q1, Q3)	71 (61, 100)	80 (54, 125)	.461
HBV genotype, n (%)			
A	0	85 (7)	.192
B	2 (10)	246 (19)	
C	16 (76)	602 (47)	
D	3 (14)	326 (26)	
Other or unknown	0	18 (1)	
Mean FibroTest score (SD)	0.63 (0.211)	0.37 (0.229)	<.0001
Cirrhosis, n (%)[a]	8 (38)	110 (9)	<.0001
Median AFP, ng/mL (Q1, Q3)	8.4 (4.9, 24.6)	3.4 (2.4, 5.6)	<.0001
Median platelet count, 10^3/μL (Q1, Q3)	142 (105, 180)	193 (160, 233)	<.0001

[a]FibroTest score category ≥0.75 to 1.00 (approximately Metavir F4). AFP, alpha fetoprotein; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; Q, quartile.

- Compared to patients without HCC, those with HCC were significantly older, were more likely to be male, and had higher FibroTest scores and rates of cirrhosis at baseline

HBV DNA and ALT Normalization in Patients With or Without HCC Over 8 Years (384 Weeks)



[a]2018 AASLD criteria (≤35 and ≤25 U/L for males and females, respectively). All results in figures are expressed as missing = excluded. AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Rates of viral suppression were similar in those with/without HCC, whereas lower rates of ALT normalization were seen in the first 48 (TAF) to 144 (TDF→TAF) weeks of treatment in patients with HCC
- The proportion of patients with ALT normalization increased among those with HCC after they switched from TDF to TAF

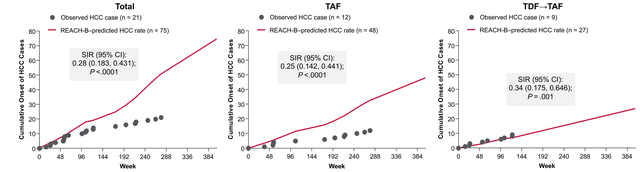
Baseline and On-treatment Factors Associated With HCC Development (Multivariate Analysis)

Predictor	Hazard Ratio	95% CI	*P*-value
Male sex	8.30	1.88–36.73	.005
Age, years	1.11	1.06–1.17	<.0001
Platelet count at baseline, 10^3/μL	0.99	0.98–0.99	.002
No ALT normalization at week 24	5.22	1.51–18.10	.009

ALT, alanine aminotransferase; HCC, hepatocellular carcinoma.

- Male sex, older age, lower baseline platelet count, and lack of ALT normalization at week 24 were predictors of HCC development

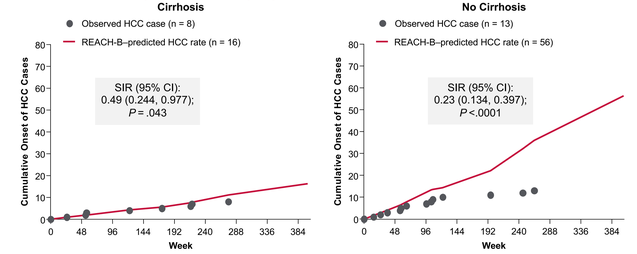
Observed Cases vs Predicted HCC Rates by REACH-B Analysis Over 8 Years (384 Weeks) Overall and by Treatment Group



HCC, hepatocellular carcinoma; SIR, standard incidence ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Treatment with TAF or TDF→TAF significantly reduced HCC incidence (observed cases, n = 21; model-predicted cases, n = 75) by the REACH-B model

Observed Cases vs Predicted HCC Rates by REACH-B Analysis Over 8 Years (384 Weeks) by Baseline Cirrhosis Status



HCC, hepatocellular carcinoma; SIR, standard incidence ratio.

- Treatment with TAF or TDF→TAF significantly reduced HCC incidence among patients with and without cirrhosis

Baseline Characteristics by HCC Risk Category

	Low Risk	Medium Risk	High Risk
aMAP	n/N = 818/1297 (63%)	n/N = 400/1297 (31%)	n/N = 79/1297 (6%)
Treatment arm, n (%)[a]			
TAF	553 (68)	266 (67)	46 (58)
TDF→TAF	265 (32)	134 (34)	33 (42)
Mean baseline aMAP score (range)	43.00 (20.44–50.00[b])	54.09 (50.00–59.99)	62.92 (60.02–72.57)
HCC cases during study period, n (%)	2 (0.2)	8 (2.0)	11 (14)
mPAGE-B	n/N = 710/1297 (55%)	n/N = 463/1297 (36%)	n/N = 124/1297 (10%)[a]
Treatment arm, n (%)[a]			
TAF	486 (69)	307 (66)	72 (58)
TDF→TAF	224 (32)	156 (34)	52 (42)
Mean baseline mPAGE-B score (range)	5.5 (0–8.0)	10.2 (9.0–12.0)	13.9 (13.0–18.0)
HCC cases during study period, n (%)	2 (0.3)	5 (1.1)	14 (11.3)

Low-risk group: aMAP score 0.00 to <50.00, mPAGE-B score 0 to 8; medium-risk group: aMAP score 50.00 to ≤60.00, mPAGE-B score 9 to 12; high-risk group: aMAP score >60, mPAGE-B score ≥13. One participant did not have baseline HCC risk score value and was excluded from the analysis.
[a]Percentages may add up to >100% due to rounding. [b]One score of 49.997 was rounded to 50.00 for the summary table.
HCC, hepatocellular carcinoma; mPAGE-B, modified PAGE-B; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Shifts in HCC Risk From Baseline to Year 8 (Week 384)

aMAP

Week 384 n (%)	Baseline: Low Risk n = 818	Baseline: Medium Risk n = 400	Baseline: High Risk n = 79
Low Risk	494 (98)	131 (45)	2 (4)
Medium Risk	10 (2)	160 (55)	34 (68)
High Risk	0	2 (1)	14 (28)
Missing	314	107	29

mPage-B

Week 384 n (%)	Baseline: Low Risk n = 710	Baseline: Medium Risk n = 463	Baseline: High Risk n = 124
Low Risk	420 (97)	91 (27)	1 (1)
Medium Risk	13 (3)	243 (72)	39 (49)
High Risk	0	2 (1)	39 (49)
Missing	277	127	45

HCC, hepatocellular carcinoma; mPAGE-B, modified PAGE-B.

- Among patients predicted to be at low risk for HCC at baseline, nearly all remained low risk at year 8 (aMAP, 98%; mPAGE-B, 97%)
- Substantial proportions of patients considered medium risk at baseline shifted to low risk at year 8 (aMAP, 45%; mPAGE-B, 27%), with only a few (1% by both methods) shifting to high risk
- Of patients considered high risk at baseline, substantial proportions shifted to medium risk at year 8 by both scoring systems, with a few patients shifting from high to low risk at year 8 by each system