Impact of Treatment With Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate on Hepatocellular Carcinoma Incidence in Patients with Chronic Hepatitis B

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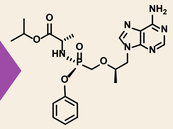
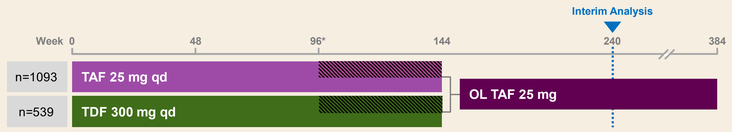
Background and Aim

TAF
Nucleotide reverse transcriptase inhibitor



- Tenofovir alafenamide (TAF)
  - Novel tenofovir (TFV) prodrug with greater plasma stability, enhanced hepatic uptake, and lower circulating TFV levels relative to tenofovir disoproxil fumarate (TDF)[1–3]
  - TAF has shown efficacy noninferior to TDF with improved bone and renal safety through 96 weeks in viremic chronic hepatitis B (CHB) patients,[4] and 48 weeks in virally suppressed patients who switched from TDF to TAF[5]
- Antiviral therapy reduces the risk of hepatocellular carcinoma (HCC) in CHB patients[6,7]
  - Recent studies suggest differences may exist in HCC risk reduction among first-line treatments for CHB (TDF and entecavir)[8-10]
- **Study aim**:
  - Evaluate HCC incidence and impact of antiviral treatment with TAF or TDF over 5 years in two ongoing Phase 3 studies

Study Design



- Two Phase 3, randomized, DB, active-controlled trials (global[§] and China[ǂ] cohorts)
  - Study 108 (N=579): HBeAg-negative patients
  - Study 110 (N=1053): HBeAg-positive patients
- 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; no evidence of HCC (recent imaging)
- 2:1 randomization: stratified by HBV DNA level and treatment status (naïve/experienced)

*Amended to extend double-blind (DB) to Week 144 and open-label (OL) to Week 384 (Year 8); Shaded areas represent patients who rolled over to OL TAF at Week 96 (TAF n=360; TAF n=180); [§]ClinicalTrials.gov NCT01940341 and NCT01940471 (global), [ǂ]CT02836249 and NCT02836236 (China). ALT, alanine aminotransferase; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBeAg, hepatitis B e antigen

Methods: Hepatocellular Carcinoma Assessment

- HCC was a predefined adverse event (AE)
  - Screening, diagnosis, and treatment as per local standards of care
  - Hepatic ultrasonography (every 6 mo) added at Week 96
- Cumulative HCC incidence plotted by Kaplan-Meier method, baseline and on-treatment predictors for HCC assessed by multivariate (MV) analysis using Cox proportional hazards regression model
- Predicted HCC incidence calculated by REACH-B risk score[†]
  - Standardized incidence ratios (SIRs) for observed vs predicted cases calculated through Week 240 (using maximum observed time for each patient); 95% confidence intervals (CI) calculated by Poisson regression

AE, adverse event; CI, confidence interval; REACH-B, risk estimation for HCC in CHB. 11.Yang HI et al. Lancet Oncol. 2011;12:568-74.

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AUSTRALIA PW Angus, N Bak, W Cheng, J George, I Kronborg, MC Ngu, S Pianko, S Roberts, J Sasadeusz, S Strasser, A Thompson BULGARIA R Balabanska, K Katzarov, D Petrova, K Tchernev, CANADA C Coffin, B Conway, M Elkashab, J Farley, S Fung, HLA Janssen, K Kaita, P Kwan, M Ma, A Ramji, E Tam, F Wong CHINA Chen Yu, Shanming Wu, Guozhong Gong, Jinlin Hou, Li Jun, Zhang Mingxiang, Lin Feng, Chen Chengwei, Cheng Jun, Huang Jan, Lin Shumei, Tang Hong, Mu Zhuangbo, Yang Yongfeng, Zhang Lunli, Niu Junqi, Su Minghua, Xie Qing, Dou Xiaoguang, Gao Zhiliang, Jia Jidong, Ning Qin, Cheng Jun, Li Wu, Nan Yuemin, Rao Huijing, Wang Fu-Sheng, Wang Guiqiang, Duan Zhongping FRANCE F Haberselzer, P Marcellin, V Ratziu, D Samuel HONG KONG HLY Chan, AJ Hui, MLK Kong, TYO Tsang, WK Seto, MF Yuen INDIA SK Acharya, A Arora, A Chowdhury, A Duseja, G Gupta, S Gupta, MA Habeeb, D Kapoor, A Konar, R Mehta, S Mukewar, M Prasad, S Shah, M Sharma, ITALY A Alberti, P Andreone, M Brunetto, E Erne, G Raimondo, T Santantonio, M Zuin JAPAN Y Asahina, N Furusyo, T Ide, F Ikeda, T Inokuma, Y Itoh, N Izumi, N Kawada, S Kawata, M Kudo, M Mizokami, `M Nakamuta, S Nishiguchi, H Nomura, M Omata, Y Osaki, N Sakamoto, M Saito, K Takaguchi, T Takehara, Y Ueno, H Yatsuhashi NEW ZEALAND E Gane, F Weilert POLAND R Flisiak, A Horban, W Halota, M Jablkowski, W Mazur, K Simon KOREA SH Ahn, SH Bae, SK Baik, KS Byun, SM Cho, B Han, J Heo, JS Hwang, SH Jeong, HJ Kim, HS Kim, YJ Kim, W Kim, SY Kwon, KS Lee, JS Lee, T Lee, YS Lim, SW Paik, N Park, WY Tak, KT Yoon ROMANIA F Caruntu, E Ceausu, S Rugina, I Sporea, C Stanciu, A Streinu-Cercel, RUSSIA D Abdurakhmanov, E Bessonova, V Isakov, I Klevtsova, V Morozov, E Nurmukhametova, P Ogurtsov, M Osipenko, T Sologub, T Stepanova, A Yakovlev, O Zheltova SPAIN M Buti, JL Calleja Panero, M Prieto, JM Pascasio, R Morillas TAIWAN TT Chang, CY Chen, WL Chuang, CT Hu, JH Kao, TH Lee, CY Peng, SS Yang TURKEY U Akarca, M Celen, S Gurel, F Tabak, C Yurdaydin UNITED KINGDOM K Agarwal, G Foster, W Rosenberg, S Ryder USA H Bae, S Chan, G Galler, R Ghalib, HW Hann, S Jafri, H Lee, X Ma, M Nguyen, TT Nguyen, C Pan, N Ravendhran, E Schiff, M Tong, H Trinh, K Viveiros

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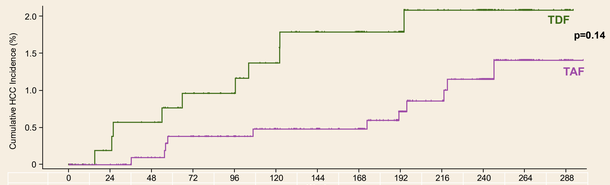
Results

HCC Incidence and Onset



	TAF, n=1093	TDF, n=539	Total, N=1632
HCC cases, n (%)*	11 (1.0)	10 (1.9)	21 (1.3)
Double-blind phase, n (%)	5 (0.5)	6 (1.1)	11 (0.7)
Open-label TAF phase, n (%)	6 (0.5)	4 (0.7)[†]	10 (0.6)
Median time to HCC onset, wk (Q1, Q3)[‡]	173 (56, 217)	81 (26, 122)	104 (55, 191)

*p=0.165; [†]All OL cases occurred within 48 weeks after switching to TAF; [‡]p=0.085. Q, quartile.

Demographics: HCC vs No HCC

		HCC n=21	No HCC n=1611	p-Value
Median age, y (Q1, Q3)		53 (49, 59)	39 (31, 48)	<0.001
Male, n (%)		19 (90)	1044 (65)	0.014
Asian, n (%)		20 (95)	1334 (83)	0.682
Median HBV DNA, log_{10} IU/mL (Q1, Q3)		6.5 (5.7, 7.1)	7.3 (5.6, 8.2)	0.116
Median ALT, U/L (Q1, Q3)		69 (54, 100)	82 (55, 132)	0.215
HBeAg-negative, n (%)		10 (48)	583 (36)	0.279
HBV genotype, n (%)	A	0	85 (5)	0.287
	B	2 (10)	369 (23)	
	C	16 (76)	807 (50)	
	D	3 (14)	328 (20)	
Median Fibrotest score (Q1, Q3)		0.64 (0.59, 0.77)	0.32 (0.18, 0.54)	<0.001
Cirrhosis, n (%)*		7 (33)	148/1573 (9)	<0.001

*Cirrhosis defined as baseline Fibrotest score ≥0.75.

- Baseline predictors of HCC by MV analysis: Age (HR 1.11; p <0.001), male gender (HR 7.57; p=0.007)

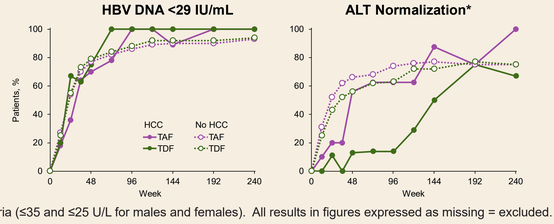
Baseline Demographics and Disposition: TAF and TDF HCC Cases

	HCC	
	TAF n=11	TDF n=10
Median age, y (Q1, Q3)	54 (49, 59)	52 (48, 59)
Male, n (%)	11 (100)	8 (80)
Asian, n (%)	10 (91)	10 (100)
Median HBV DNA, log_{10} IU/mL (Q1, Q3)	7.0 (5.7, 7.4)	6.2 (5.6, 6.6)
Median ALT, U/L (Q1, Q3)	93 (62,110)	60 (42, 69)
Treatment naïve, n (%)	7 (64)	10 (100)
Median Fibrotest score (Q1, Q3)	0.63 (0.59, 0.78)	0.65 (0.53, 0.77)
Cirrhosis, n (%)*	4 (36)	3 (30)
Median AFP, ng/mL (Q1, Q3)	10.2 (5.6, 34.3)	11.5 (5.3, 24.6)

*Cirrhosis defined as Fibrotest score ≥0.75. AFP, alpha-fetoprotein.

- Early discontinuations: TAF n=3 (AE, withdrew consent, death); TDF n=4 (AE, investigator discretion, withdrew consent, noncompliance)

HBV DNA and ALT Normalization Over 240 Weeks

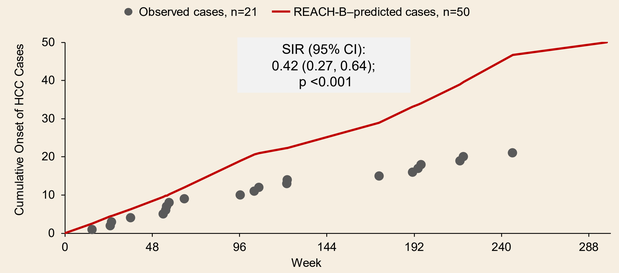


*2018 AASLD criteria (≤35 and ≤25 U/L for males and females). All results in figures expressed as missing = excluded.

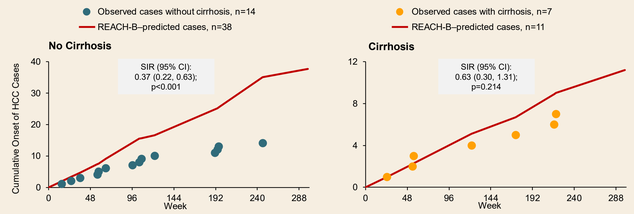
- Baseline/on-treatment predictors of HCC development by MV analysis:
  - Lack of ALT normalization at Week 24 (HR 6.90; p=0.011), Cirrhosis (HR 4.18; p=0.006), baseline HBsAg level (HR 0.53; p=0.006), and baseline hypertension (HR 5.55; p<0.001)

Observed vs Predicted Cases of HCC

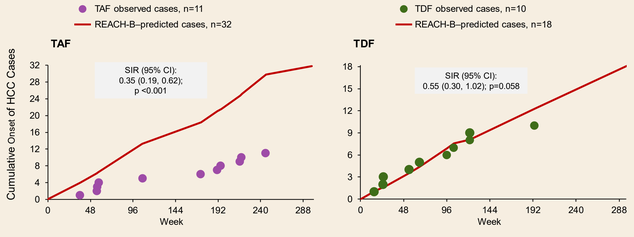
All Cases



No Cirrhosis and Cirrhosis



By Treatment



SIR is Standardized Incidence Ratio of observed cases/predicted cases as determined by REACH-B

Conclusions

- In >1600 HBeAg-positive and -negative patients with CHB enrolled in 2 large Phase 3 studies, antiviral treatment for 5 years demonstrated:
  - Low rates of HCC with TAF or TDF treatment (1.0% and 1.9%, respectively); cumulative incidence (by KM) did not differ for TAF vs TDF
  - Lack of ALT normalization at Week 24, advanced age, male gender, and cirrhosis were predictors of HCC development by MV analysis
- Significant reduction in HCC incidence vs predicted rates by REACH-B was seen for all cases and for patients with no cirrhosis at baseline
  - In patients treated with TAF, a significant reduction in SIR was seen; for TDF there was a trend toward a significant reduction
- Additional follow-up and further assessment of HCC risk reduction using other risk estimators is needed to confirm these results

1. Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-906; 2. Murakami E, et al. Antimicrob Agents Chemother 2015;59:3563-69; 3. Agarwal K, et al. J Hepatol 2015;62:533-40; 4. Agarwal K, et al. J Hepatol 2018;68:672-81; 5. Lampertico P et al. EASL 2019, poster FRI-183; 6. Kim WR et al. Cancer 2015;121:3631-8; 7. Papatheodoridis GV et al. J Hepatol 2015;62:956-67; 8. Choi J et al. JAMA Oncol 2019;5:30-36. doi:10.1001/jamaoncol.2018.40709. Yip T et al. Gastroenterol 2019;Sep 28. doi: 10.1053/j.gastro.2019.09.025. [Epub ahead of print]; 10. Wang X et al. Gut and Liver (published online Oct 18, 2019).