Off-treatment Outcomes After Discontinuing Tenofovir-based Treatment in Hepatitis B e Antigen–positive and Hepatitis B e Antigen–negative Patients With Chronic Hepatitis B Virus

FRI-390

Maria Buti[1,2], Henry Lik Yuen Chan[3], Scott K Fung[4], Cheng-Yuan Peng[5], Frida Abramov[6], Dana Tedesco[6], Hongyuan Wang[6], Leland J Yee[6], John F Flaherty[6], Edward J Gane[7], Young-Suk Lim[8], Harry LA Janssen[9,10], Kosh Agarwal[11]

[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [2]CIBEREHD del Instituto Carlos III, Madrid, Spain; [3]Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong; [4]University of Toronto, Department of Medicine, Toronto, Canada; [5]School of Medicine, China Medical University, Taichung, Taiwan, and Division of Hepatogastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; [6]Gilead Sciences, Inc., Foster City, CA, USA; [7]Auckland Clinical Studies, Auckland, New Zealand; [8]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [9]Toronto Centre for Liver Disease, University Health Network, Toronto, Canada; [10]Erasmus Medical Center, Rotterdam, the Netherlands; [11]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK

Conclusions

- Within weeks after stopping NAs, virologic and biochemical relapse occurred frequently; serologically, few achieved HBsAg loss (<2%), and up to 20% achieved HBeAg loss
  - Despite the low rate of HBsAg loss, some patients were able to achieve an LRS (HBV DNA <2000 IU/mL and ALT ≤ULN) within a short duration of follow-up, and this was more commonly observed in HBeAg-negative patients
  - Loss of virologic suppression occurred early (week 4) in most patients. Thereafter, approximately 19% to 31% maintained virologic suppression overall, with higher rates observed in HBeAg-negative patients compared to HBeAg-positive patients
  - Among patients who did not complete 24-week TFFU, 98/107 (92%) resumed NA treatment
- Approximately 25% and 20% of patients experienced a Grade 3 or 4 elevation in ALT or AST, respectively, while 1% had a Grade 3 bilirubin elevation off treatment
  - Overall, 14% and 3% of patients met the protocol definitions for ALT elevation and ALT flare, respectively
  - No patient experienced an event of hepatic decompensation, and there were no deaths
- Although our results were derived over a relatively short duration of follow-up, the majority of patients safely tolerated discontinuation of therapy after up to 8 years of tenofovir-based treatment

Plain Language Summary

- A group of patients who completed up to 8 years of antiviral treatment for hepatitis B were monitored for up to 24 weeks after stopping treatment
- Over 24 weeks, many patients experienced worsening of hepatitis B, many of whom had to restart antiviral treatment

References: **1.** World Health Organization. Hepatitis B fact sheet. 2024. **2.** Seto WK, et al. *Lancet*. 2018;392:2313-24. **3.** Lampertico P, et al. *J Hepatol*. 2017;67(2):370-98. **4.** Papatheodoridis G, et al. *Hepatology*. 2016;63:1481-92. **5.** Berg T, et al. *J Hepatol*. 2017;67:918-24. **6.** Dusheiko G, et al. *N Engl J Med*. 2023;388:55-69. **7.** Chan HLY, et al. *Lancet Gastroenterol Hepatol*. 2016;1:185-95. **8**. Buti M, et al. *Lancet Gastroenterol Hepatol*. 2016;1:196-206. **9.** Terrault NA, et al. *Hepatology*. 2018;67(4):1560-99.

Acknowledgements: We extend our thanks to the patients and their families and all participating investigators. These studies were funded by Gilead Sciences, Inc. Medical writing support was provided by Rob Coover, MPH, of AlphaScientia, a Red Nucleus company, and was funded by Gilead Sciences, Inc.

Disclosures: **MB** reports speaker fees, research support, and consulting fees from AbbVie; Gilead Sciences, Inc.; and Janssen. **HLYC** served as an advisor for Aligos Therapeutics; Gilead Sciences, Inc.; GSK; Roche; Vaccitech; Vir Biotechnology; and Virion Therapeutics; and reports speaker fees from Gilead Sciences, Inc.; Roche; and Viatris. **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. **CYP** served as an advisor for Bristol Myers Squibb and Gilead Sciences, Inc. **FA**, **HW**, **LJY**, and **JFF** are employees and stockholders of Gilead Sciences, Inc. **DT** is an employee of Gilead Sciences, Inc., and may hold Gilead stock or stock options. **EJG** served as an advisor for AbbVie; Aligos Therapeutics; Arbutus Biopharma; Gilead Sciences, Inc.; Janssen; Roche; Vir Biotechnology; and Virion Therapeutics. **YSL** reports no conflict of interest. **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. **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; Sagimet Biosciences; and Sobi; and his institution received research support from Gilead Sciences, Inc.

Introduction

- Hepatitis B virus (HBV) infection affects approximately 254 million individuals globally and is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma[1,2]
- While nucleos(t)ide analogue (NA) therapy is the mainstay for chronic HBV (CHB), few experience functional cure with existing treatments, thereby requiring long-term therapy in most patients to optimise outcomes
- Treatment guidelines permit stopping NA therapy with appropriate monitoring in patients with CHB who have undetectable HBV DNA, are noncirrhotic, and are hepatitis B e antigen (HBeAg) negative, with the aim of potentially achieving functional cure (hepatitis B surface antigen [HBsAg] loss) or maintaining virologic remission[3]
- The durability and effectiveness of stopping NA therapy appears to be poor, with results from several studies reporting virologic remission response rates of approximately 30% to 50%[4-6]

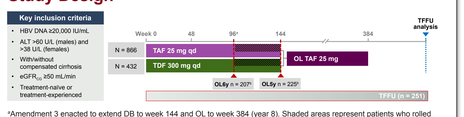
Objective

- To evaluate efficacy and safety outcomes in patients with CHB who were enrolled in 2 completed trials of tenofovir alafenamide and discontinued NA therapy after up to 8 years of treatment

Methods

- Two Phase 3, randomised, double-blind, active-controlled trials
  - Study 108 (NCT01940341; N = 425 originally randomised and treated): HBeAg-negative patients
  - Study 110 (NCT01940471; N = 873 originally randomised and treated): HBeAg-positive patients
  - Methods for Studies 108 and 110 are described elsewhere[7,8]
- In both studies, all patients who discontinued treatment at any time, including following completion of the study, for reasons other than confirmed HBsAg seroconversion and who did not immediately initiate NA therapy were required by protocol to enter a treatment-free follow-up (TFFU) phase for up to 24 weeks to ensure appropriate monitoring for patient safety was provided

Study Design



*Amendment 3 enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded areas represent patients who rolled over to OL TAF at week 96 (OL6y) or week 144 (OL5y) based on the timing of the amendment. †Patients who received DB TDF and switched to TAF.
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; TFFU, treatment-free follow-up; y, year.

- During TFFU, patients were assessed at the end of their treatment (TFFU baseline [BL]) and monitored every 4 weeks for up to 24 weeks
- Patients were monitored for the following:
  - Off-treatment safety: standard safety assessments, including alanine aminotransferase (ALT) elevation and flare
    - ALT elevation was defined as ALT measuring >2-fold of TFFU BL and >10-fold the upper limit of normal (ULN), determined by central laboratory cutoff
    - ALT flare was defined as ALT elevations occurring at 2 consecutive visits
  - Off-treatment efficacy: HBV DNA and ALT levels every 4 weeks; changes in HBV serologies every 12 weeks

Virologic Response

- HBV DNA <29 IU/mL (missing = excluded analysis)
  - COBAS TaqMan HBV Test, v2.0 (Roche Diagnostics, Indianapolis, IN, USA; lower limit of quantitation, 20 IU/mL)
  - Change in HBV DNA from BL

Biochemical Response

- Normal ALT by central laboratory (men ≤43 U/L and women ≤34 U/L [≥69 y: men ≤35 U/L and women ≤32 U/L]) and 2018 American Association for the Study of Liver Diseases (AASLD) criteria (men ≤35 U/L and women ≤25 U/L)[9] (missing = excluded analysis)

Assessment of "Low Replicative State"

- Low replicative state (LRS) definition: HBV DNA <2000 IU/mL and ALT ≤ULN

Serology

- HBeAg loss/seroconversion (missing = excluded analysis)
- HBsAg loss/seroconversion (missing = excluded analysis)
- Change in quantitative HBsAg from TFFU BL

Results

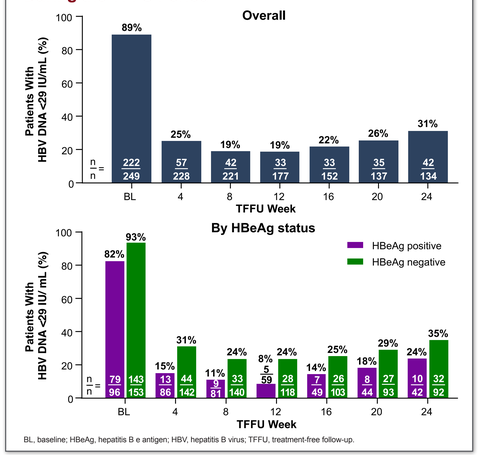
TFFU Baseline Characteristics

	HBeAg Positive (n = 96)	HBeAg Negative (n = 155)	Overall (N = 251)
Age, years, mean (SD)	40 (10.7)	48 (11.8)	45 (12.0)
Male	68 (71)	104 (67)	172 (69)
Asian	81 (84)	97 (63)	178 (71)
White	14 (15)	56 (36)	70 (28)
Black/African American or other	1 (1)	2 (1)	3 (1)
HBV DNA, log$_{10}$ IU/mL, mean (SD)	1.9 (1.73)	1.4 (0.48)	1.6 (1.16)
HBV DNA <29 IU/mL	79 (82)	145 (94)	224 (89)
HBV DNA <29 IU/mL, target not detected	41 (43)	92 (60)	133 (53)
HBsAg positive	96 (100)	144 (93)	240 (96)
HBsAg, log$_{10}$ IU/mL, mean (SD)	3.6 (0.66)	2.6 (1.50)	3.0 (1.33)
ALT, U/L, median (Q1, Q3)	28 (22, 41)	23 (16, 33)	26 (18, 35)
ALT ≤ULN (central laboratory)[a]	71 (74)	134 (87)	205 (82)
FibroTest score ≥0.75[b]	3 (3)	7 (5)	10 (4)
HBeAb positive, n/N (%)[c]	4/18 (22)	136/155 (88)	140/173 (81)
Time since first achieving HBV DNA <29 IU/mL, weeks, median (Q1, Q3)	321 (177, 353)	364 (351, 374)	356 (316, 371)
Total duration of study treatment, years, median (Q1, Q3)	7.4 (7.3, 7.4)	7.4 (7.4, 7.4)	7.4 (7.3, 7.4)
Duration of TFFU, weeks, mean (SD)	17.9 (7.53)	20.8 (6.81)	19.7 (7.21)

Data are presented as n (%) unless otherwise indicated. [a]ALT ≤ULN: central laboratory, males ≤43 U/L and females ≤34 U/L (≥69 y: men ≤35 U/L and women ≤32 U/L). [b]Suggestive of cirrhosis (ie, Metavir F4; BioPredictive SAS, Paris, France). [c]78 HBeAg-positive patients had missing HBeAb data.
ALT, alanine aminotransferase; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Q, quartile; TFFU, treatment-free follow-up; ULN, upper limit of normal.

- Out of 251 patients who entered the TFFU phase, 177 (71%) completed 12 weeks of TFFU, and 144 (57%) completed the entire 24-week follow-up period
- During the TFFU phase, 107 (43%) patients discontinued prematurely, with a significant majority (98; 92%) of patients resuming NA treatment at the discretion of the investigator

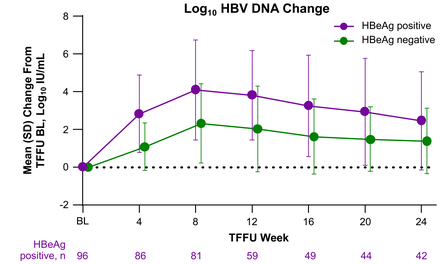
Percentages of Patients With HBV DNA <29 IU/mL During the TFFU Period



BL, baseline; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TFFU, treatment-free follow-up.

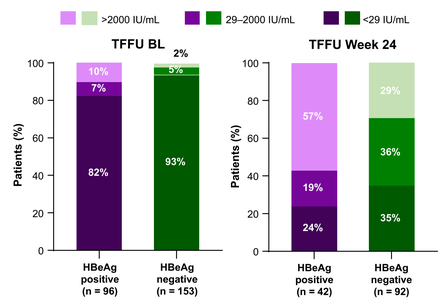
- Loss of virologic suppression occurred early (week 4) in most patients. Thereafter, 19% to 31% had virologic suppression overall
- The proportion of patients with HBV DNA <29 IU/mL was higher among HBeAg-negative patients compared with HBeAg-positive patients at TFFU BL and at each timepoint through TFFU week 24

HBV DNA Response Over 24 Weeks



	BL	4	8	12	16	20	24
HBeAg positive, n	96	86	81	59	49	44	42
HBeAg negative, n	153	142	140	118	103	93	92

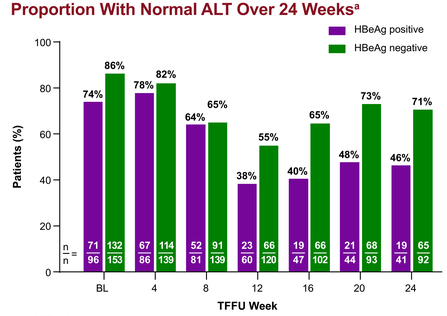
HBV DNA Levels



BL, baseline; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TFFU, treatment-free follow-up.

- A greater proportion of HBeAg-negative patients maintained lower HBV DNA levels than did HBeAg-positive patients at TFFU week 24

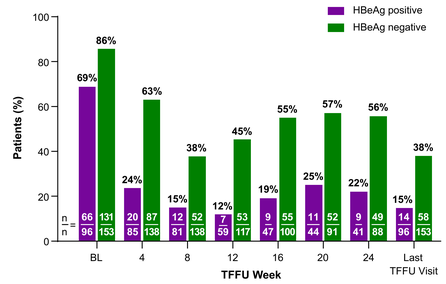
Proportion With Normal ALT Over 24 Weeks[a]



[a]Normal ALT as determined by central laboratory.
ALT, alanine aminotransferase; BL, baseline; HBeAg, hepatitis B e antigen; TFFU, treatment-free follow-up.

- The proportion of patients with ALT ≤ULN was comparable in each group at TFFU weeks 4 and 8
  - After week 8, a higher proportion of HBeAg-negative patients retained normal ALT by central laboratory and AASLD criteria (data not shown) compared with HBeAg-positive patients
  - Loss of normal ALT status was temporally associated with viral kinetics in the TFFU period, with virologic relapse generally preceding ALT elevation
- Median ALT changes from TFFU baseline in HBeAg-positive and HBeAg-negative patients were 13.0 and 5.5 U/L, respectively, at week 12 and were 10.0 and 3.0 at week 24

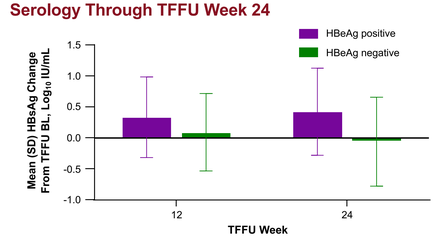
Maintenance of LRS Over 24 Weeks



LRS was defined as HBV DNA <2000 IU/mL and ALT ≤ULN.
ALT, alanine aminotransferase; BL, baseline; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LRS, low replicative state; TFFU, treatment-free follow-up; ULN, upper limit of normal.

- At TFFU week 24, HBeAg-negative patients were ~3-fold more likely to maintain an LRS than HBeAg-positive patients

Serology Through TFFU Week 24



	Patients, n/n (%)	HBeAg Positive (n = 96)	HBeAg Negative (n = 143)
HBeAg loss and seroconversion[a]	Week 12	2/59 (3)	NA
	Week 24	8/41 (20)	NA
HBsAg loss	Week 12	0/63	1/111 (1)
	Week 24	0/43	2/85 (2)[b]

[a]Population used for serology analysis included only patients who were HBeAg-positive and HBeAg-negative or missing at TFFU baseline. [b]One patient achieved anti-HBsAg seroconversion.
BL, baseline; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NA, not applicable; TFFU, treatment-free follow-up.

Safety: Off-treatment Adverse Events and Laboratory Abnormalities

	Patients, n (%)	Overall (N = 251)
AEs	Any AE	60 (24)
	Grade 3 or 4 AE	14 (6)
	Hepatitis	2 (1)
	Hepatitis B	4 (2)
	Chronic hepatitis B	1 (<1)
	ALT increased	7 (3)
	Serious AE[a]	6 (2)
	Death	0
Grade 3 or 4 laboratory abnormalities, >1 patient	Any Grade 3 or 4	78 (31)
	ALT	61 (25)
	AST	42 (17)
	Amylase	2 (1)
	Bilirubin	3 (1)
	GGT	2 (1)
	Occult blood urine	10 (4)
	Urine glucose	5 (2)

[a]Hepatitis B (n = 3), hepatitis (n = 2), head injury (n = 1), plica syndrome (n = 1).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

- 35/251 (14%) of patients had ALT elevation, and 8/251 (3%) had ALT flare
  - In 69% of patients, ALT elevation could not be retested to assess ALT flare due to lack of further follow-up