Poster 183

Switching from TDF and/or Other OAV to TAF in Virally Suppressed Chronic Hepatitis B Patients with Hepatic Impairment: Final 2 Year Efficacy and Safety Results from a Phase 2 Open-Label Study

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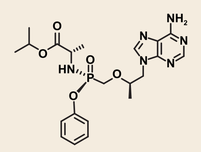
Introduction

Tenofovir Alafenamide (TAF)

- Novel tenofovir prodrug; greater plasma stability, with enhanced hepatic delivery of active drug and lower circulating levels of tenofovir relative to tenofovir disoproxil fumarate (TDF)[1-4]

TAF
Nucleotide reverse transcriptase inhibitor



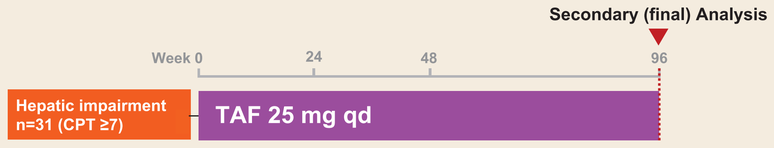
- Noninferior efficacy vs TDF at Weeks 48 and 96 in virally suppressed chronic hepatitis B (CHB) patients with/without compensated cirrhosis, and creatinine clearance (estimated glomerular filtration rate by Cockcroft-Gault method [$eGFR_{CG}$]) ≥50 mL/min switched to TAF, with improved bone and renal safety[5,6]
- Week-48 results from the present study have shown that following the switch to TAF, viral suppression is well maintained, while bone and renal safety remain stable in hepatically impaired patients with CHB[7]

Objective

- To evaluate the efficacy and safety 2 y after switching to TAF in virally suppressed CHB patients with moderate–severe hepatic impairment

Methods

GS-US-320-4035 Study Design*



*ClinicalTrials.gov NCT03180619. CPT, Child-Pugh-Turcotte.

- Open-label, Phase 2 switch study
- Key inclusion criteria:
  - Treatment with TDF and/or other oral antivirals (OAVs) for ≥48 wk; virally suppressed with hepatitis B virus (HBV) DNA < lower limit of quantitation for ≥24 wk and HBV DNA <20 IU/mL at screening
  - Hepatic impairment categorized as CPT score ≥7 and ≤12 at screening (or history of CPT ≥7 and any CPT score ≤12 at screening)
  - Creatinine clearance ≥30 mL/min
- Secondary analysis endpoints:
  - Safety and tolerability of TAF 25 mg at Week 96
  - Proportion of patients achieving virologic responses (HBV DNA <20 IU/mL), serologic responses, and biochemical responses at Week 96 (missing = failure and missing = excluded approach)

Results

Baseline Demographics and Characteristics

		Total: N=31
Median age, y (range)		57 (20–73)
Age ≥65 y, n (%)		6 (19)
Men, n (%)		21 (68)
Asian, n (%)		25 (81)
HBeAg-negative, n (%)		28 (90)
Median ALT, U/L (Q1, Q3) / ALT ≤ULN (2018 AASLD criteria), n (%)*		27 (18, 33) / 21 (68)
FibroTest™ ≥0.75† / history of cirrhosis, n (%)		19 (61) / 30 (97)
Median $eGFR_{CG}$, mL/min (Q1, Q3)		99 (73, 130)
Normal BMD status (T-score ≥-1.0), n (%)	Hip	18 (58)
	Spine	16 (52)
Comorbidities, n (%)	Hypertension/cardiovascular disease	7 (23) / 4 (13)
	Diabetes/hyperlipidemia	7 (23) / 4 (13)
CPT class, n (%)	A	19 (61)‡
	B	9 (29)
	C	3 (10)
Median MELD score (Q1, Q3)		10 (7.5, 14.2)

*Upper limit of normal (ULN) 25 U/L for women and 35 U/L for men; †BioPredictive S.A.S, Paris, France; ‡2 patients had CPT ≥7 at screening and 17 patients by history.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; BMD, bone mineral density; HBeAg, hepatitis B e antigen; MELD, Model for End-Stage Liver Disease; Q, quartile.

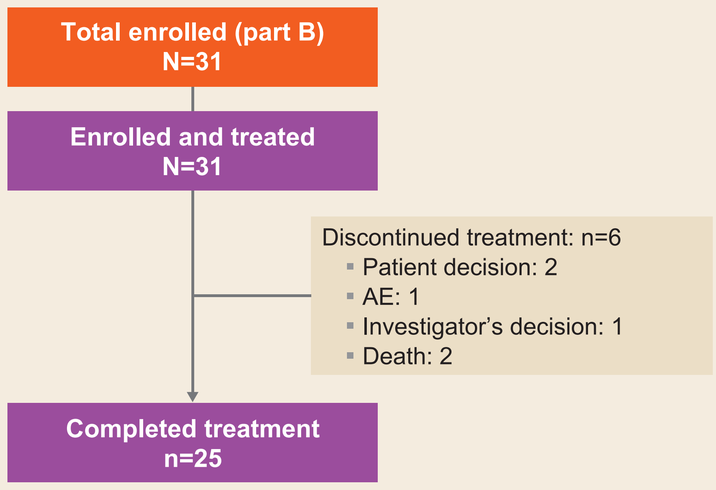
Prior Oral Antiviral Treatment

Patients, n (%)*	Total: N=31
TDF	21 (68)
At screening	21 (68)
Lamivudine	14 (45)
Adefovir	10 (32)
Entecavir	14 (45)
At screening	10 (32)
Telbivudine	2 (6)
Emtricitabine/TDF	1 (3)

*Patients could have taken >1 agent previously.

Results, cont'd

Disposition



AE, adverse event.

Efficacy at Week 96

	Missing = Failure	Missing = Excluded
HBV DNA <20 IU/mL, n/N (%)	24/31 (77)	24/25 (96)
HBV DNA <20 IU/mL, target not detected	24/31 (77)	24/25 (96)
HBV DNA ≥20 IU/mL (nonmissing), n/N (%)	—	1/25 (4)
ALT normal (2018 AASLD criteria), n (%)*	18/31 (58)	18/25 (72)
HBeAg loss, n/N†	0/3	0/3
HBsAg loss, n/N (%)‡	2/30 (7)	2/24 (8)
Mean change in qHBsAg from baseline, log_{10} IU/mL (SD)	—	-0.20 (0.17)
Median change in CPT class (Q1, Q3)	—	0 (-1, 0)
Median change in MELD score (Q1, Q3)	—	-0.6 (-1.3, 0.0)
Median change in FibroTest score (Q1, Q3)	—	-0.01 (-0.04, 0.02)

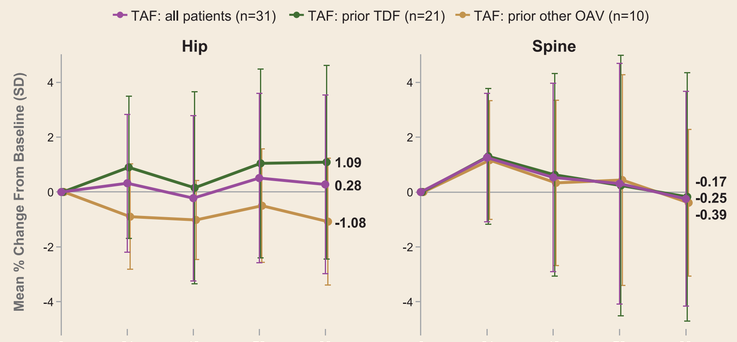
*ALT ≤ULN at Week 48 regardless of baseline ALT level; †Patients who were HBeAg-positive at baseline; ‡No patient had HBeAg seroconversion.
HBsAg, hepatitis B surface antigen; qHBsAg, quantitative HBsAg; SD, standard deviation.

Overall Safety Summary

Patients, n (%)	Total: N=31
Any AE	24 (77)
Grade 3–4 AE*	8 (26)
Serious AE*	10 (32)
D/C of study treatment due to AE	1 (3)†
Death	2 (6)‡
Grade 3–4 laboratory abnormality	17 (55)
Grade 3–4 laboratory abnormalities seen in ≥2 patients	
Hemoglobin	3 (10)
Lymphocytes	7 (23)
Platelets	4 (13)
Bilirubin	4 (13)
Fasting glucose	2 (7)
Urine glucose	3 (10)

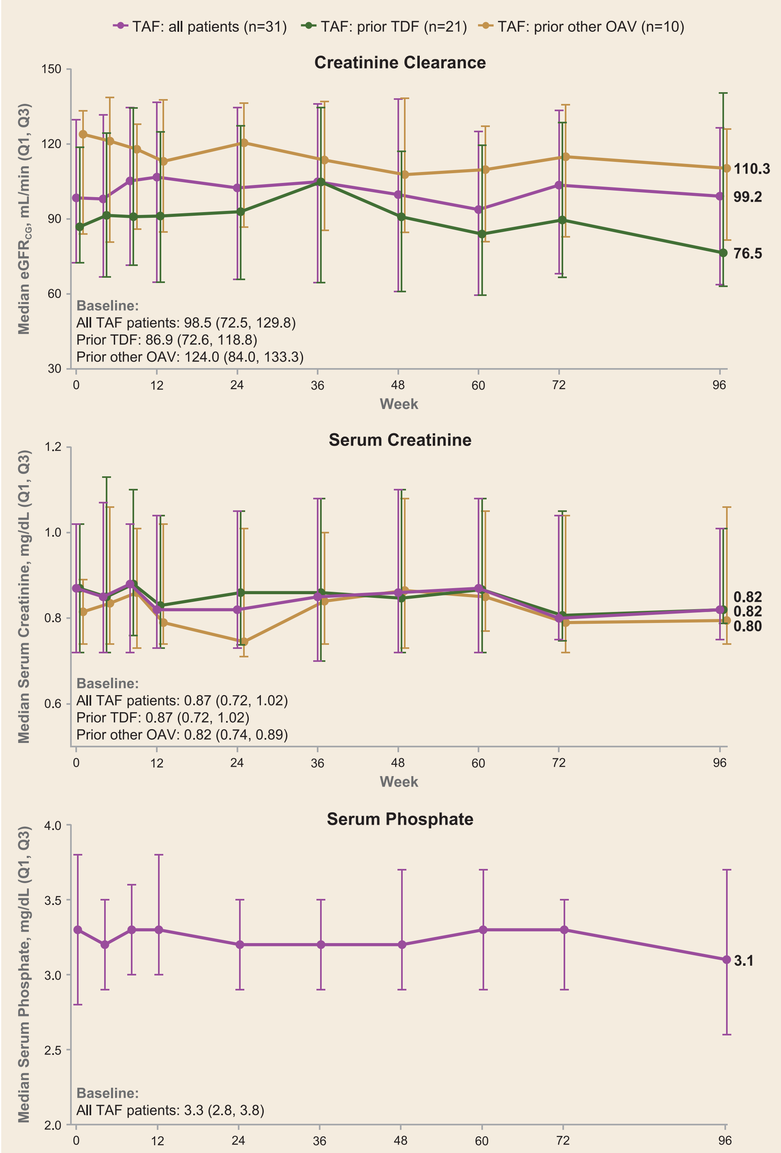
*No Grade 3–4 or serious AEs were judged to be related to study treatment; †Man aged 73 y with blood creatinine increased on Day 334 (Grade 2, nonserious, and related to study treatment); ‡Man aged 57 y died due to respiratory failure with worsening clinical condition (MELD score 35) on Day 612; woman aged 49 y died due to aspiration pneumonia on Day 651. D/C, discontinuation.

Changes in Bone Mineral Density Over 96 Weeks



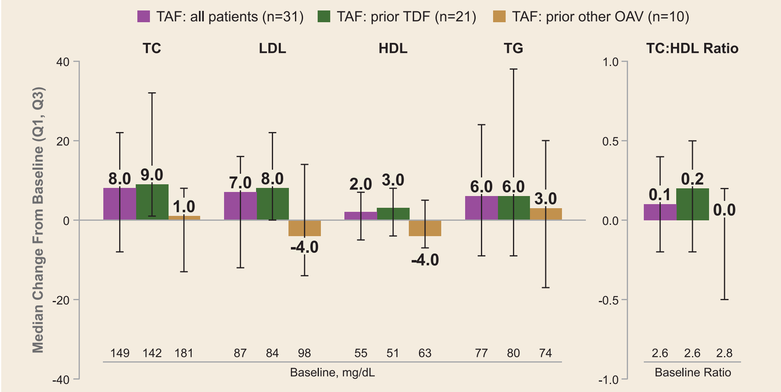
- Following switch to TAF, hip and spine BMD remained stable through Week 96

Renal Parameter Results Over 96 Weeks



- Following switch to TAF, all 3 renal parameters remained stable through Week 96

Fasting and Lipid and Other Metabolic Changes at Week 96



HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol, TG, triglycerides.

- Small increases were seen for all lipid parameters in overall population; similar changes were seen in prior-TDF patients
- Patients on OAVs other than TDF at baseline showed either very small increases or small decreases in lipids (TC/HDL did not change)
- Median (Q1, Q3) body weight at baseline: 71 (59, 87) kg; median (Q1, Q3) change at Week 96: 2.4 (-1.8, 6.0) kg
- Median (Q1, Q3) fasting serum glucose at baseline: 96 (89, 108) mg/dL; median (Q1, Q3) change at Week 96: 5 (-2, 11) mg/dL

Conclusions

- Hepatically impaired patients with CHB who were virally suppressed on TDF and/or other OAVs and switched to TAF treatment for 2 y showed the following:
  - Viral suppression was well maintained, ALT levels remained within the normal range in most patients on treatment and serologic responses were low
  - Hepatic function remained stable as assessed by change in FibroTest, CPT, and MELD scores
  - TAF was safe and well tolerated; the incidences of Grade 3 and 4, and serious AEs, and deaths (n=2) are reflective of patients with advanced liver disease and underlying comorbidities
  - Bone and renal safety parameters remained stable
  - The small changes in fasting lipids, body weight, and other metabolic parameters were not considered clinically important

References: **1.** Agarwal K, et al. J Hepatol 2015;62:533-40; **2.** Babusis D, et al. Mol Pharm 2013;10:459-66; **3.** Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-906; **4.** Murakami E, et al. Antimicrob Agents Chemother 2015;59:3563-9; **5.** Lampertico P, et al. EASL 2020, oral 091; **6.** Lampertico P, et al. Lancet Gastroenterol Hepatol. 2020;5:441-53; **7.** Lim Y-S, et al. EASL 2020, poster SAT442.

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