Safety and Efficacy at 1 Year in Children and Adolescents With Chronic Hepatitis B Receiving Tenofovir Alafenamide

Abstract No 117

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Conclusions

In children and adolescents with CHB, continued treatment for 48 weeks showed:

- Rates of viral suppression and ALT normalization that progressively increased in those treated with TAF, while improved responses in the PBO→TAF group mirrored the week 24 (DB phase) results with TAF
- Increasing proportions achieved HBeAg loss and seroconversion
- No patients experienced HBsAg loss
- No resistance to TAF was detected through 48 weeks of treatment

TAF continues to be safe and well tolerated in this pediatric population

Similar increases were observed in spine and whole-body BMD compared with PBO→TAF compared to TAF treatment for 48 weeks

No clinically meaningful changes in renal safety were seen over 48 weeks

The benefit/risk for TAF treatment in this population remains positive at week 48

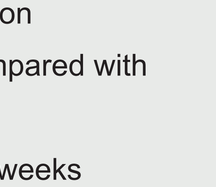
References:
1. EASL 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection. J Hepatol. 2017;67:370–98. 2. Jonas MM, et al. Hepatology. 2016;63:377–87. 3. Murray KF, et al. Hepatology. 2012;56:2018–26. 4. Terrault NA, et al. Hepatology. 2018;67:1560–99. 5. Agarwal K, et al. J Hepatol. 2018;68:672–81. 6. Buti M, et al. Lancet Gastroenterol Hepatol. 2016;1:196–206. 7. Chan HLY, et al. Lancet Gastroenterol Hepatol. 2016;1:185–95. 8. Lampertico P, et al. J Hepatol. 2020;73:S67. Abstr AS091. 9. Lampertico P, et al. Lancet Gastroenterol Hepatol. 2020;5:441–53. 10. Chan HLY, et al. Hepatology. 2020;72:490A. Abstract 803. 11. Schwarz K, et al. J Hepatol. 2022;77(S1):S866. Abstract SAT425.

Acknowledgments:
We extend our thanks to the patients and their families, and all participating investigators: Belgium: E Sokal; Hong Kong: GLH Wong; India: A Chowdhury, R Mehta, Dr. Shalimar, A Shukla, M Tandon; New Zealand: H Evans; Republic of Korea: BH Choe, YH Choe, KM Kim; Romania: D Pacurar, A Streinu-Cercel; Russian Federation: I Khaertynova, Y Lobzin, V Morozov, T Strokova; Taiwan: MH Chang, MW Lai, HH Shih, JF Wu, YJ Yang; USA: J Bezerra, J Daniel, L Gillis, JR Honegger, S Horslen, CH Lin, N Mittal, D Mogul, K Murray, MR Narkewicz, D Pan, Y Pham, G Rao, P Rosenthal, K Schwarz, M Whitworth. This study was funded by Gilead Sciences, Inc., Foster City, CA, USA. Editing and production assistance were provided by Danielle Shepherd, PhD, AlphaScientia, San Francisco, CA, USA, and funded by Gilead Sciences, Inc. Disclosures: KS reports research grants funded by Gilead Sciences, Inc.; Albireo; and NIDDK; consulting for Gilead Sciences, Inc.; Mirum; Sarepta; and Up to Date. JB reports grant and research support from Gilead Sciences, Inc. and Shyer. BHC, IK, S, JFW, MT, VM, ES, and MHC report no conflicts of interest. CHL reports grants and research support from Mirum and Gilead Sciences, Inc. FA, AN, YL, and JF are employees of Gilead Sciences, Inc., and may own stock or stock options. DP reports speaking and teaching opportunities from Bristol Myers Squibb; Secom; Dr Phyto; and Angellini; grant and research support from Gilead Sciences, Inc. KMK reports grant and research support from Celltrion. PR reports grants and research support from Gilead Sciences, Inc.; Merck; AbbVie; Albireo; Arrowhead; Mirum; Takeda; and Travere; consulting for Ambrys; Albireo; Audentes; BioMarin; Dicerna; Encoded; Gilead Sciences, Inc.; Mirum; MedinCell; Takeda; and Travere.

Introduction

- Children and adolescents with chronic hepatitis B (CHB) have an increased lifetime risk for clinical complications, including progression to cirrhosis, decompensated liver disease, and liver cancer[1]
- First-line treatment options for children with CHB are generally similar to those for adults; however, there are potential safety and efficacy limitations, including reduced response rates and/or resistance development in patients receiving entecavir with prior lamivudine experience and bone mineral density reductions (relative to placebo) with use of tenofovir disoproxil fumarate (TDF)[2–4]
- Tenofovir alafenamide (TAF)
  - In comparative trials in viremic and suppressed hepatitis B e antigen (HBeAg)-negative and -positive adults with CHB, TAF demonstrated antiviral efficacy noninferior to that of TDF, with improved renal and bone safety at weeks 48 and 96[5–9]
  - No resistance has been detected in adults through 5 years of treatment[10]

TAF
Nucleotide reverse transcriptase inhibitor

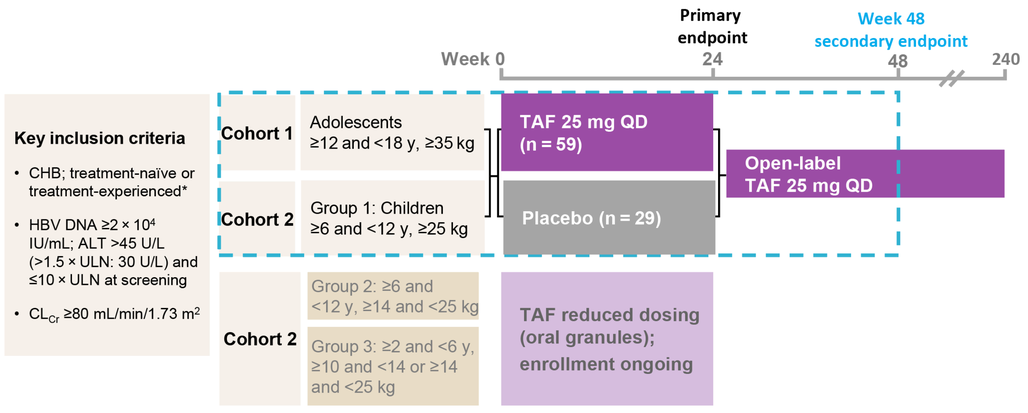


Objective

- To evaluate efficacy and safety of TAF 25 mg once daily (QD) when given for 48 weeks compared with PBO treatment for 24 weeks followed by TAF 25 mg QD for 24 weeks in adolescents (aged 12 to <18 years, weighing ≥35 kg) and children (aged ≥6 to <12 years, weighing ≥25 kg) with CHB

Methods

Study Design: Cohort 1 and Cohort 2, Group 1



- Randomized (2:1), double-blind, PBO-controlled, multicenter study (GS-US-320-1092, ClinicalTrials.gov NCT02932150, EudraCT 2016-000785-37)
- Two study groups: Cohort 1 (adolescents) and Cohort 2, Group 1 (children aged 6 to <12 y weighing at least 25 kg)
- Randomized phase: TAF 25 mg QD vs PBO for 24 weeks (completed for Cohort 1 and Cohort 2, Group 1)
- Open-label (OL) extension phase (all patients): TAF 25 mg QD through week 240

Study Endpoints (Week 48)

Efficacy endpoints

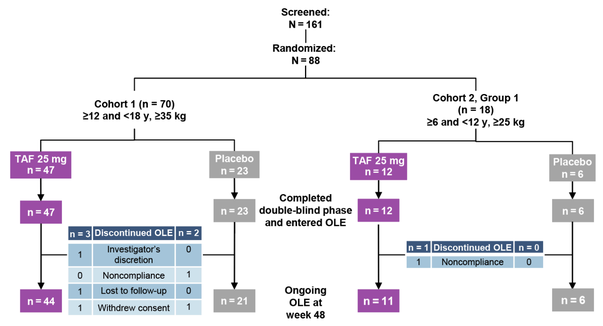
- Antiviral efficacy: HBV DNA <20 IU/mL; log_{10} IU/mL change in HBV DNA from baseline
  - COBAS AmpliPrep/COBAS TaqMan HBV test, v2.0 (Roche Diagnostics, Indianapolis, Indiana, USA; lower limit of quantitation: 20 IU/mL)
- Biochemical efficacy: alanine aminotransferase (ALT) normalization by Central laboratory and American Association for the Study of Liver Diseases criteria
- Serology: HBeAg and hepatitis B surface antigen (HBsAg) loss/seroconversion; HBsAg change from baseline (log_{10} IU/mL)
- Resistance
  - HBV polymerase/reverse transcriptase (pol/RT) deep sequencing was conducted for patients with HBV DNA ≥69 IU/mL at week 48

Efficacy endpoints

- Overall: Graded adverse events (AEs) and laboratory abnormalities
- Bone: Mean (SD) percent changes in spine and whole-body (minus head) bone mineral density (BMD) measured by dual energy x-ray absorptiometry, mean (SD) change in bone Z-scores for spine and whole-body (minus head)
- Renal: Changes in estimated creatine clearance (CL_{Cr}; Schwartz formula = k × L/s_{Cr}; where k is a proportionality constant, L is height [cm], and sCr is serum creatinine), s_{Cr}, and serum phosphorus (sPO_4)

Results

Patient Disposition



OLE, open-label extension; TAF, tenofovir alafenamide; y, years.

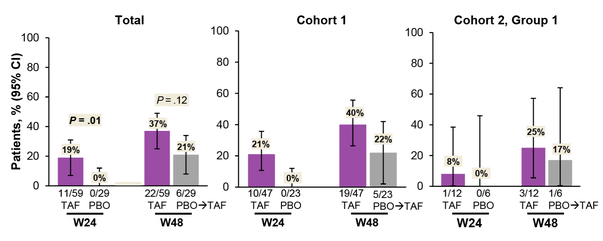
- 82 patients remain in the ongoing OL extension of TAF treatment

Baseline Characteristics (Total Population)

	TAF, n=59	Placebo, n = 29
Age, years, mean (range)	14 (7–17)	13 (7–17)
Sex, 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)
BMI, kg/m², mean (SD)	20.2 (2.91)	19.8 (3.02)
Prior OAV, n (%)	15 (25)	5 (17)
Prior IFN, n (%)	11 (19)	2 (7)
HBV DNA, log_{10} IU/mL, mean (SD)	7.9 (1.12)	8.1 (0.72)
HBV DNA ≥8, log_{10} IU/mL, n (%)	39 (66)	21 (72)
HBsAg, log_{10} IU/mL, mean (SD)	4.4 (0.58)	4.6 (0.55)
HBeAg positive, n (%)	58 (98)	29 (100)
ALT, U/L, median (Q1, Q3)	65 (50, 109)	66 (54, 89)
CL_{Cr}, mL/min/1.73 m², median (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. †Six patients had an undetermined genotype (TAF, n = 4; placebo, n = 2). ALT, alanine aminotransferase; BMI, body mass index; CL_{Cr}, creatinine clearance; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon; OAV, oral antiviral; Q, quartile; SD, standard deviation; TAF, tenofovir alafenamide.

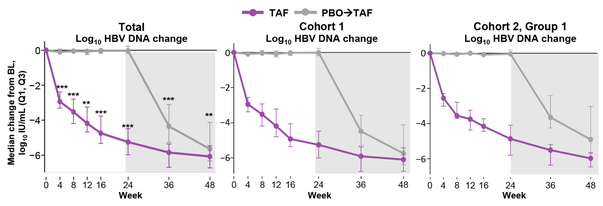
Proportion With HBV DNA <20 IU/mL



P-values based on two-sided Cochran-Mantel-Haenszel test adjusted for age at baseline. Proportion of patients with HBV DNA <20 IU/mL (missing = failure; W24, 1 missing from TAF group, 2 missing from PBO; W48, 2 missing from TAF group). CI, confidence interval; HBV, hepatitis B virus; PBO, placebo; TAF, tenofovir alafenamide; W, week.

- Overall, the percentage of patients with HBV DNA <20 IU/mL in the TAF group progressively increased from week 24 to week 48, while results for the PBO→TAF group (21%) at week 48 were similar to those in the TAF group at week 24 (19%), confirming antiviral activity with TAF
- Proportions with HBV DNA <20 IU/mL in the TAF groups progressively increased from week 24 to week 48 for both cohorts
- A disproportionately higher proportion of TAF patients in Cohort 2, Group 1 had HBV DNA ≥8, log10 IU/mL at baseline (Cohort 1 TAF, 63.8%; Cohort 2, Group 1 TAF, 75.0%) and genotype D infection (Cohort 1 TAF, 39.5%; Cohort 2, Group 1 TAF, 58.3%), which may explain the lower responses in this group at weeks 24 and 48

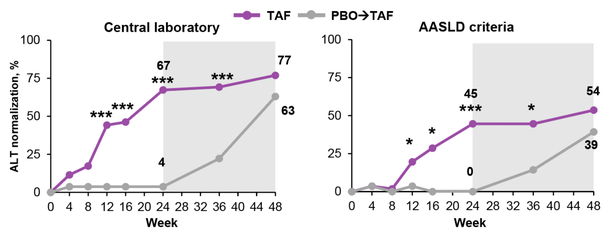
HBV DNA Response Over 48 Weeks



P-values were based on a two-sided Wilcoxon rank sum test. Shaded area of figure indicates OL phase. **P <.01 (two-sided Wilcoxon rank sum test). ***P <.001 (two-sided Wilcoxon rank sum test). BL, baseline; HBV, hepatitis B virus; OL, open label; PBO, placebo; Q, quartile; TAF, tenofovir alafenamide.

- PBO→TAF patients showed similar significant declines in HBV DNA during OL TAF treatment relative to the TAF group during the double-blind (DB) phase
- In both groups (Cohort 1 and Cohort 2, Group 1), treatment with TAF resulted in rapid, similar, and substantial median declines in HBV DNA levels

ALT Normalization Over 48 Weeks (Total Population)



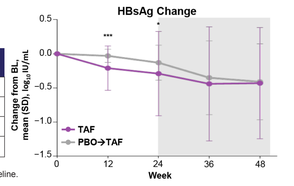
Population used for analysis of ALT normalization included only patients with ALT >ULN at baseline; central laboratory ULN: 34 U/L for females aged ≥2 y and males aged 1–9 y, and 43 U/L for males aged ≥9 y; 2018 AASLD ULN: 30 U/L for pediatric males and females. Shaded area of figure indicates OL phase. *P <.05 (two-sided Cochran-Mantel-Haenszel test adjusted for age at baseline). ***P <.001 (two-sided Cochran-Mantel-Haenszel test adjusted for age at baseline). AASLD, American Association for the Study of Liver Disease; ALT, alanine aminotransferase; OL, open-label; PBO, placebo; TAF, tenofovir alafenamide; ULN, upper limit of normal; y, years.

- At week 48, proportions of patients with ALT normalization progressively increased in the TAF group
- 24 weeks after switching from PBO to TAF, the proportions with ALT normalization in the PBO→TAF group were approaching those in the TAF group (not significantly different)

Serology Results Over 48 Weeks (Total Population)

	Patients, n/N (%)	TAF n=58	PBO → TAF n = 29	P-value
HBeAg†	Loss	10/58 (17)	2/29 (7)	0.19
	Seroconversion	8/58 (14)	2/29 (7)	0.35
HBsAg	Loss	0	0	—
	Seroconversion	0	0	—

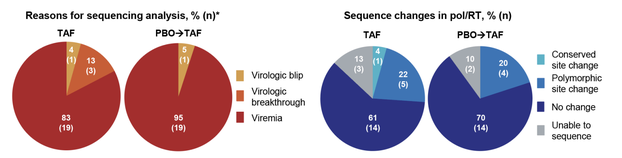
P-value based on two-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.



†Population used for HBeAg analysis included only patients who were HBeAg positive and HBeAb negative or missing at baseline. HBsAg analysis included all available data. Shaded area of figure indicates OL phase. *P <.05 (two-sided Wilcoxon rank sum test). ***P <.001 (two-sided Wilcoxon rank sum test). BL, baseline; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; OL, open label; PBO, placebo; SD, standard deviation; TAF, tenofovir alafenamide.

- At week 48, increasing proportions of patients experienced HBeAg loss and seroconversion with TAF treatment
- Small mean declines in HBsAg levels seen with TAF were significantly greater than PBO through week 24
- No patient treated with TAF had HBsAg loss or seroconversion

Resistance Analysis at Week 48



*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 virologic breakthrough criterion at only 1 visit; viremia: persistent HBV DNA >20 IU/mL over treatment course. HBV, hepatitis B virus; PBO, placebo; pol/RT, polymerase/reverse transcriptase; TAF, tenofovir alafenamide.

- Virologic breakthrough was infrequent (n = 3; TAF group only) and was not associated with sequence changes in pol/RT
- Majority of patients had no sequence change from baseline
- One patient qualified for phenotypic analysis due to a conserved site change
  - Week 48 isolate remained sensitive to TAF in vitro (fold-change in EC_{50} <2 from baseline)

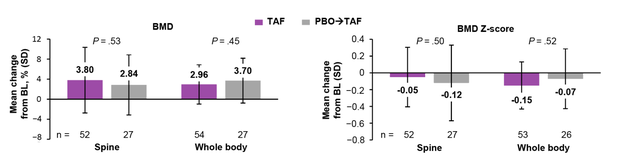
Safety (Open-label TAF Phase)

	Patients, n (%)	TAF, n=59	PBO → TAF, n = 29
AEs	Any AE	38 (64)	16 (55)
	Grade 3–4 AE	3 (5)	0
	Serious AE	1 (2)*	0
	D/C due to AE	0	0
	Death	0	0
Grade 3 or 4 laboratory abnormalities	Any Grade 3 or 4	9 (15)	3 (10)
	ALT (increased)	1 (2)	1 (3)
	Hemoglobin (decreased)	1 (2)	0
	Neutrophils (decreased)	1 (2)	0
	Platelets (decreased)	1 (2)	0
	Creatine kinase (increased)	1 (2)	0
	Occult blood urine	3 (5)	2 (7)

*Suicidal ideation (not related to treatment). AE, adverse event; ALT, alanine aminotransferase; D/C, discontinuation; PBO, placebo; TAF, tenofovir alafenamide.

- Most AEs during the OL phase were mild-moderate, and no patients had a Grade 3 or 4 AE
- No patients discontinued OL treatment due to an AE
- TAF remained safe and well tolerated with longer-term treatment

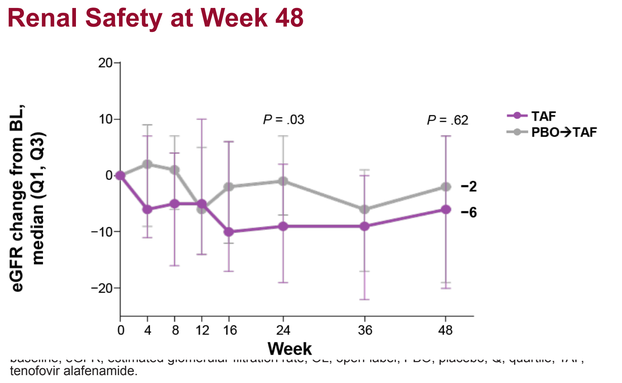
Change in BMD and BMD Z-scores at Week 48



P-value for mean change from BL based on an ANOVA model, including treatment as a fixed effect. P-value for BMD Z-scores was based on a two-sided Wilcoxon rank sum test. ANOVA, analysis of variance; BL, baseline; BMD, bone mineral density; PBO, placebo; TAF, tenofovir alafenamide.

- The PBO→TAF group had similar increases in spine and whole-body BMD and BMD Z-score changes compared with the TAF group

Renal Safety at Week 48



tenofovir alafenamide.

- eGFR change was similar between TAF and PBO→TAF groups at week 48, and no patient on TAF treatment had an eGFR value < 90 mL/min/1.73 m²
- At week 48, sCr and sPO4 levels were similar between the two groups (data not shown)
- No patient had a confirmed (ie, on 2 consecutive visits) renal abnormality, as follows:
  - sCr ≥0.3 mg/dL from BL
  - sPO_4 below 2.0 mg/dL
  - eGFR <50 mL/min/1.73m2, or <70 mL/min/1.73 m²