7-1-2021

Switching from tenofovir disoproxil fumarate and/or other oral antivirals to tenofovir alafenamide in virally suppressed CHB patients with moderate or severe renal impairment or ESRD on HD: final week 96 efficacy and safety results from a phase 2 study

H L.A. Janssen

P Lampertico

C-H Chen

J Heo

C Fournier

See next page for additional authors

Recommended Citation
Janssen HLA, Lampertico P, Chen C-H, Heo J, Fournier C, Ahn SH, Tsang TYO, Coffin CS, Huang Y-H, Reggiani GM, Hui AJ, Elkhashab M, Chen C-Y, Jafri S-M, Tan S, Zhao Y, Suri V, Flaherty JF, Gaggar A, Brainard D, Chuang W-L, Agarwal K, Gane E, and Lim Y-S. Switching from tenofovir disoproxil fumarate and/or other oral antivirals to tenofovir alafenamide in virally suppressed CHB patients with moderate or severe renal impairment or ESRD on HD: final week 96 efficacy and safety results from a phase 2 study. J Hepatol 2021; 75:S756-S757.

Authors

H L.A. Janssen, P Lampertico, C-H Chen, J Heo, C Fournier, S H. Ahn, T Y.O. Tsang, C S. Coffin, Y-H Huang, G M. Reggiani, A J. Hui, M Elkhashab, C-Y Chen, Syed-Mohammed Jafri, S Tan, Y Zhao, V Suri, J F. Flaherty, A Gaggar, D Brainard, W-L Chuang, K Agarwal, E Gane, and Y-S Lim

[$eGFR_{CG}$], serum creatinine) parameters, viral suppression, and serological and biochemical responses were serially assessed.
Results: Of 31 patients enrolled, mean age was 55 y (29% ≥60 y), 68% male, 81% Asian, and 90% HBeAg-negative; median (Q1, Q3) CTP and MELD scores were 6 (5, 8) and 10 (7.5, 14.2), respectively, median $eGFR_{CG}$ 98.5 ml/min; 19% had osteoporosis on spine DXA. Twenty-five (81%) patients completed 96 weeks of TAF treatment (6 discontinued early: 2-withdrew consent, 1-adverse event [AE; Grade 2 creatinine increase], 1-investigator decision, and 2-death [respiratory failure and aspiration pneumonia-both not treatment-related]). Week 96 efficacy/safety results are summarized in the Table. 96% of patients on TAF treatment had HBV DNA <20 IU/ml with a high proportion having normal ALT levels. Bone and renal parameters remained stable. TAF was well tolerated with no patients having a Grade 3 or 4 AE or a serious AE related to treatment.

n/N (%), or median (Q1, Q3)	TAF 25 mg QD	
	Missing = Failure	Missing = Excluded
Efficacy		
HBV DNA <20 IU/mL	24/31 (77)	24/25 (96)[a]
ALT normal (2018 AASLD criteria)[b,c]	18/31 (58)	18/25 (72)
ALT normal (Central lab criteria)[b,d]	22/31 (71)	22/25 (88)
HBsAg loss[e]	2/30 (7)	2/24 (8)
qHBsAg, log_{10} change (IU/mL)		-0.15 (-0.32, -0.08)
CTP score change		0 (-1, 0)
MELD score change		-0.6 (-1.3, 0.0)
Bone safety		
Hip BMD, % change		+0.15 (-1.167, 2.677)
Spine BMD, % change		-0.13 (-2.192, 2.736)
CTX, % change (ng/mL)[f]		-6.3 (-25.0, 7.1)
P1NP, % change (ng/mL)[g]		-3.8 (-19.3, 25.4)
Renal safety		
sCr, change (mg/dL)		0.02 (-0.05, 0.90)
sPO_4, change (mg/dL)		-0.1 (-0.4, 0.3)
$eGFR_{CG}$, change (mL/min)		-2.4 (-11.4, 10.7)
RBP/Cr, % change[h]		-22.5 (-42.7, 14.7)
β2MG/Cr, % change[i]		-20.5 (-52.5, 27.3)

[a]1 patient had HBV DNA ≥20 IU/ml but <69 IU/mL; [b]ALT normal is proportion with ALT ≤ULN at Week 96 regardless of baseline ALT level; [c]ULN ≤35 U/L males, ≤25 U/L females; [d]ULN ≤43 U/L men and ≤35 U/L for men ≥65y; ≤34 U/L women and ≤32 for women ≥65y; [e]No patient had HBsAg seroconversion. [f]Serum C-type collagen sequence (bone resorption marker); [g]Serum procollagen type 1 N-terminal propeptide (bone formation marker); [h]Urine retinol binding protein/creatinine ratio (proximal tubular marker); [i]Urine beta-2 microglobulin/creatinine ratio (proximal tubular marker).
BMD, bone mineral density by DXA scan; sCr, serum creatinine; $eGFR_{CG}$, estimated creatinine clearance (Cockcroft-Gault method); sPO_4, serum phosphorus.

Conclusion: At 2 years, CHB patients with hepatic impairment who were switched to TAF maintained high rates of viral suppression and normal ALT values while bone and renal parameters remained stable.

PO-2395

Switching from tenofovir disoproxil fumarate and/or other oral antivirals to tenofovir alafenamide in virally suppressed CHB patients with moderate or severe renal impairment or ESRD on HD: final week 96 efficacy and safety results from a phase 2 study

Harry LA Janssen[1], Pietro Lampertico[2], Chien-Hung Chen[3], Jeong Heo[4], Claire Fournier[5], Sang Hoon Ahn[6], Tak Yin Owen Tsang[7], Carla S. Coffin[8], Yi-Hsiang Huang[9], Giulio Marchesini Reggiani[10], Aric Josun Hui[11], Magdy Elkhashab[12], Chi-Yi Chen[13], Syed-Mohammed Jafri[14], Susanna Tan[15], Yang Zhao[15], Vithika Suri[15], John F. Flaherty[15], Anuj Gaggar[15], Diana Brainard[15], Wan-Long Chuang[16], Kosh Agarwal[17], Edward Gane[18], Young-Suk Lim[19]. *[1]Erasmus Universiteit Rotterdam, Rotterdam, Netherlands; [2]University of Milan, Milan, Italy; [3]National Taiwan University Hospital, Taipei City, Taiwan; [4]Pusan National University School of Medicine, Korea, Rep. of South; [5]Service d'Hépatologie, CHUM, Canada; [6]Yonsei University College of Medicine, Seoul, Korea, Rep. of South; [7]Chinese University of Hong Kong, Central Ave, Hong Kong; [8]University of Calgary; [9]Taipei Veterans General Hospital, Taipei, Taiwan; [10]University of Bologna, Italy; [11]Alice Ho Miu Ling Nethersole Hospital, Hong Kong; [12]Toronto Liver Centre, Canada; [13]Chia-Yi Christian Hospital, Taiwan; [14]Henry Ford Health System, United States; [15]Gilead Sciences Inc., Foster City, United States; [16]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan; [17]Institute of Liver Studies, King's College Hospital, United Kingdom; [18]University of Auckland, New Zealand; [19]Asan Medical Center, University of Ulsan College of Medicine, Korea, Rep. of South*
Email: vithika.suri@gilead.com

Background and aims: We have previously shown in renally impaired (RI) chronic hepatitis B (CHB) patients, including those with end-stage renal disease (ESRD) on hemodialysis (HD), that switching to tenofovir alafenamide (TAF) from tenofovir disoproxil fumarate (TDF) and/or other oral antivirals (OAVs) maintains high rates of viral suppression with stable bone and renal safety parameters at Week 48. Here we present the final Week 96 results.
Method: In this Phase 2 study (NCT03180619), virally suppressed CHB patients (HBV DNA <LLOQ× ≥ 6 months and <20 IU/ml at screening) with moderate or severe RI or with ESRD on HD at screening while receiving TDF and/or other OAVs for ≥ 48 weeks were enrolled and switched to TAF 25 mg QD for 96 weeks. Safety assessments including adverse events (AEs) and changes in bone (hip and spine BMD) and renal (creatinine clearance by Cockcroft-Gault [$eGFR_{CG}$], serum phosphorus, and serum creatinine -except in ESRD patients) parameters, viral suppression, and serological and biochemical responses were serially assessed.

Table. Final Results at Week 96: Efficacy and Bone and Renal Parameters

n/N (%), or median (Q1, Q3)	Moderate – Severe RI[a] (n=78)		ESRD on HD[b] (n=15)	
	M = F[c]	M = E[d]	M = F	M = E
HBV DNA <20 IU/mL	65/78 (83)	65/65 (100)	13/15 (87)	13/13 (100)
HBV DNA <20 IU/mL and target not detected (<LLOD)	54/78 (69)	54/65 (83)	10/15 (67)	10/13 (77)
Normal ALT (2018 AASLD criteria)[e,f]	58/78 (74)	58/65 (89)	13/15 (87)	13/13 (100)
Normal ALT (Central lab criteria)[e,g]	64/78 (82)	64/65 (98)	13/15 (87)	13/13 (100)
HBeAg loss[h]	0/13	0/9	1/3 (33)	1/3 (33)
HBsAg loss	0/78	0/66	0/15	0/13
qHBsAg, log_{10} IU/mL change		-0.10 (-0.16, -0.01)		-0.11 (-0.17, -0.02)
Hip BMD, % change		+0.94 (-1.285, 2.282)		-1.54 (-3.620, 1.721)
Spine BMD, % change		+1.21 (-1.230, 3.452)		-1.32 (-3.459, 1.910)
CTX, % change (ng/mL)[i]		-18.9 (-35.0, 0.0)		-9.9 (-38.6, 23.9)
P1NP, % change (ng/mL)[j]		-13.8 (-29.3, 8.0)		-20.8 (-28.7, 16.5)
sCr, change (mg/dL)		-0.04 (-0.120, 0.080)		NA
sPO_4,change (mg/dL)		0.1 (-0.2, 0.4)		NA
$eGFR_{CG}$, change (mL/min)		+1.0 (-2.8, 4.5)		NA
RBP/Cr, % change[k]		-38.5 (-62.5, 29.5)		NA
β2MG/Cr, % change[l]		-57.0 (-77.0, 62.0)		NA

[a]Moderate to severe renal impairment: $eGFR_{CG}$ 15 - <60 mL/min at screening;
[b]ESRD on HD: $eGFR_{CG}$ < 15 mL/min maintained on chronic hemodialysis
[c]M=F, missing equal failure analysis; [d]M=E, missing equal excluded analysis (i.e. observed data)
[e]ALT value within normal range at Week 96 regardless of baseline ALT level; [f]ULN ≤35 U/L males and ≤25 U/L females
[g]ULN ≤43 U/L men and ≤35 U/L for men ≥65y; ≤34 U/L women and ≤32 for women ≥65y
[h]Only includes patients HBeAg-positive at baseline. [i]Serum C-type collagen sequence (bone resorption marker); [j]Serum procollagen type 1 N-terminal propeptide (bone formation marker)
[k]Urine retinol binding protein/creatinine (renal tubular marker); [l]Urine beta-2 microglobulin/creatinine (renal tubular marker).
Abbreviations: $eGFR_{CG}$, estimated creatinine clearance (Cockcroft-Gault method); ESRD, end-stage renal disease; BMD, bone mineral density by DXA scan); LLOD, lower limit of detection; NA, not applicable (hemodialysis patients)

Results: Of 93 patients (mod-severe RI 78; ESRD on HD 15) enrolled, most (74%) were male and Asian (77%), with 51% ≥65 y, 83% HBeAg-negative, 34% with cirrhosis, and median ALT 17 U/L. Up to 24% had osteoporosis at hip and/or spine, with most having comorbidities (HTN 60%, CV disease 22%, DM 25%). Twelve (13%; 11 mod-severe RI and 1 ESRD) patients discontinued the study early (5-withdrew consent, 3-deaths [none treatment-related], 2-AE, and 2-investigator decision). Key efficacy/safety results at Week 96 are summarized in the Table. Viral suppression (HBV DNA<20IU/ml) was maintained in all patients remaining on treatment (i.e. missing equals excluded); a

high proportion had target not detected. Overall, TAF was well tolerated with no Grade 3 or 4 AEs or serious AEs related to study treatment. Relative to baseline levels, switching to TAF resulted in small median % increases in hip/spine BMD in those with moderate to severe RI, and small median decreases in ESRD patients. 2 patients with mod-severe RI had a bone fracture (ankle, rib). Median $eGFR_{CG}$ increased while urinary markers of proximal tubular function progressively decreased in moderate to severe RI patients.
Conclusion: Renally-impaired CHB patients, including ESRD patients on HD, who were switched to TAF from TDF and/or other OAVs maintained high rates of viral suppression, and bone and renal parameters remained stable or slightly improved after 2 years of treatment.

PO-2422

Safety, efficacy, and pharmacodynamic (PD) activity of 12 weeks treatment with oral RIG-I agonist, inarigivir (IRIG), plus 48 weeks of tenofovir alafenamide in adult patients with chronic hepatitis B: a phase 2 collaboration study

Young-Suk Lim[1], Aric J. Hui[2], Jeong-Won Jang[3], Won-Young Tak[4], Sang Hoon Ahn[5], Byoung Kuk Jang[6], Tak Yin Owen Tsang[7], Won Kim[8], Jenny Yang[9], Diana Chen[9], Circe McDonald[9], Liao Zhang[9], Anuj Gaggar[9], Bing Gao[9], Kwan Soo Byun[10], Kwan Sik Lee[11], Hyung Joon Yim[12], Henry L.Y. Chan[13]. *[1]Asan Medical Center, University of Ulsan College of Medicine Seoul-Korea, Seoul, Korea, Rep. of South; [2]Alice Ho Miu Ling Nethersole Hospital, Hong Kong; [3]The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Rep. of South; [4]Kyungpook National University Hospital, Kyungpook National University School of Medicine, Korea, Rep. of South; [5]Yonsei University College of Medicine, Korea, Rep. of South; [6]Keimyung University Dong Sang Hospital, Korea, Rep. of South; [7]Princess Margaret Hospital, Hong Kong; [8]Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Korea, Rep. of South; [9]Gilead Sciences Inc., Foster City, United States; [10]Korea University College of Medicine, Korea University Guro Hospital, Korea, Rep. of South; [11]Gangnam Severance Hospital, Yonsei University College of Medicine, Korea, Rep. of South; [12]Korea University Ansan Hospital, Ansan-si, Gyeonggi-do-Korea, Korea, Rep. of South; [13]Prince of Wales Hospital, Hong Kong*
Email: jenny.yang@gilead.com

Background and aims: IRIG, RIG-I agonist, has demonstrated antiviral activity in CHB patients. The MOA of IRIG suggests a direct antiviral and an immune modulatory pathway. This study evaluated safety, efficacy, and PD activity of IRIG ≤400 mg ± TAF in CHB pts.
Method: IA CHB pts were enrolled into 4 cohorts: 48WK TAF alone or TAF+IRIG 50, 200, and 400 mg QD for 12WK; and virally suppressed (VS) cohort of 12WK IRIG 100 mg. Safety included AEs and lab abnormalities. Primary obj: %pts with HBsAg ≥-0.5 log10 IU/ml at WK12. Secondary obj: change from BL in immune PD biomarkers. Final WK48 data and immunological characterization of 400 mg cohort to be presented.
Results: 102 IA and 21 VS Asian CHB pts enrolled. Table shows BL and mean change at WK12 of viral markers. More TAF and IRIG 50 mg pts at BL had GT C (≥75%), higher HBV DNA and ALT vs IRIG 200 mg and 400 mg. No difference at WK12 in HBV DNA decline observed; TAF and IRIG 50 mg had numerically greater decline in HBsAg vs IRIG ≥200 mg. In VS pts, no change in HBsAg with IRIG 100 mg observed. Prelim WK12 safety showed, no G4 AEs; 3 IRIG and 1 TAF pts had G3 AEs. Majority of IRIG 400 mg pts had slight increase in ALT at WK16 (mean (SD) change in ALT = 9 (65) U/L); similar trends were not observed at lower doses. AEs reported by 41% (46/111) IRIG and 58% (7/12) TAF pts. Frequent (>1 pt) AE related to study drug were: ALT increase (n = 5), constipation, dizziness, and headache (n = 2 each) all in IRIG pts. PD analysis demonstrates minimal changes to ISG expression with IRIG 50 mg and 200 mg. Peripheral cytokine and HBV-specific T cell response was similar between TAF and IRIG 50 mg.
Conclusion: No dose dependent changes in HBV DNA or HBsAg were observed with IRIG ≤400 mg+NUC. IRIG was generally safe and well tolerated at doses ≤400 mg for 12WK. IRIG development has been discontinued due to IRIG-related hepatoxicity.

Table: (abstract: PO-2422):

	TAF (N = 12)	IRIG 50 mg (N = 30)	IRIG 200 mg (N = 30)	IRIG 400 mg (N = 30)	IRIG 100 mg VS Patients (N = 21)
HBV DNA, mean log10 IU/ml (range)	**7.1 (3.9–8.8)**	**7.1 (3.8–9.4)**	6.3 (3.5–8.8)	6.6 (3.7–9.2)	<1.3
HBsAg, mean log10 IU/ml (range)	4.1 (2.8–4.8)	3.9 (2.2–5.1)	3.4 (1.9–4.9)	3.5 (1.5–5.1)	3.2 (2.1–4.2)
ALT, mean U/ml (range)	**163 (48–630)**	**104 (31–439)**	74 (25–154)	73 (26–461)	23 (8–52)
Mean WK12 Change (range)					
HBV DNA, log10 IU/ml	−4.2 (−6.4, −2.6)	−4.2 (−6.4, −2.3)	−4.0 (−5.5, −1.7)	−3.9 (−6.1, −2.4)	N/A
HBsAg, log10 IU/ml	**−0.44 (−1.62, 0.02)**	**−0.24 (−0.96, 0.08)**	0.02 (−0.46, 1.02)	−0.03 (−0.86, 1.06)	−0.02 (−0.12, 0.06)
ALT, U/L	−117 (−611, 13)	−57 (−403, 160)	−38 (−135, 46)	−12 (−196, 47)	7 (−5, 50)

PO-2429

Safety and efficacy of oral TLR8 agonist, selgantolimod, in viremic adult patients with chronic hepatitis B

Harry L.A. Janssen[1], Young-Suk Lim[2], Hyung Joon Kim[3], Cheng-Hao Tseng[4], Carla S. Coffin[5], Magdy Elkashab[6], Sang Hoon Ahn[7], Anh-Hoa Nguyen[8], Diana Chen[8], Jeffrey Wallin[8], Susanna Tan[8], Jenny Yang[8], Anuj Gaggar[8], Diana Brainard[8], Scott Fung[1], Yoon Jun Kim[9], Jia-Horng Kao[10], Wan-Long Chuang[11], Anna Brooks[12,13], P. Rod Dunbar[12,13]. *[1]Toronto Centre for Liver Disease, Toronto General Hospital Research Institute, University Health Network, Canada; [2]Asan Medical Center, University of Ulsan College of Medicine, Korea, Rep. of South; [3]Chung-Ang University College of Medicine, Korea, Rep. of South; [4]E-Da Hospital, Taiwan; [5]University of Calgary, Cumming School of Medicine, Canada; [6]Toronto Liver Centre, Canada; [7]Yonsei University College of Medicine, Korea, Rep. of South; [8]Gilead Sciences Inc., Foster City, United States; [9]Seoul National University Hospital, Department of Internal Medicine and Liver Research Institute, Korea, Rep. of South; [10]National Taiwan University Hospital, Taiwan; [11]Kaohsiung Medical University Hospital, Taiwan; [12]School of Biological Sciences, University of Auckland, Auckland, New Zealand; [13]Maurice Wilkins Centre Auckland, University of Auckland, Auckland, New Zealand*
Email: harry.janssen@uhn.ca

Background and aims: Selgantolimod (GS-9688, SLGN) is an oral, Toll-like receptor 8 agonist in clinical development for the treatment of chronic hepatitis B (CHB). Here we present the results through week 48 on the safety and efficacy of 24 weeks of SLGN treatment in viremic CHB patients.
Method: In this multicenter, double-blind, phase 2 study, viremic CHB patients were randomized (2:2:1) to SLGN 3 mg, 1.5 mg, and placebo (PBO) once a week for 24 weeks in combination with tenofovir alafenamide. Safety assessments included monitoring of treatment emergent adverse events (TEAE) and laboratory abnormalities. The primary efficacy end point was the proportion of patients with ≥1 log_{10}IU/ml decline in HBsAg levels from baseline at week 24. Exploratory end points include changes in pharmacodynamic (PD) markers (e.g. IL-12p40 and IL-1RA) and changes in peripheral T- cell, myeloid and NK-cell subsets.
Results: 67 patients (39 HBeAg-positive) were randomized. Baseline characteristics were similar across groups: majority were Asian (98.5%), male (58%) with a median (IQR) age of 47 (35–54) years, HBsAg level of 4.1 (3.5–4.7) log_{10}IU/ml, and HBV DNA level of 7.5 (5.4–8.3) log_{10}IU/ml. No patients achieved the primary end point of ≥1 log_{10}IU/ml decline in HBsAg levels at week 24; however, 3 (6%) patients in the SLGN-treated achieved HBsAg decline ≥0.5 log_{10}IU/ml compared to none in the placebo group. At week 48, 4 (7.4%) patients