Long-term Safety Profile of Tenofovir Alafenamide in Chronic Hepatitis B Patients: Final 8-Year Results of 2 Phase 3 Studies

SAT-153

Young-Suk Lim[1], Henry Lik Yuen Chan[2], Kosh Agarwal[3], Patrick Marcellin[4], Maurizia R Brunetto[5], Wan-Long Chuang[6], Harry LA Janssen[7,8], Scott K Fung[9], Namiki Izumi[10], Maciej S Jablkowski[11], Frida Abramov[12], Hongyuan Wang[12], Leland J Yee[12], John F Flaherty[12], Calvin Pan[13], Dr Shalimar[14], Wai-Kay Seto[15], Edward J Gane[16], Maria Buti[17,18]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Faculty of Medicine, the Chinese University of Hong Kong, HMA Office, Tai Wai, Shatin, Hong Kong; [3]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom; [4]Hepatology Department, Hôpital Beaujon, APHP, INSERM, University of Paris, Clichy, France; [5]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [6]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan; [7]Toronto Centre for Liver Disease, University Health Network, Toronto, Canada; [8]Erasmus Medical Center, Rotterdam, Netherlands; [9]University of Toronto, Department of Medicine, Toronto, Canada; [10]Department of Gastroenterology and Hepatology, Japanese Red Cross Musashino Hospital, Tokyo, Japan; [11]Medical University of Łódź, Łódź, Poland; [12]Gilead Sciences, Inc., Foster City, CA, USA; [13]NYU Langone Health, New York University Grossman School of Medicine, New York, NY, USA; [14]All India Institute of Medical Sciences, New Delhi, India; [15]Department of Medicine and School of Clinical Medicine, The University of Hong Kong, Hong Kong; [16]Auckland Clinical Studies, Auckland, New Zealand; [17]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [18]CIBEREHD del Instituto Carlos III, Madrid, Spain

Key Findings

- Through 8 years of treatment, no new safety signals were identified for TAF
- Increases in fasting lipids and body weight were observed, which plateaued after year 5
- Minimal declines in $eGFR_{CG}$ and in hip and spine BMD occurred among patients treated with TAF over 8 years
- Among those treated with DB TDF, the early declines in renal function and BMD steadily improved after switching to TAF

Conclusions

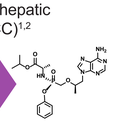
Over 8 years, treatment with TAF was safe and well tolerated by patients with chronic HBV; switching from TDF to TAF after 2 or 3 years resulted in improvements in renal and bone safety parameters

These results provide further support for use of TAF as a preferred treatment for chronic HBV infection

Introduction

- Hepatitis B virus (HBV) infection affects approximately 296 million individuals globally and is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC)[1,2]
- Tenofovir alafenamide (TAF):
  - A novel tenofovir (TFV) prodrug with greater plasma stability, enhanced hepatic delivery of active drug (TFV-diphosphate) to hepatocytes, and lower circulating levels of TFV compared with tenofovir disoproxil fumarate (TDF)[3-6]
  - In comparative trials, TAF demonstrated noninferior antiviral efficacy and improved renal and bone safety compared with TDF at weeks 48 and 96 among viremic and virally suppressed hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients[7-9]
    - Patients from these trials were eligible to receive open-label (OL) TAF, and favorable renal and bone safety were observed during a 5-year interim analysis[10]

TAF
Nucleotide reverse transcriptase inhibitor



References: 1. World Health Organization. *Hepatitis B* fact sheet. 2021; **2.** Seto WK, *et al. Lancet.* 2018;392:2313-24; **3.** Agarwal K, *et al. J Hepatol.* 2015;62:533-40; **4.** Babuais D, *et al. Mol Pharm.* 2013;10:459-66; **5.** Lee WA, *et al. Antimicrob Agents Chemother.* 2005;49:1898-906; **6.** Murakami E, *et al. Antimicrob Agents Chemother.* 2015;59:3563-9; **7.** Agarwal K, *et al. J Hepatol.* 2018;68:672-81; **8.** Buti M, *et al. Lancet Gastroenterol Hepatol.* 2016;1(3):196-206; **9.** Chan HLY, *et al. Lancet Gastroenterol Hepatol.* 2016;1(3):185-95; **10.** Chan HLY, *et al. Hepatology.* 2020;72:490A. Abstract 803; **11.** Huhn GD, *et al. Open Forum Infect Dis.* 2019 Nov 11;7(1):ofz477. **12.** Santos JR, *et al., Clin Infect Dis.* 2015;61(3):403-8. **13.** Wasnich R. Osteoporosis: critique and practicum. Banyan Press; 1989; **14.** Weinstein JR, *et al. Adv Chronic Kidney Dis.* 2010;17:302-7.

Acknowledgments: 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 Charlotte Bavley, PhD, of AlphaScientia, a Red Nucleus company, and was funded by Gilead Sciences, Inc.

Disclosures: HLYC served as an advisor for Allgos, GSK, Gilead Sciences, Inc., Roche, Vaccitech, Vir Biotechnology, Inc., and Virion Therapeutics and reports speaker fees from Gilead Sciences, Inc., Roche, and Viatris; **KA** served as a speaker, consultant, and/or advisory board member for Assembly Biosciences, Allgos Therapeutics, Arbutus Biopharma, Boehringer Ingelheim, Bristol Myers Squibb, Drug Far, Gilead Sciences, Inc., GSK, Janssen, Roche, Saigmet, and Sobi, and his institution received research support from Gilead Sciences, Inc.; **PM** received grants from AbbVie, Allgos, Assembly Biosciences, Bristol Myers Squibb, Gilead Sciences, Inc., Humedics, Madrigal, Novo Nordisk, Pfizer, Roche, and Intercept; **MRB** reports speaker and consultancy fees from AbbVie, Eisai-MSD, Gilead Sciences, Inc., Janssen, and Roche; **HLAJ** received research grants from Gilead Sciences, Inc., GSK, Janssen, Roche, and Vir Biotechnology, Inc., and served as a consultant for Allgos, Antios, Eiger, Gilead Sciences, Inc., GSK, Janssen, Roche, and Vir Biotechnology, 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.; **FA**, **HW**, **LJY**, and **JFF** are employees and stockholders of Gilead Sciences, Inc.; **CP** received research support 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; **EJG** served as an advisor for AbbVie, Allgos, Arbutus, 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**, **WLC**, **NI**, **MSJ**, and **DS** report no conflicts of interest.

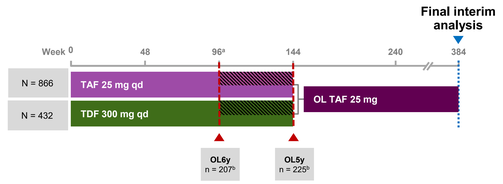
Objective

- To evaluate safety outcomes at year 8 (week 384) in patients with HBeAg-negative and HBeAg-positive chronic HBV treated with TAF (double blind [DB] and OL) or TDF (DB) followed by TAF (OL)

Methods

Study Design

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

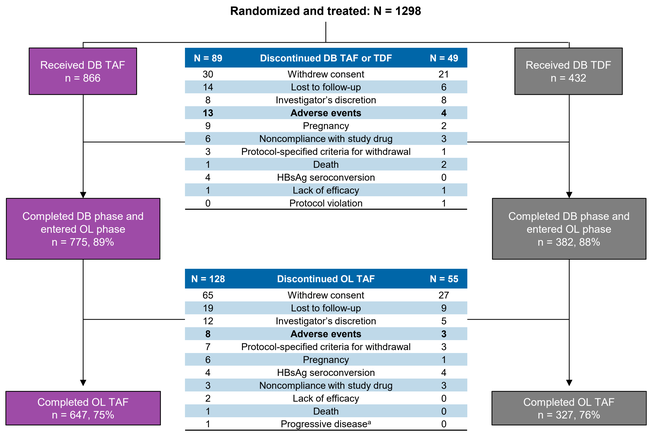


[a]Amendment 3 enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded areas represent patients who rolled over to OL TAF at week 96 (OL6y) or week 144 (OL5y) based upon the timing of the amendment. [b]Patients who received DB TDF and switched to TAF. ALT, alanine aminotransferase; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; qd, once daily.

- Two Phase 3, randomized, DB, active-controlled trials
  - Study 108 (NCT01940341; N = 425 originally randomized and treated): HBeAg-negative patients
  - Study 110 (NCT01940471; N = 873 originally randomized and treated): HBeAg-positive patients
  - Methods for Studies 108 and 110 are described elsewhere[8,9]
- After completion of the DB phase, all patients were eligible to receive OL TAF through year 8
- Safety endpoints:
  - Cumulative adverse events (AEs), serious AEs, and graded laboratory abnormalities during the OL phase
  - **Bone:** changes in hip and spine bone mineral density (BMD) by dual energy X-ray absorptiometry and serum markers of bone turnover
  - **Renal:** changes in estimated glomerular filtration rate by Cockcroft-Gault ($eGFR_{CG}$) and quantitative urinary markers of tubular proteinuria—ratio of retinol-binding protein (RBP) to creatinine (Cr) and ratio of β_2-microglobulin (β_2M) to Cr
  - **Metabolic parameters:** changes in fasting lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), and TC/HDL ratio; change in body weight

Results

Patient Disposition



[a]Metastatic HCC. HBsAg, hepatitis B surface antigen.

- 974 of 1298 (75%) patients completed the OL phase
- Overall excellent patient retention with very few patients (n = 11; <1%) discontinuing OL TAF due to an AE

Baseline Demographics and Disease Characteristics[a]

	TAF n = 866	TDF→TAF n = 432
Age, y, mean (SD)	40 (11.8)	41 (12.3)
Male, n (%)	544 (63)	275 (64)
Asian, n (%)	687 (79)	333 (77)
White, n (%)	167 (19)	87 (21)
Black or African American, n (%)	7 (1)	6 (1)
Other race, n (%)	5 (1)	6 (1)
BMI, kg/m², median (Q1, Q3)	24 (21, 27)	24 (22, 27)
Body weight, kg, median (Q1, Q3)	67 (57, 76)	66 (58, 78)
HBeAg positive, n (%)	569 (66)	290 (67)
ALT, U/L, median (Q1, Q3)	80 (56, 123)	80 (53, 130)
FibroTest score ≥0.75, n/N (%)[b]	76/846 (9)	42/421 (10)
$eGFR_{CG}$, mL/min, median (Q1, Q3)	106 (91, 125)	105 (90, 124)
Osteoporosis by spine BMD T-score, n (%)[c]	57 (7)	29 (7)
Osteoporosis by hip BMD T-score, n (%)[c]	12 (1)	2 (<1)
Diabetes mellitus, n (%)	57 (7)	29 (7)
Hypertension, n (%)	99 (11)	62 (14)
Hyperlipidemia, n (%)	76 (9)	44 (10)

[a]Among all patients who were randomized and treated with DB TAF or TDF (Safety Analysis Set); [b]Suggestive of cirrhosis (ie, Metavir F4; BioPredictive S.A.S, Paris, France); [c]T-score <–2.5. ALT, alanine aminotransferase; BMI, body mass index; Q, quartile.

Open-Label Safety: Adverse Events[a]

Patients, n or n/n (%)	TAF n = 775	TDF→TAF n = 382
Any AE	525 (68)	271 (71)
Grade 3 or 4 AE	60 (8)	27 (7)
Grade 3 or 4 AE related to study drug AE (1 patient each)	2 (<1) cerebrovascular accident; renal neoplasm	0
Serious AE	97 (13)	49 (13)
Serious AE related to study drug AE (1 patient each)	4 (1) cerebrovascular accident; renal neoplasm; ALT increase; osteonecrosis	0
D/C due to AE AE (1 patient each)	9 (1) cardiopulmonary failure; myelodysplastic syndrome; HCC; pancreatic carcinoma; cerebrovascular accident; gamma-glutamyltransferase increased; osteonecrosis; osteoporosis; proteinuria	3 (1) tuberculosis; ascites; pemphigoid
Death[b]	1 (<1)	0
HCC[c]	8 (1)	6 (2)
Adverse events occurring in ≥5% of patients		
Headache	59 (8)	30 (8)
Upper respiratory tract infection	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)

[a]Among patients in the OL safety analysis who received ≥1 dose of OL study drug (OL Safety Analysis Set); [b]Treatment-emergent death. There were 6 deaths in total (5 DB and 1 OL; TAF 3, TDF 3); [c]A total of 14 HCC cases occurred during the OL phase, while overall, 21 patients developed HCC during the DB and OL phases of the study. D/C, discontinuation.

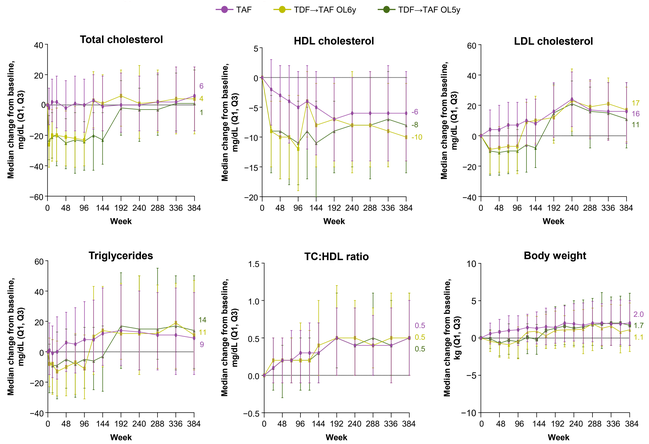
Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 2% of Patients[a]

Patients, n or n/n (%)	TAF n = 775	TDF→TAF n = 382
Maximum postbaseline toxicity grade	185/772 (24)	93/378 (25)
Amylase	15/772 (2)	10/377 (3)
Creatine kinase	11/772 (1)	8/377 (2)
Fasting cholesterol[b]	11/767 (1)	11/373 (3)
Fasting LDL cholesterol[b]	45/760 (6)	30/373 (8)
Increased fasting glucose[b]	12/767 (2)	7/373 (2)
Fasting triglycerides	5/767 (1)	7/373 (2)
Urine occult blood[b]	26/772 (3)	12/377 (3)

[a]Among patients in the OL safety analysis who received ≥1 dose of OL study drug; [b]Grade 3 abnormalities only (no Grade 4 events reported).

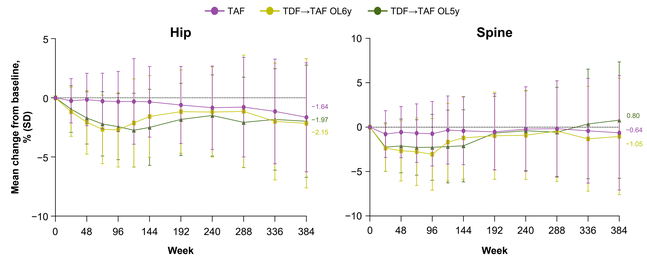
- Through 8 years of treatment, no new safety signals have been identified for TAF

Median Change in Fasting Lipids and Body Weight Over 8 Years



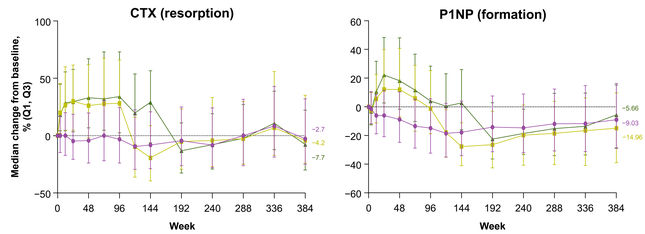
- Among patients receiving TAF, small median increases in TC, LDL, and TG and a small median decrease in HDL were observed
- Among TDF→TAF patients, modest decreases in TC, HDL, LDL, and TG were observed during DB TDF treatment, consistent with the known lipid-lowering effect of TDF[11,12]
  - Following the switch from TDF to TAF, levels of TC, HDL, LDL, and TG stabilized to levels observed in the TAF-only treatment group
- Notably, TC:HDL ratio, a marker of cardiovascular risk, increased minimally (≤0.5 fold) over 8 years in all groups
- Small (≤2.0 kg) median increases in body weight were seen after 8 years of treatment across study groups

Mean % Change in Hip and Spine BMD Over 8 Years



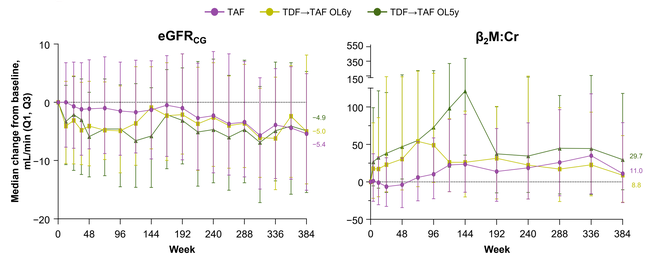
- Among patients receiving TAF, decreases in hip and spine BMD were minimal at year 8 (<2% and <1%, respectively), consistent with the rates of BMD decline seen with advancing age[13]
- Switching from TDF to TAF at year 2 (week 96) or year 3 (week 144) was associated with increases in BMD, indicating that TDF-induced bone loss can be reversible

Median % Change in Bone Biomarkers Over 8 Years



CTX, C-terminal telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type 1 procollagen.

Changes in Renal Parameters Over 8 Years



- Among patients receiving TAF, median $eGFR_{CG}$ decreased by ~5 mL/min over 8 years, consistent with declines with normal aging[14]
  - After switching from TDF to TAF, median $eGFR_{CG}$ increased to levels similar to the TAF group, showing reversibility in early TDF-associated declines
- Over 8 years of TAF treatment, median % increases in β_2M:Cr were small (11%) and remained relatively stable; tubular proteinuria increased during DB TDF treatment and then markedly improved after switching from TDF to TAF (similar findings were seen with RBP:Cr, data not shown)

Additional data from this study describing the efficacy of TAF at year 8 will be presented in presentation OS-067