SAT425

A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide in Children and Adolescent Patients With Chronic Hepatitis B

Kathleen B. Schwarz,[1] Jorge Bezerra,[2] Byung-Ho Choe,[3] Chuan-Hao Lin,[4] Frida Abramov,[5] Anh-Hoa Nguyen,[5] Yang Liu,[5] Rory Leisegang,[5] John F. Flaherty,[5] Daniela Pacurar,[6] Kyung Mo Kim,[7] Ilsiyar Khaertynova,[8] Shalimar,[9] Jia-Feng Wu,[10] Manish Tandon,[11] Philip Rosenthal,[12] Viacheslav Morozov,[13] Etienne Sokal,[14] Mei-Hwei Chang[15]

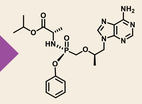
[1]UC San Diego School of Medicine, La Jolla, and Rady Children's Hospital-San Diego, California, USA; [2]University of Cincinnati, Cincinnati Children's Hospital Medical Center, Ohio, USA; [3]Kyungpook National University College of Medicine, Daegu, Republic of Korea; [4]Children's Hospital Los Angeles, California; [5]Gilead Sciences, Inc., Foster City, California; [6]Universitatea de Medicina si Farmacie "Carol Davila" din Bucuresti, Spitalul Clinic de Urgenta pentru Copii "Grigore Alexandrescu," Bucuresti, Romania; [7]University of Ulsan College of Medicine, Asan Medical Center Children's Hospital, Seoul, Republic of Korea; [8]Kazan State Medical University, Kazan, Russian Federation; [9]All India Institute of Medical Sciences, New Delhi, India; [10]National Taiwan University Hospital, Taipei City, Taiwan; [11]M. V. Hospital and Research Centre, Lucknow, India; [12]University of California San Francisco; [13]Hepatolog, Samara, Russian Federation; [14]Université Catholique de Louvain, Louvain-la-Neuve, and Cliniques Universitaires Saint-Luc, Bruxelles, Belgique; [15]National Taiwan University Children's Hospital, Taipei City

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California, USA 94404
800-445-3235

Introduction

- Children and adolescents with chronic hepatitis B virus (HBV) are at an increased lifetime risk of significant clinical complications including the development of cirrhosis, decompensated liver disease, and liver cancer[1]
- While treatment options for children are similar to those for adults, important safety and efficacy limitations exist, including reduced response rates in patients with prior lamivudine exposure observed with entecavir, and risk of bone and renal toxicities associated with tenofovir disoproxil fumarate (TDF)[2-4]
- Tenofovir alafenamide (TAF):
  - Novel tenofovir prodrug; greater plasma stability, with enhanced hepatic delivery of active drug and lower circulating levels of tenofovir relative to TDF[5-8]
  - In comparative trials in viremic and suppressed hepatitis B e antigen (HBeAg)–negative and –positive adults with chronic HBV, TAF demonstrated antiviral efficacy noninferior to that of TDF, with improved renal and bone safety at Weeks 48 and 96[9-13]

TAF
Nucleotide reverse transcriptase inhibitor

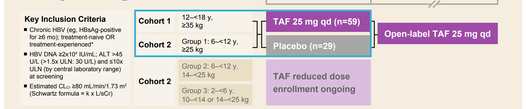


Objective

- To evaluate the efficacy and safety of 24 wk of TAF compared with placebo in children and adolescents aged 6–<18 y and weighing ≥25 kg with chronic HBV

Methods

Study Design



*Treatment-naive: <12 wk of oral antiviral (OAV) treatment with any oral nucleos(t)ide analogue; treatment-experienced: meeting all entry criteria (including HBV DNA and serum alanine aminotransferase [ALT] criteria) and >12 wk of OAV treatment with any oral nucleos(t)ide analogue. CL_{Cr}, creatinine clearance; HBsAg, hepatitis B surface antigen; sCr, serum creatinine; ULN, upper limit of normal.

- Randomized (2:1), double-blind, placebo-controlled, multicenter study (GS-US-320-1092, ClinicalTrials.gov NCT02932150, EudraCT 2016-000785-37)
- Cohort 1 (adolescents) and Cohort 2 Group 1
  - Randomized phase: TAF 25 mg qd or placebo for 24 wk
  - Open-label extension phase: TAF 25 mg qd through Week 240
  - Intensive pharmacokinetic substudy (Part A) to confirm TAF dose in Cohort 2 Group 1; Part B: following dose confirmation, additional patients were enrolled and enrollment into the next group was initiated

Study Endpoints

- **Efficacy**
  - **Primary endpoint:** HBV DNA <20 IU/mL at Week 24
    - Superiority to placebo (Cohort 1 to enroll ≥69 patients to provide 87% power to detect a 32% treatment difference; Cohort 2 Group 1 was combined with Cohort 1 to provide results for all patients treated with TAF 25 mg)
    - COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0 (Roche Diagnostics, Indianapolis, Indiana, USA; lower limit of quantitation: 20 IU/mL)
  - **Secondary endpoints**
    - ALT normalization (central laboratory and American Association for the Study of Liver Diseases [AASLD] laboratory criteria)
    - Serology (HBeAg and HBsAg loss/seroconversion)
    - Composite virologic, biochemical, and serologic endpoints
  - **Resistance**
    - Resistance surveillance was conducted in patients receiving TAF
    - HBV polymerase/reverse transcriptase (pol/RT) deep sequencing was conducted for patients with HBV DNA ≥69 IU/mL at Week 24
- **Safety**
  - **Overall:** adverse events (AEs) and laboratory abnormalities
  - **Bone:** changes in spine and whole body (minus head) bone mineral density (BMD; measured by dual energy x-ray absorptiometry)
  - **Renal:** changes in sCr, serum phosphorus (sPO_4), and CL_{Cr}

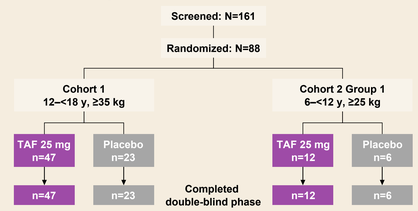
Results

Baseline Characteristics

	TAF: n=59	Placebo: n=29
Mean age, y (range)	14 (7–17)	13 (7–17)
Male, n (%)	34 (58)	17 (59)
Asian, n (%)	37 (63)	21 (72)
White, n (%)	16 (27)	6 (21)
Asia region, n (%)*	18 (31)	13 (45)
Mean BMI, kg/m² (SD)	20.2 (2.91)	19.8 (3.02)
Prior HBV treatment, n (%)†	20 (34)	5 (17)
Mean HBV DNA, log_{10} IU/mL (SD)	7.9 (1.12)	8.1 (0.72)
HBV DNA ≥8 log_{10} IU/mL, n (%)	39 (66)	21 (72)
Mean HBsAg, log_{10} IU/mL (SD)	4.4 (0.58)	4.6 (0.55)
HBeAg positive, n (%)	58 (98)	29 (100)
Median ALT, U/L (Q1, Q3)	65 (50, 109)	66 (54, 89)
Median CL_{Cr}, mL/min/1.73 m² (Q1, Q3)	154 (137, 169)	149 (143, 180)
HBV genotype, n (%)‡		
A	5 (9)	1 (4)
B	13 (24)	6 (22)
C	12 (22)	8 (30)
D	24 (44)	12 (44)
Mixed	1 (2)	0

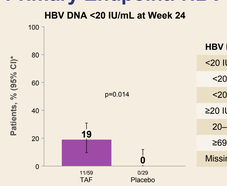
*Denotes Hong Kong, India, Republic of Korea, and Taiwan; †Includes OAVs and interferon-α; ‡6 patients had undetermined genotype. BMI, body mass index; Q, quartile; SD, standard deviation.

Patient Disposition



- All 88 patients completed the 24-wk double-blind treatment phase

Primary Endpoint: HBV DNA <20 IU/mL

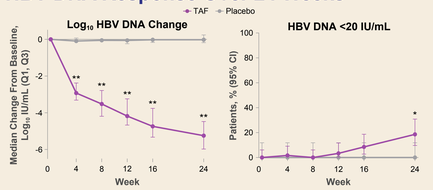


Virologic Outcomes at Week 24

HBV DNA, n (%)	TAF n=59	Placebo n=29
<20 IU/mL	11 (19)	0
<20 IU/mL, not detected	2 (3)	0
<20 IU/mL, detected	9 (15)	0
≥20 IU/mL	48 (81)	29 (100)
20–<69 IU/mL	8 (14)	0
≥69 IU/mL	39 (66)	27 (93)
Missing data	1 (2)	2 (7)

*p-values based on 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline. CI, confidence interval.

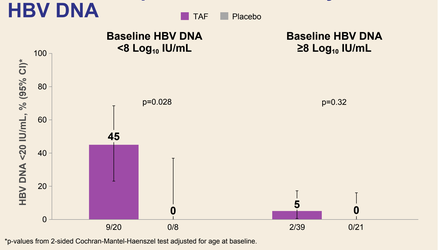
HBV DNA Response Over 24 Weeks



*p<0.05 (Cochran-Mantel-Haenszel test adjusted for age at baseline); **p<0.001 (2-sided Wilcoxon rank-sum test).

- A steady and significant trend away from baseline viral load towards virologic suppression was observed
- Emerging virologic suppression was observed over time with TAF, reaching significance at Week 24

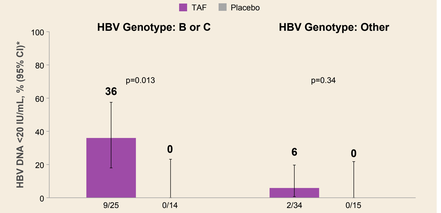
HBV DNA Response at Week 24 by Baseline HBV DNA



*p-values from 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.

- The subgroup with high baseline viral load (≥8 log_{10} IU/mL), representing most patients (68%), showed a lower response with TAF

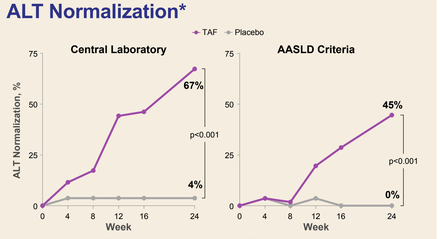
HBV DNA Response at Week 24 by Genotype



*p-values from 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.

- HBV genotype D comprised most of the Other category; a lower response rate with TAF treatment was observed in patients with genotype D
- Consistent with previous subgroup analyses in adults, a longer duration of treatment is likely required to see more patients with genotype D or high viral load achieve full viral suppression (HBV DNA <20 IU/mL)

ALT Normalization*



*Population used for analysis of ALT normalization included only patients with ALT > ULN at baseline; central laboratory ULN: 34 U/L for females aged ≥2 y and males aged 1–9 y, and 43 U/L for males aged ≥9 y; 2018 AASLD ULN: 30 U/L for pediatric males and females.[4]

- Significantly higher rates of ALT normalization were observed at Week 24 with TAF vs placebo
- At Week 24, the median (Q1, Q3) changes from baseline in ALT were -32.0 (-65.0, -7.0) U/L for TAF and -2.5 (-15.0, 22.0) U/L for placebo; p<0.001

Serology at Week 24

	Patients, n/n (%)	TAF n=59	Placebo n=29	p-Value
HBeAg*	Loss	4/58 (7)	1/29 (3)	0.52
	Seroconversion	4/58 (7)	1/29 (3)	0.52
HBsAg	Loss	0	0	—
	Seroconversion	0	0	—

*Population used for serologic analysis included only patients who were HBeAg positive and HBeAg negative or missing at baseline.

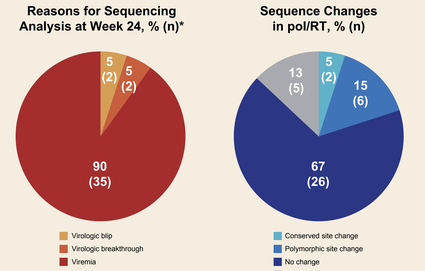
Other Efficacy Endpoints at Week 24

Patients, n/n (%)	TAF n=59	Placebo n=29	p-Value*
Composite of 2 endpoints: HBV DNA <20 IU/mL and ALT normalization (central laboratory)	10/52 (19)	0/27	0.016
Composite of 3 endpoints: HBV DNA <20 IU/mL, ALT normalization (central laboratory), and HBeAg loss	2/51 (4)	0/27	0.31

*Based on 2-sided stratum adjusted Cochran-Mantel-Haenszel test.

- Similar results were seen for 2- and 3-composite endpoints using ALT normalization by AASLD criteria

Resistance Analysis at Week 24



*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; virologic blip: met 1 of the virologic breakthrough criteria at only 1 visit; viremia: persistent HBV DNA >20 IU/mL over course of treatment.

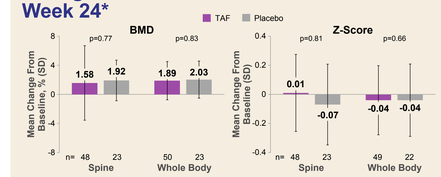
- 39/59 TAF-treated patients (66%) qualified for testing
  - Most (n=35/39 [90%]) were persistently viremic in the absence of virologic breakthrough
  - Virologic breakthrough was infrequent (n=2) and not associated with sequence changes in pol/RT
- Sequence analysis showed that most patients had no sequence change from baseline
- No HBV amino-acid substitutions associated with resistance to TAF were detected through 24 wk of TAF treatment

Safety

	Patients, n (%)	TAF n=59	Placebo n=29
AEs	Any AE	35 (59)	16 (55)
	Grade 3–4 AE	0	2 (7)
	Serious AE	1 (2)	2 (7)
	D/C due to AE	0	0
	Death	0	0
Grade 3 or 4 Laboratory Abnormalities (≥5%)	Any Grade 3 or 4	7 (12)	4 (14)
	ALT	4 (7)	2 (7)
	AST	0	2 (7)

AST, aspartate aminotransferase; D/C, discontinuation.

Changes in BMD and BMD Z-Scores at Week 24*



*p-values based on 2-sided Wilcoxon rank-sum test.

- The TAF group had similar BMD increases in spine and whole-body BMD compared with the placebo group
- 2% and 6% of TAF patients had ≥4% decreases over 24 wk in whole body and spine BMD, respectively, vs 0% of placebo patients
  - No patient experienced both ≥4% decreases in spine and whole body BMD at Week 24
  - By BMD Z-scores, all patients with ≥4% decreases in BMD remained within normal range for their age and gender

Renal Safety at Week 24*

	TAF n=59	Placebo n=29	p-Value
sCr change, mg/dL	0.04 (0.00, 0.10)	0.01 (-0.03, 0.05)	0.03
PO_4 change, mg/dL	0.0 (-6.8, 5.7)	0.9 (-7.5, 7.9)	0.54
CL_{Cr} change, mL/min/1.73 m²	-9 (-19, 2)	-1 (-7, 7)	0.03
Confirmed renal events, n (%)			
sCr ≥0.3 mg/dL from baseline	0	0	—
PO_4 <2.0 mg/dL	0	0	—
CL_{Cr} <50 mL/min/1.73m²	0	0	—

*Continuous data are expressed as median (Q1, Q3); p-values based on 2-sided Wilcoxon rank-sum test.

Conclusions

- In mostly HBeAg-positive pediatric patients with chronic HBV, aged 6–<18 y, and weighing ≥25 kg, treatment with TAF for 24 wk demonstrated:
  - Superior efficacy to placebo for the proportion with HBV DNA <20 IU/mL
  - Significantly higher rates of ALT normalization
  - Rates of HBeAg loss and seroconversion similar to placebo
  - No development of resistance to TAF
- TAF was safe and well tolerated in pediatric patients with chronic HBV, aged 6–<18 y, and weighing ≥25 kg
  - Rates of treatment-emergent AEs were similar to placebo
  - Similar increases were observed in spine and whole-body BMD compared with placebo
  - Greater declines in CL_{Cr} were observed vs placebo; however, no patient in either treatment group dropped below the normal range cutoff of 90 mL/min/1.73 m²

References: **1.** EASL 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection. J Hepatol 2017;67:370-98; **2.** Jonas MM, et al. Hepatology 2016;63:377-87; **3.** Murray KF, et al. Hepatology 2012;56:2018-26; **4.** Terrault NA, et al. Hepatology 2018;67:1560-99; **5.** Agarwal K, et al. J Hepatol 2015;62:533-40; **6.** Babusis D, et al. Mol Pharm 2013;10:459-66; **7.** Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-906; **8.** Murakami E, et al. Antimicrob Agents Chemother 2015;59:3963-9; **9.** Agarwal K, et al. J Hepatol 2018;68:672-81; **10.** Buti M, et al. Lancet Gastroenterol Hepatol 2016;1:196-206; **11.** Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;1:185-95; **12.** Lampertico P, et al. EASL 2020, *abstr 91*; **13.** Lampertico P, et al. Lancet Gastroenterol Hepatol 2020;5:441-53.

Acknowledgments: We extend our thanks to the patients and their families, and all participating investigators: *Belgique:* E. Sokal; *Hong Kong:* G. L.-H. Wong; *India:* A. Chowdhury, R. Mehta, Shalimar, A. Shukla, M. Tandon; *New Zealand:* H. Evans; *Republic of Korea:* B.-H. Choe, Y.-H. Choe, K.M. Kim; *Romania:* D. Pacurar, A. Streinu-Cercel; *Russian Federation:* I. Khaertynova, Y. Lobzin, V. Morozov, T. Strokova; *Taiwan:* M.-H. Chang, M.-W. Lai, H.-H. Shih, J.-F. Wu, Y.-J. Yang; *USA:* J. Bezerra, J. Daniel, L. Gillis, J.R. Honegger, S. Horslen, C.-H. Lin, N. Mittal, D. Mogul, K. Murray, M.R. Narkewicz, D. Pan, Y. Pham, G. Rao, P. Rosenthal, K. Schwarz, M. Whitworth. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, New York, USA, funded by Gilead

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DOI: 10.3252/pso.eu.ILC2022.2022

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