Results From a Phase 2a, Open-Label Study to Evaluate the Safety and Efficacy of Novel Combination Therapies Containing VIR-2218, Selgantolimod, and Nivolumab for the Treatment of Chronic Hepatitis B

1380

Grace Lai-Hung Wong[1], Seng Gee Lim[2], Kosh Agarwal[3], Anchalee Avihingsanon[4], Young-Suk Lim[5], Leonard Sowah[6], Ran Duan[6], Irina Botros[6], Savrina Manhas[6], Andre Arizpe[7], Daniel Cloutier[7], Frida Abramov[6], Audrey H Lau[6], Tawesak Tanwandee[8], Man-Fung Yuen[9], Edward J Gane[10]

[1]Medical Data Analytics Centre, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China; [2]National University Hospital (NUH), Singapore; [3]King's College Hospital, London, UK; [4]Thai Red Cross AIDS Research Centre (HIV-NAT), Bangkok, Thailand; [5]Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea; [6]Gilead Sciences, Inc., Foster City, CA, USA; [7]Vir Biotechnology Inc., San Francisco, CA, USA; [8]Siriraj Hospital, Bangkok, Thailand; [9]Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; [10]University of Auckland, Auckland, New Zealand

Conclusions

- Combinations of VIR-2218, nivolumab (NIVO), and selgantolimod for hepatitis B virus (HBV) functional cure led to low rates of hepatitis B surface antigen (HBsAg) loss in this trial
- The use of NIVO in this combination was associated with the emergence of immune-related adverse events and minimal therapeutic benefit in this population of patients with chronic HBV infection
- HBsAg decline was only observed in cohorts treated with VIR-2218 combinations, which suggests HBsAg decline may be primarily mediated by the mechanism of action of the small interfering RNA (siRNA)
- Biomarker analysis revealed minimal immunologic changes with siRNA lead-in, limited increases in HBV-specific T-cell responses, and expected pharmacodynamic responses of immune modulators (data not shown; see AASLD 2024 poster 1134)

Plain Language Summary

- Multiple approved treatment options for patients with chronic hepatitis B are available, but they rarely result in a cure
- Investigating drug combinations may uncover a successful cure in the future
- In this study, adding nivolumab, a drug that helps the immune system fight cancer, to 2 other drugs was associated with immune-related side effects and did not result in a substantial benefit for patients with chronic hepatitis B

References: **1.** World Health Organization. Hepatitis B fact sheet. 2024. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed Sep 9, 2024. **2.** Seto WK, et al. *Lancet*. 2018;392:2313-24. **3.** Kim G-A, et al. *Gut*. 2014;63:1325-32.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Allison Yankey, PhD, of Red Nucleus, and funded by Gilead Sciences, Inc.

Disclosures: **GLHW** has served as an advisory committee member for AstraZeneca; Gilead Sciences, Inc.; GSK; and Janssen; has served as a speaker for Abbott; AbbVie; Gilead Sciences, Inc.; and GSK; and has received a research grant from Gilead Sciences, Inc. **SGL** has served as an advisory committee member for Abbott; Aligos Therapeutics; Arbutus Biopharma; Assembly Biosciences; AusperBio; Gilead Sciences, Inc.; Grifols; GSK; Janssen; Roche; and Sysmex; has served as a speaker for Gilead Sciences, Inc.; GSK; Janssen; Roche; and Sysmex; has received research grants from Abbott; Fibronostics; Gilead Sciences, Inc.; and Sysmex; and owns stock in IRnovate. **KA** served as a speaker, consultant, and/or advisory board member for Aligos Therapeutics; Arbutus Biopharma; Assembly Biosciences; Boehringer Ingelheim; Bristol Myers Squibb; Drug Farm; Gilead Sciences, Inc.; GSK; Janssen; Roche; Sagimet Biosciences; and Swedish Orphan Biovitrum, and his institution received research support from Gilead Sciences, Inc. **AAv** reports research grants from Gilead Sciences, Inc.; Merck Sharp & Dohme; Roche; and ViiV Healthcare/GSK; and speaker fees from Abbott. **YSL** reports no conflicts of interest. **LS**, **RD**, **IB**, **SM**, **FA**, and **AHL** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **AAr** is an employee of Vir Biotechnology and reports owning stock. **DC** is a previous employee and shareholder of Vir Biotechnology and is an employee and shareholder of Revagenix. **TT** reports research grants from Altimmune; Gilead Sciences, Inc.; Merck Sharp & Dohme; and Roche. **MFY** received consulting or speaker fees from Abbott; AbbVie; Antios Therapeutics; Arbutus Biopharma; Arrowhead Pharmaceuticals; Assembly Biosciences; ClearB Therapeutics; Dicerna Pharmaceuticals; Finch Therapeutics; Fujirebio; Gilead Sciences, Inc.; GSK; Immunocore; Janssen; Precision BioSciences; Roche; Sysmex; Tune Therapeutics; Vir Biotechnology; and Visirna Therapeutics; and has served as an advisory committee member for Aligos Therapeutics and Suzhou Ribo Life Science. **EJG** served as an advisor for AbbVie; Aligos Therapeutics; Arbutus Biopharma; Gilead Sciences, Inc.; Janssen; Roche; Vir Biotechnology; and Virion Therapeutics.

Introduction

- Hepatitis B virus (HBV) infection affects 254 million individuals globally and is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) if not properly treated[1,2]
- Approved nucleos(t)ide analogues (NAs) suppress viral replication and improve liver outcomes, but functional cure with NAs alone is rare
  - — Patients who achieve functional cure have a lower risk for adverse liver outcomes and HCC[3]
  - — A functional cure is characterized by durable loss of all viral markers, which is maintained by the immune system
- Therapeutic combinations that reduce viral protein production and aim to reinvigorate the dysfunctional immune responses in people living with chronic hepatitis B (CHB) are needed
- Here, we present the follow-up week 24 (FU W24) results from an ongoing Phase 2a study evaluating novel combinations of 2 immunomodulators with or without VIR-2218, a small interfering RNA (siRNA) that targets the HBx region of the HBV genome, in virally suppressed and viremic individuals living with CHB:
  - — Nivolumab (NIVO), an anti–programmed cell death protein 1 monoclonal antibody to reduce T-cell exhaustion
  - — Selgantolimod (SLGN), a toll-like receptor 8 agonist to increase the production of antiviral cytokines such as tumor necrosis factor-α and interferon-γ

Objective

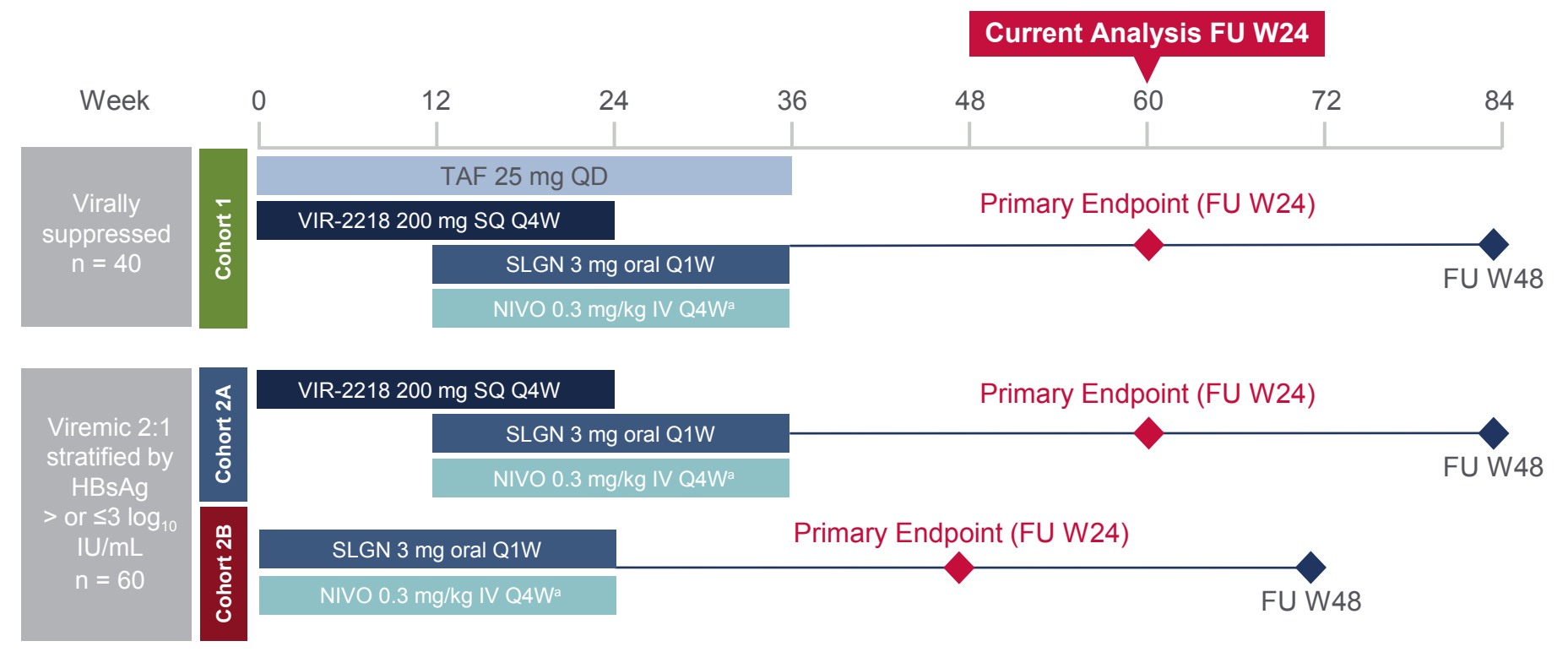
- To evaluate efficacy at FU W24 (primary endpoint) and safety outcomes of combination treatments including VIR-2218, NIVO, and SLGN in virally suppressed and viremic patients with CHB

Methods

Study Design

Key Inclusion Criteria

- Adult males and nonpregnant, nonlactating females, aged 18–65 years at screening
- Noncirrhotic
- Documented HBV with HBsAg >1.5 $\log_{10}$ IU/mL (~31.4 IU/mL)
- No history of autoimmune diseases with ANA <1:80, anti-SMA <1:80, AMA <1:40, and anti-TPO <35 IU/mL
- **For viremic cohorts** [2A and 2B]: HBV DNA >2000 IU/mL for HBeAg negative and >20,000 IU/mL for HBeAg positive



Per protocol amendment, patients in cohort 1 receiving TAF were allowed to continue TAF during the FU period; patients that had entered treatment-free FU were allowed to continue with or without NA treatment based on investigator discretion.

[a]NIVO was discontinued early in cohorts 1 and 2A, with the whole of cohort 2B (SLGN + NIVO) discontinued early due to a low likelihood of efficacy with SLGN alone.

AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; anti-SMA, anti–smooth muscle antibodies; anti-TPO, anti–thyroid peroxidase antibodies; FU, follow-up; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IV, intravenous; NA, nucleos(t)ide analogue; NIVO, nivolumab; Q1W, every 1 week; Q4W, every 4 weeks; QD, once daily; SLGN, selgantolimod; SQ, subcutaneous; TAF, tenofovir alafenamide; W, week.

- This open-label, Phase 2a study (GS-US-465-4439 [NCT04891770]) was designed to evaluate the safety and efficacy of combination treatment with siRNA and/or 2 immunomodulators, SLGN and NIVO, in viremic and virally suppressed patients with noncirrhotic CHB
- Primary endpoint:
  - — The proportion of patients who achieve functional cure, defined as hepatitis B surface antigen (HBsAg) loss and HBV DNA less than the lower limit of quantitation at FU W24
- Secondary and exploratory endpoints:
  - — The proportion of patients with HBsAg loss with and without anti-HBsAg seroconversion
  - — The proportion of patients with hepatitis B e antigen (HBeAg) loss with and without anti-HBeAg seroconversion
  - — The proportion of patients who remain off NA treatment during FU
- Safety was assessed throughout the study period, including cumulative adverse events (AEs), serious AEs, graded laboratory abnormalities, and alanine aminotransferase (ALT) flares (>2 × baseline and ≥5 × upper limit of normal) confirmed by 2 consecutive tests

Results

Baseline Demographic and Disease Characteristics

Patients		Cohort 1 TAF + VIR-2218 + SLGN + NIVO (Virally Suppressed) n = 42						Cohort 2A VIR-2218 + SLGN + NIVO (Viremic) n = 40						Cohort 2B SLGN + NIVO (Viremic) n = 20						Total N = 102					
Age, years, mean (range)		48 (32, 62)						42 (26, 61)						44 (26, 57)						45 (26, 62)					
Male		26 (62)						15 (38)						10 (50)						51 (50)					
Race																									
Asian		41 (98)						37 (93)						18 (90)						96 (94)					
Black or African American		1 (2)						2 (5)						0						3 (3)					
Other race		0						1 (3)						2 (10)						3 (3)					
BMI, kg/m², mean (SD)		24.3 (3.63)						23.6 (3.57)						24.4 (3.14)						24.1 (3.50)					
ALT, U/L, median (Q1, Q3)		22 (18, 30)						30 (18, 41)						37 (23, 55)						26 (18, 38)					
HBV DNA, $\log_{10}$ IU/mL, mean (SD)		1.29 (0.046)						5.90 (1.893)						5.76 (2.040)						3.97 (2.695)					
HBV DNA <LLOQ		41 (98)						0						0						41 (40)					
HBsAg, $\log_{10}$ IU/mL, mean (SD)		2.96 (1.044)						3.79 (0.658)						3.81 (0.801)						3.45 (0.950)					
HBsAg ($\log_{10}$ IU/mL) category	<2	6 (14)						0						0						6 (6)					
	≥2 to <3	10 (24)						6 (15)						3 (15)						19 (19)					
	≥3 to <4	22 (52)						19 (48)						9 (45)						50 (49)					
	≥4	4 (10)						15 (38)						8 (40)						27 (27)					
HBeAg positive		18 (43)						16 (40)						6 (30)						40 (39)					
HBV genotype (A; B; C; D, E; other[a])		1 (2)	6 (14)	22 (52)	2 (5)	0	11 (26)	0	14 (35)	21 (52)	1 (3)	2 (5)	2 (5)	0	3 (15)	14 (70)	1 (5)	0	2 (10)	1 (1)	23 (23)	57 (56)	4 (4)	2 (2)	15 (15)
FibroTest score ≤0.48[b]		39 (93)						36 (90)						19 (95)						94 (92)					

Data presented as n (%) unless otherwise indicated.

[a]Other includes quantity not sufficient, missing, or unclassified. [b]Suggestive of no or minimal fibrosis (ie, Metavir F0–F1; BioPredictive S.A.S, Paris, France).

ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NIVO, nivolumab; Q, quartile; SLGN, selgantolimod; TAF, tenofovir alafenamide.

NIVO Completion Disposition

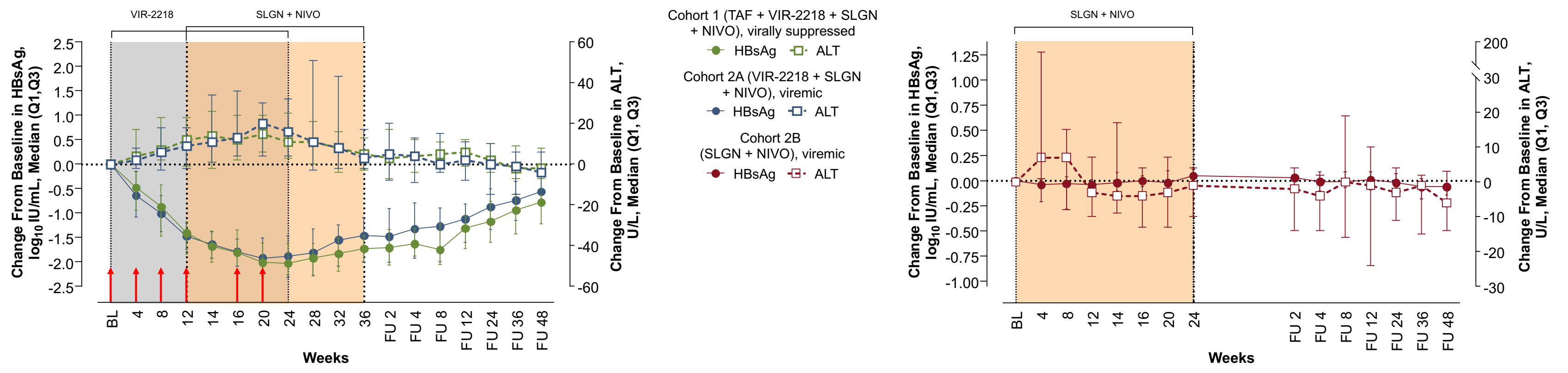
Patients	Cohort 1 TAF + VIR-2218 + SLGN + NIVO (Virally Suppressed) n = 42	Cohort 2A VIR-2218 + SLGN + NIVO (Viremic) n = 40	Cohort 2B SLGN + NIVO (Viremic) n = 20	Total N = 102
NIVO completion status, n (%)				
Not initiated	0	2 (5)	0	2 (2)
Completed	33 (79)	23 (58)	16 (80)	72 (71)
Premature discontinuation	9 (21)	15 (38)	4 (20)	28 (28)
Reason for NIVO premature discontinuation, n (%)				
AE	5 (12)	2 (5)	2 (10)	9 (9)
Discontinued based on sponsor decision	4 (10)	10 (25)	2 (10)	16 (16)
Patient decision	0	3 (8)	0	3 (3)

The denominator for the percentage calculation is the total number of patients in the safety analysis set corresponding to that column.

AE, adverse event; NIVO, nivolumab; SLGN, selgantolimod; TAF, tenofovir alafenamide.

- The change in HBsAg level during VIR-2218 treatment was similar in virally suppressed and viremic patients
- Through FU W24, no apparent additive effect of NIVO + SLGN and VIR-2218 on HBsAg kinetics was observed
- Off-treatment rebound of HBsAg was observed after cessation of siRNA
- Cohort 2B did not exhibit appreciable declines in HBsAg

Median (Q1, Q3) Change From Baseline in HBsAg ($\log_{10}$ IU/mL) and ALT (U/L)



ALT, alanine aminotransferase; BL, baseline; FU, follow-up; HBsAg, hepatitis B surface antigen; NIVO, nivolumab; Q, quartile; SLGN, selgantolimod; TAF, tenofovir alafenamide; W, week.

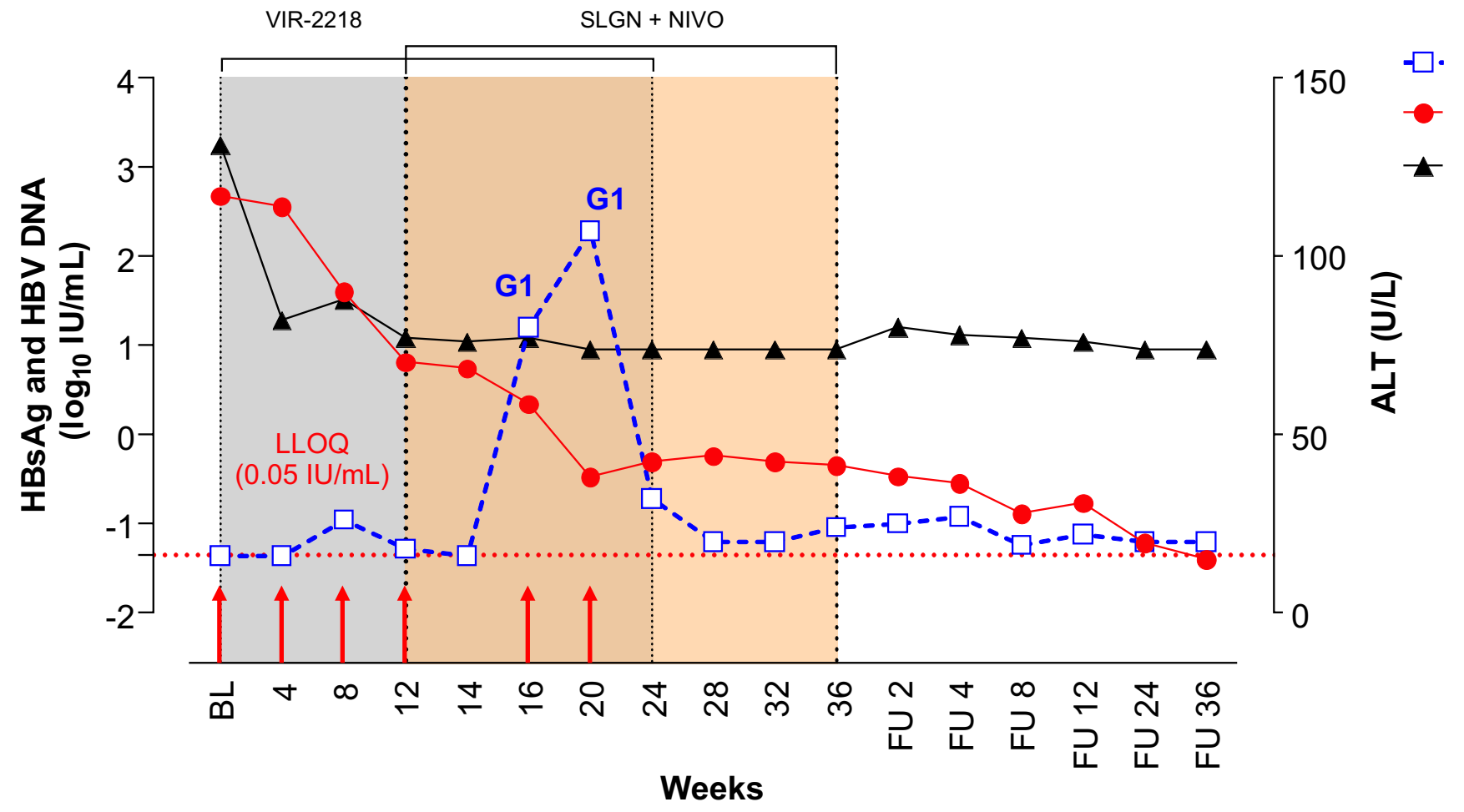
Virologic Outcomes at FU W24

Patients	Cohort 1 TAF + VIR-2218 + SLGN + NIVO (Virally Suppressed) n = 42	Cohort 2A VIR-2218 + SLGN + NIVO (Viremic) n = 40			Cohort 2B SLGN + NIVO (Viremic) n = 20			Total N = 102
		>3 $\log_{10}$ IU/mL (n = 34)	≤3 $\log_{10}$ IU/mL (n = 6)	Total (n = 40)	>3 $\log_{10}$ IU/mL (n = 17)	≤3 $\log_{10}$ IU/mL (n = 3)	Total (n = 20)	
HBsAg loss and HBV DNA <LLOQ,[a] n (%) (95% CI)	1 (2)[b] (0.1, 12.6)	0 (0.0, 10.3)	1 (17) (0.4, 64.1)	1 (3) (0.1, 13.2)	0	0	0	2 (2)[c] (0.2, 6.9)
HBsAg loss,[a] n (%) (95% CI)	2 (5)[b] (0.6, 16.2)	0 (0.0, 10.3)	1 (17) (0.4, 64.1)	1 (3) (0.1, 13.2)	0	0	0	3 (3) (0.6, 8.4)
HBeAg loss,[d] n/N (%)	1/18 (6)	2/16 (13)	0/0	2/16 (13)	0/6	0/0	0/0	3/40 (8)
HBV DNA <LLOQ,[e] n/N (%)	27/42 (64)	5/34 (15)	1/6 (17)	6/40 (15)	3/17 (18)	0/3	3/20 (15)	36/102 (35)
Patients who remain off NA treatment during follow-up,[e] n/N (%)	6/42 (14)	18/30 (60)	5/6 (83)	23/36 (64)	13/17 (76)	3/3 (100)	16/20 (80)	45/90 (46)

[a]No patient had anti-HBsAg seroconversion. [b]The 2 patients with HBsAg loss at FU W24 in cohort 1 were enrolled with screening HBsAg <1.5 $\log_{10}$ IU/mL and violated inclusion criteria. [c]Neither patient was treated with NAs at FU W24. [d]Includes only patients who were HBeAg positive at baseline. [e]Some cohort 1 patients stopped TAF at the end of study treatment at the investigator's discretion after meeting prespecified criteria. Some cohort 2 patients initiated NAs for safety reasons.

FU, follow-up; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NA, nucleos(t)ide analogue; NIVO, nivolumab; SLGN, selgantolimod; TAF, tenofovir alafenamide; W, week.

One Patient (Cohort 2A) Experienced HBsAg Loss per Protocol[a]



Patient Characteristics

- Asian female aged 39 years
- HBeAg negative, anti-HBeAg antibody positive
- Baseline HBsAg: 2.67 $\log_{10}$ IU/mL
- Baseline HBV DNA: 3.24 $\log_{10}$ IU/mL
- Genotype B
- Baseline ALT ≤ULN (16 U/L)
- Grade 1 ALT elevation after second dose of NIVO at W16 resolved by W24 visit
  - — HBsAg rapidly declined, became undetectable at FU W24, and was maintained at FU W36

[a]Two other patients (cohort 1) lost HBsAg; however, BL HBsAg levels violated I/E criteria #3 *"HBsAg >1.5 $\log_{10}$ IU/mL."*

ALT, alanine aminotransferase; BL, baseline; FU, follow-up; G1, Grade 1; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NIVO, nivolumab; SLGN, selgantolimod; ULN, upper limit of normal; W, week.

Overall Safety

Patients, n (%)	Cohort 1 TAF + VIR-2218 + SLGN + NIVO (Virally Suppressed) n = 42	Cohort 2A VIR-2218 + SLGN + NIVO (Viremic) n = 40	Cohort 2B SLGN + NIVO (Viremic) n = 20	Total N = 102
Any TEAE	39 (93)	40 (100)	19 (95)	98 (96)
TEAE related to study drug	29 (69)	30 (75)	15 (75)	74 (73)
TEAE Grade ≥3	5 (12)	11 (28)	7 (35)	23 (23)
TEAE Grade ≥3 related to study drug	2 (5)	5 (13)	5 (25)	12 (12)
TE SAE	2 (5)	5 (13)	3 (15)	10 (10)
TE SAE related to study drug	0	1 (3)	3 (15)	4 (4)
TEAE leading to d/c	7 (17)	6 (15)	2 (10)	15 (15)
AE leading to d/c of SLGN	5 (12)	5 (13)	1 (5)	11 (11)
AE leading to d/c of NIVO	5 (12)	2 (5)	2 (10)	9 (9)
AE leading to d/c of VIR-2218	0	0	N/A	0
Non-TEAE[a]	17 (41)	21 (53)	11 (55)	49 (48)
Non-TEAE Grade ≥3	2 (5)	6 (15)	1 (5)	9 (9)
Death	0	0	0	0

[a]Non-TEAEs are defined as any AEs with an onset date after the composite last on-treatment date + 30 days after permanent discontinuation of the study drug through the end of the study or the last available visit for those who were still in the study.

AE, adverse event; d/c, discontinuation; FU, follow-up; N/A, not applicable; NIVO, nivolumab; SAE, serious adverse event; SLGN, selgantolimod; TAF, tenofovir alafenamide; TE, treatment-emergent; TEAE, treatment-emergent adverse event; W, week.

Grade 3 or 4 Laboratory Abnormalities at FU W24, ≥2 Patients in Any Cohort

Patients, n (%)	Cohort 1 TAF + VIR-2218 + SLGN + NIVO (Virally Suppressed) n = 42	Cohort 2A VIR-2218 + SLGN + NIVO (Viremic) n = 40	Cohort 2B SLGN + NIVO (Viremic) n = 20	Total N = 102
Any Grade 3 or 4	10 (24)	21 (53)	13 (65)	44 (43)
ALT (increased)	1 (2)	13 (33)	7 (35)	21 (21)
AST (increased)	1 (2)	10 (25)	2 (10)	13 (13)
GGT (increased)	1 (2)	2 (5)	2 (10)	5 (5)
Creatine kinase (increased)	2 (5)	0	0	2 (2)
LDL (increased)	1 (2)	2 (5)	0	3 (3)
Lipase (increased)	1 (2)	2 (5)	2 (10)	5 (5)
Occult blood (urine)	4 (10)	5 (13)	2 (10)	11 (11)
Urine RBC	2 (5)	5 (13)	1 (5)	8 (8)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDL, low-density lipoprotein; NIVO, nivolumab; RBC, red blood cell; SLGN, selgantolimod; TAF, tenofovir alafenamide.

- Across all cohorts, 16 patients had a confirmed ALT flare through FU W24; no ALT flares were accompanied by evidence of hepatotoxicity or were associated with HBsAg decline
- Seven AEs were assessed by the investigator as immune-related AEs (irAEs) related to NIVO
- Given the emerging safety profile of repeated low doses of NIVO in this study population, NIVO was stopped early in this trial based on sponsor decision

Immune-Related Adverse Events Assessed as NIVO Related by Investigator

		Cohort 1 TAF + VIR-2218 + SLGN + NIVO (Virally Suppressed) n = 42	Cohort 2A VIR-2218 + SLGN + NIVO (Viremic) n = 40	Cohort 2B SLGN + NIVO (Viremic) n = 20	Total N = 102
Hypothyroidism	Nonserious, Grade 1–2	2 (5)	0	0	2 (2)
Thyroiditis	Nonserious, Grade 2	1 (2)	0	0	1 (1)
Psoriasis	Nonserious, Grade 2	0	0	1 (5)	1 (1)
Immune-mediated hepatitis	SAE, Grade 3	0	1 (3)	0	1 (1)
Optic neuropathy	Nonserious, Grade 1	0	0	1 (5)	1 (1)
Type 1 diabetes mellitus	SAE, Grade 3	0	0	1 (5)	1 (1)

NIVO, nivolumab; SAE, serious adverse event; SLGN, selgantolimod; TAF, tenofovir alafenamide.

- For further details on the irAEs from this Phase 2a study, see AASLD 2024 poster 1332