Poster 182

Improved Bone and Renal Parameters Across Multiple Chronic HBV (CHB) Patient Types Treated with Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)

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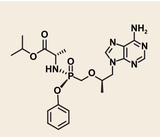
Introduction & Study Objective

TAF

- Novel tenofovir prodrug; greater plasma stability than TDF[1–3]
- Enhanced delivery of active drug (TFV-diphosphate) to hepatocytes with reduced circulating TFV levels relative to TDF[1-4]
- Noninferior efficacy vs TDF with improved bone and renal safety in viremic and in virally suppressed, hepatitis B e antigen (HBeAg)–negative and HBeAg–positive patients with CHB at Week 48 and Week 96, respectively[5,6]

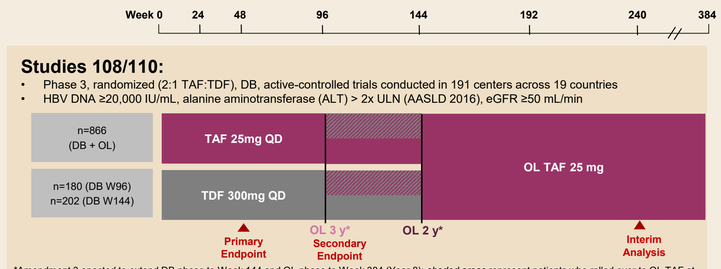
TAF
Nucleotide reverse transcriptase inhibitor



Objective

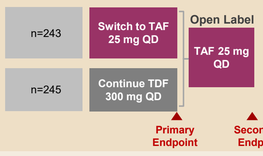
- To comprehensively review TAF bone and renal safety across the entire TAF for HBV clinical development program

Methods

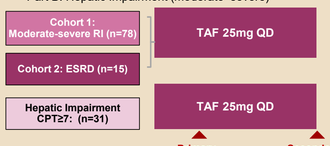


*Amendment 3 enacted to extend DB phase to Week 144 and OL phase to Week 384 (Year 8); *shaded areas* represent patients who rolled over to OL TAF at Week 96 (OL 3 y: TAF n=360; TDF n=180) or Week 144 (OL 2 y: TAF n=415; TDF n=202). Study 108, GS-US-320-0108 (NCT01940341) HBeAg-negative patients; Study 110, GS-US-320-0110 (NCT01940471): HBeAg-positive patients

Study 4018:
- Phase 3, randomized, DB, active-controlled study
- HBeAg-negative and -positive patients: HCC-free and with compensated liver disease
- Virologically suppressed and stable CHB patients on TDF ≥1 year



Study 4035:
- Phase 2, OL switch to TAF in virally-suppressed CHB patients with:
- Part A: Renal impairment: 1) moderate–severe, 2) ESRD maintained on hemodialysis,
- Part B: Hepatic Impairment (moderate–severe)



Cohort 1: $eGFR_{CG}$ of 15–<60 mL/min; Cohort 2: ESRD on chronic HD [$eGFR_{CG}$ <15 mL/min])
Hepatic impairment categorized as CPT score ≥7 and ≤12 at screening (or history of CPT ≥7 and any CPT score ≤12 at screening)

Study 3912:
- Phase 2, randomized, OL Study
- Participants with CHB who were virally suppressed, receiving TDF alone or in combination with other antivirals, with Stage 2 or greater CKD who had received a liver transplant

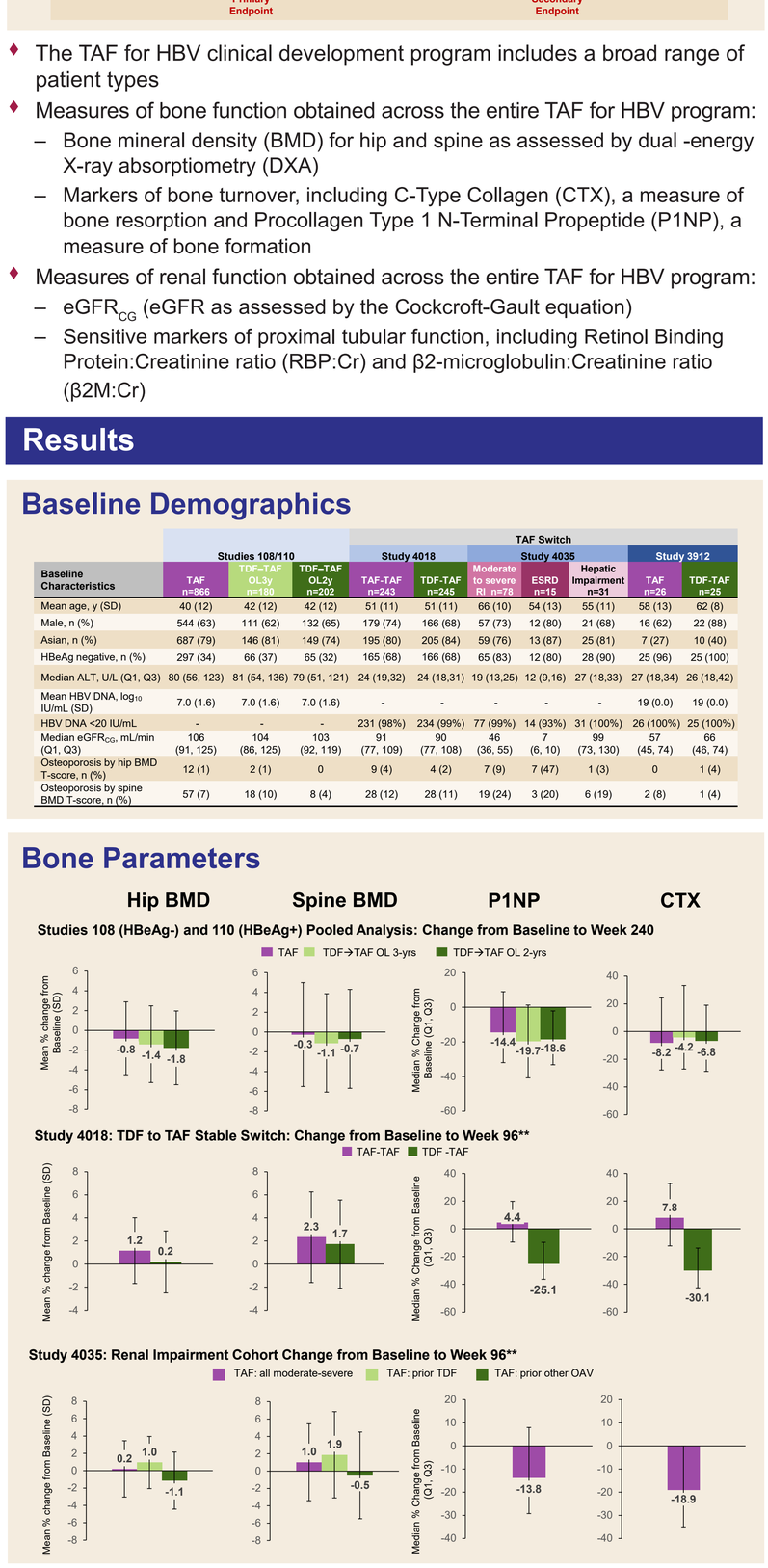
- The TAF for HBV clinical development program includes a broad range of patient types
- Measures of bone function obtained across the entire TAF for HBV program:
  - Bone mineral density (BMD) for hip and spine as assessed by dual -energy X-ray absorptiometry (DXA)
  - Markers of bone turnover, including C-Type Collagen (CTX), a measure of bone resorption and Procollagen Type 1 N-Terminal Propeptide (P1NP), a measure of bone formation
- Measures of renal function obtained across the entire TAF for HBV program:
  - $eGFR_{CG}$ (eGFR as assessed by the Cockcroft-Gault equation)
  - Sensitive markers of proximal tubular function, including Retinol Binding Protein:Creatinine ratio (RBP:Cr) and β2-microglobulin:Creatinine ratio (β2M:Cr)

Results

Baseline Demographics

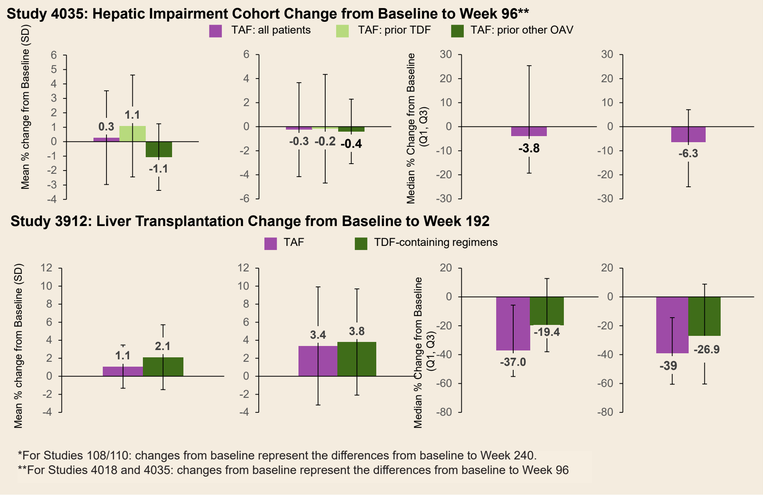
Baseline Characteristics	Studies 108/110			TAF Switch						
				Study 4018		Study 4035			Study 3912	
	TAF n=866	TDF→TAF OL3y n=180	TDF→TAF OL2y n=202	TAF-TAF n=243	TDF-TAF n=245	Moderate to severe RI n=78	ESRD n=15	Hepatic Impairment n=31	TAF n=26	TDF-TAF n=25
Mean age, y (SD)	40 (12)	42 (12)	42 (12)	51 (11)	51 (11)	66 (10)	54 (13)	55 (11)	58 (13)	62 (8)
Male, n (%)	544 (63)	111 (62)	132 (65)	179 (74)	166 (68)	57 (73)	12 (80)	21 (68)	16 (62)	22 (88)
Asian, n (%)	687 (79)	146 (81)	149 (74)	195 (80)	205 (84)	59 (76)	13 (87)	25 (81)	7 (27)	10 (40)
HBeAg negative, n (%)	297 (34)	66 (37)	65 (32)	165 (68)	166 (68)	65 (83)	12 (80)	28 (90)	25 (96)	25 (100)
Median ALT, U/L (Q1, Q3)	80 (56, 123)	81 (54, 136)	79 (51, 121)	24 (19,32)	24 (18,31)	19 (13,25)	12 (9,16)	27 (18,33)	27 (18,34)	26 (18,42)
Mean HBV DNA, log_{10} IU/mL (SD)	7.0 (1.6)	7.0 (1.6)	7.0 (1.6)	-	-	-	-	-	19 (0.0)	19 (0.0)
HBV DNA <20 IU/mL	-	-	-	231 (98%)	234 (99%)	77 (99%)	14 (93%)	31 (100%)	26 (100%)	25 (100%)
Median $eGFR_{CG}$, mL/min (Q1, Q3)	106 (91, 125)	104 (86, 125)	103 (92, 119)	91 (77, 109)	90 (77, 108)	46 (36, 55)	7 (6, 10)	99 (73, 130)	57 (45, 74)	66 (46, 74)
Osteoporosis by hip BMD T-score, n (%)	12 (1)	2 (1)	0	9 (4)	4 (2)	7 (9)	7 (47)	1 (3)	0	1 (4)
Osteoporosis by spine BMD T-score, n (%)	57 (7)	18 (10)	8 (4)	28 (12)	28 (11)	19 (24)	3 (20)	6 (19)	2 (8)	1 (4)

Bone Parameters



Results, cont'd

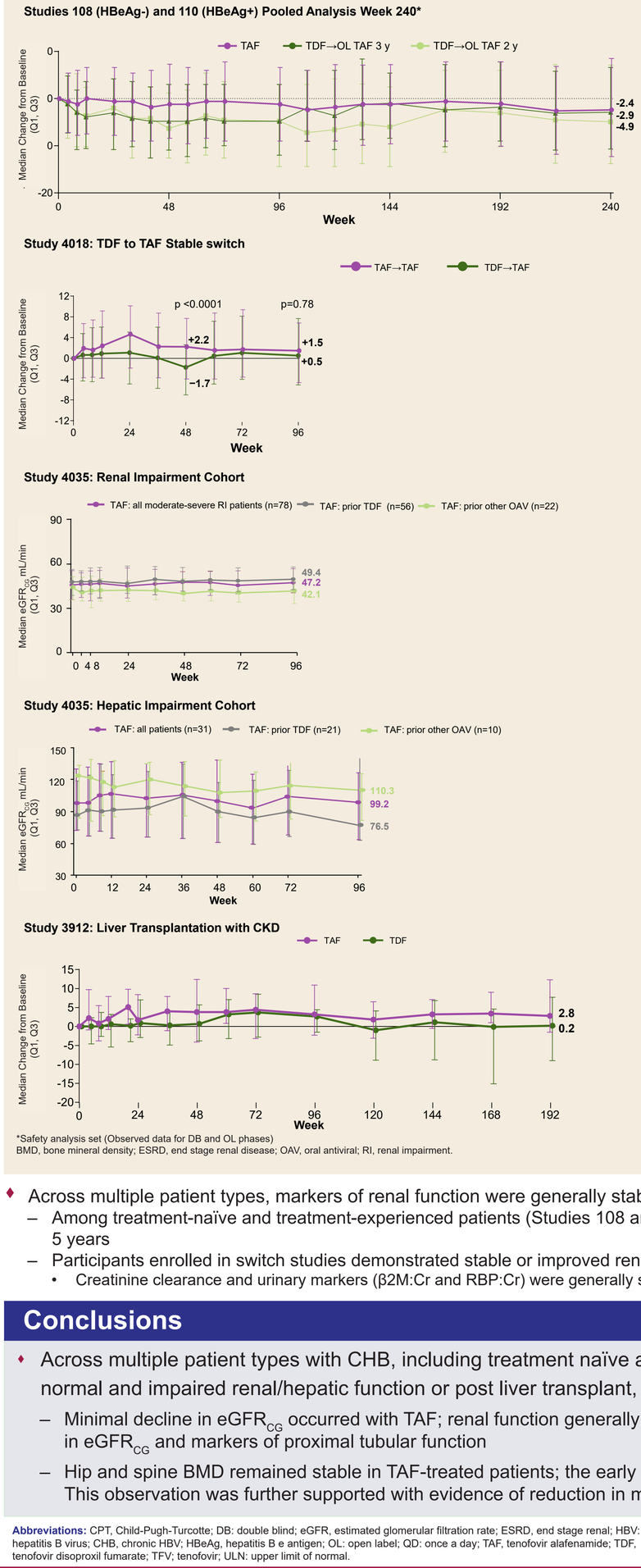
Bone Parameters, cont'd



*For Studies 108/110: changes from baseline represent the differences from baseline to Week 240.
**For Studies 4018 and 4035: changes from baseline represent the differences from baseline to Week 96

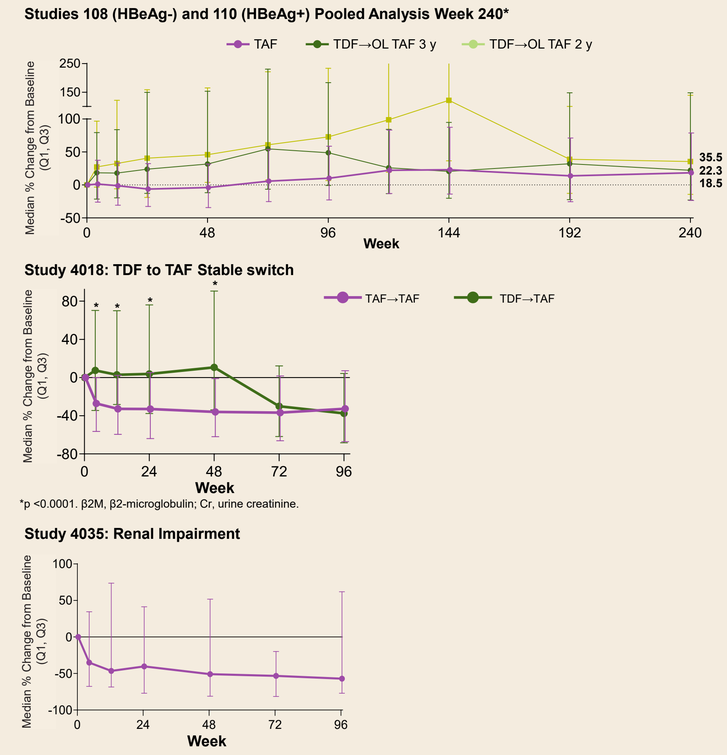
- Among treatment-naïve and treatment-experienced participants with CHB (Studies 108/110):
  - Mean % change in hip and spine BMD over 5 years of TAF treatment showed minimal decrease
  - Markers of bone turnover (P1NP (bone formation) and CTX (bone resorption)) had similar small decreases from baseline
- Among participants who switched to TAF:
  - Participants stably suppressed on TDF who switched to TAF (Study 4018) showed progressively improved BMD, minimal change in markers of bone turnover was observed amongst those randomized to TAF and decreased/ stabilized after switch to TAF at week 48 (Study 4018)
  - Among participants with renal and hepatic impairment (Study 4035), following switch to TAF, hip and spine BMD remained stable over 96 weeks; median percent decreases in markers of bone turnover following switch to TAF were also observed
  - Among liver transplant recipients with CKD (Study 3912), TAF treatment resulted in greater hip and spine BMD improvements compared with TDF-containing regimens and median percent decreases from baseline were observed in bone biomarkers in both treatment groups demonstrating reduced bone turnover after switch to TAF

Renal function: $eGFR_{CG}$

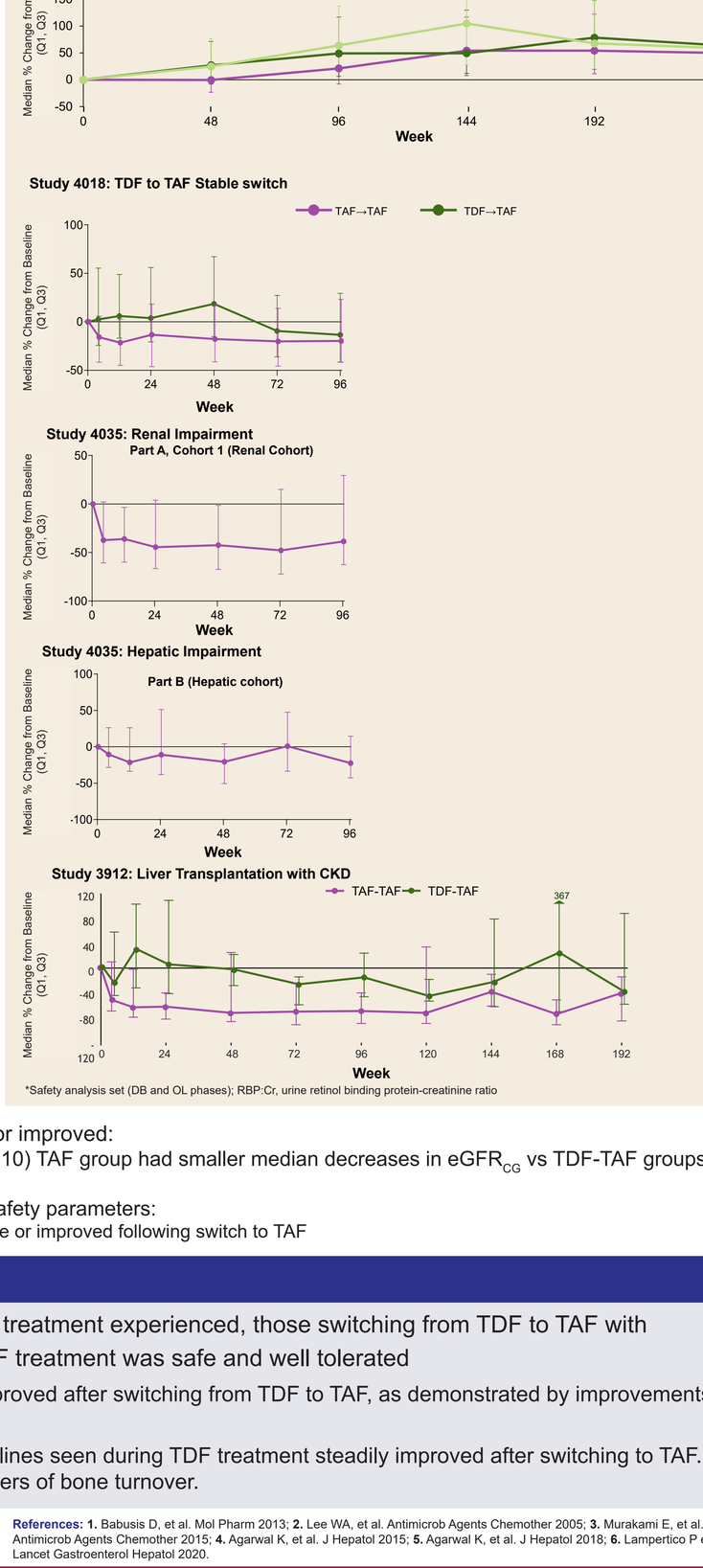


*Safety analysis set (Observed data for DB and OL phases)
BMD, bone mineral density; ESRD, end stage renal disease; OAV, oral antiviral; RI, renal impairment.

Renal function: β2M:Cr



*p <0.0001. β2M, β2-microglobulin; Cr, urine creatinine.



- Across multiple patient types, markers of renal function were generally stable or improved:
  - Among treatment-naïve and treatment-experienced patients (Studies 108 and 110) TAF group had smaller median decreases in $eGFR_{CG}$ vs TDF-TAF groups over 5 years
  - Participants enrolled in switch studies demonstrated stable or improved renal safety parameters:
    - Creatinine clearance and urinary markers (β2M:Cr and RBP:Cr) were generally stable or improved following switch to TAF

Conclusions

- Across multiple patient types with CHB, including treatment naïve and treatment experienced, those switching from TDF to TAF with normal and impaired renal/hepatic function or post liver transplant, TAF treatment was safe and well tolerated
  - Minimal decline in $eGFR_{CG}$ occurred with TAF; renal function generally improved after switching from TDF to TAF, as demonstrated by improvements in $eGFR_{CG}$ and markers of proximal tubular function
  - Hip and spine BMD remained stable in TAF-treated patients; the early declines seen during TDF treatment steadily improved after switching to TAF. This observation was further supported with evidence of reduction in markers of bone turnover.

Abbreviations: CPT, Child-Pugh-Turcotte; DB: double blind; eGFR, estimated glomerular filtration rate; ESRD, end stage renal; HBV: hepatitis B virus; CHB, chronic HBV; HBeAg, hepatitis B e antigen; OL: open label; QD: once a day; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV; tenofovir; ULN: upper limit of normal.

References: 1. Babusis D, et al. Mol Pharm 2013; **2.** Lee WA, et al. Antimicrob Agents Chemother 2005; **3.** Murakami E, et al. Antimicrob Agents Chemother 2015; **4.** Agarwal K, et al. J Hepatol 2015; **5.** Agarwal K, et al. J Hepatol 2018; **6.** Lampertico P et al. Lancet Gastroenterol Hepatol 2020.