A Phase 1b, Open-Label Study to Evaluate the Safety and Efficacy of Novel Hepatitis B Virus Combination Therapies in Patients Living With Chronic Hepatitis B

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Conclusions

- Novel treatments and combinations (nivolumab [NIVO] only, NIVO + ledipasvir [LDV]/sofosbuvir [SOF], NIVO + selgantolimod [SLGN], and GS-4224 + SLGN) for hepatitis B virus cure in this trial were generally safe and well tolerated
- Two patients (n = 1, NIVO + LDV/SOF; n = 1, NIVO + SLGN) achieved a ≥0.5 $\log_{10}$ IU/mL decline from baseline in hepatitis B surface antigen (HBsAg) at follow-up week 8
- No patient experienced HBsAg loss
- Novel antiviral and immunological therapies are needed to achieve functional cure in a significant proportion of patients with CHB

Plain Language Summary

- There are multiple approved treatment options for patients with hepatitis B virus infection, but cure is rarely achieved
- This study evaluated several combinations of novel or approved agents to achieve functional cure of hepatitis B virus
- While these novel combinations were generally safe and well tolerated, no patients achieved functional cure

References: **1.** World Health Organization. Hepatitis B fact sheet. 2022. **2.** Seto WK, et al. *Lancet.* 2018;392:2313-24. **3.** Choi HSJ, et al. *Hepatol Commun.* 2022;6(5):935-49. **4.** Liu CJ, et al. *Clin Infect Dis.* 2022;75(3):453-9. **5.** Odegard JM, et al. *J Immunother Cancer.* 2024;12:e008547.

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Introduction

- Hepatitis B virus (HBV) infection affects 254 million individuals globally[1]
- Chronic HBV (CHB) infection is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma[2]
- Current treatments for CHB infection are effective at inhibiting viral replication but rarely achieve functional cure (sustained hepatitis B surface antigen [HBsAg] loss and HBV DNA suppression following a finite course of treatment)[3]
- A functional cure may require a combination treatment strategy that suppresses viral antigen production and stimulates host immunity[3]
  - Suppression of HBsAg was previously observed in patients with HBV/hepatitis C virus coinfection who were treated with ledipasvir (LDV)/sofosbuvir (SOF),[4] leading to its evaluation as a potential agent in combination therapies to achieve an HBV cure
- In addition to drugs that suppress viral antigens, agents that can potentially reinvigorate exhausted T cells, a key feature of CHB infection, and modulate innate immune responses were explored
  - Treatment with either GS-4224, a novel small-molecule inhibitor of programmed death ligand-1 (PD-L1), or nivolumab (NIVO), a monoclonal antibody against programmed cell death protein 1 (PD-1), was evaluated for safety and tolerability
  - To improve antiviral cytokine production, antigen presentation, and T-cell activation, selgantolimod (SLGN), a toll-like receptor 8 agonist, was evaluated

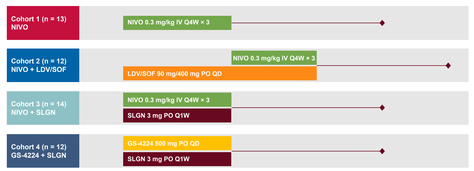
Objective

- To assess the safety and tolerability, along with the effect on peripheral cytokines and chemokines, of novel agents in combination regimens in patients with CHB

Methods

- This open-label, Phase 1b multicenter study (ACTRN12618001843246p; GS-US-493-5342) used the following agents in combination regimens in patients with CHB:
  - NIVO, an anti–PD-1 monoclonal antibody
  - SLGN, a toll-like receptor 8 agonist
  - GS-4224, a novel small-molecule PD-L1 inhibitor[5]
  - LDV/SOF, a potential suppressor of HBsAg production
- Hepatitis B e antigen-negative patients who were virologically suppressed on nucleos(t)ide analogues were enrolled into 4 cohorts

Study Design



IV, intravenous; LDV, ledipasvir; NIVO, nivolumab; PO, by mouth; Q1W, every 1 week; Q4W, every 4 weeks; QD, once daily; SLGN, selgantolimod; SOF, sofosbuvir.

- The primary efficacy endpoint was the proportion of patients with ≥0.5 $\log_{10}$ IU/mL decline in serum HBsAg from baseline to follow-up week 8 (FU W8)
- Safety, including adverse events (AEs), and laboratory parameters were assessed over the study period
- The V-Plex Plus Human Biomarker MSD multiplex assay was used to evaluate longitudinal serum concentrations for peripheral cytokines and chemokines

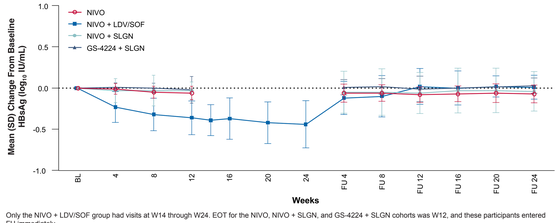
Results

Baseline Demographics and Disease Characteristics

Baseline Variables		NIVO n = 13	NIVO + LDV/SOF n = 12	NIVO + SLGN n = 14	GS-4224 + SLGN n = 12
Age, years, mean (range)		50 (36–65)	50 (33–62)	52 (39–64)	48 (38–65)
Sex, male, n (%)		9 (69)	10 (83)	11 (79)	11 (92)
Race, n (%)					
Asian		4 (31)	7 (58)	5 (36)	9 (75)
Native Hawaiian or Pacific Islander		4 (31)	3 (25)	8 (57)	2 (17)
White		4 (31)	1 (8)	0	1 (8)
Other		1 (8)	1 (8)	1 (7)	0
ALT, U/L, median (Q1, Q3)		23 (17, 25)	21 (19, 30)	20 (17, 24)	18 (15, 24)
HBV RNA, $\log_{10}$ copies/mL, mean (SD)		2.6 (0.5)	2.6 (0.3)	2.5 (0.1)	2.7 (0.5)
HBsAg, $\log_{10}$ IU/mL, mean (SD)		3.0 (1.1)	2.6 (0.7)	2.7 (0.8)	3.2 (0.6)
HBsAg, $\log_{10}$ IU/mL category, n (%)	<2	4 (31)	3 (25)	3 (21)	0
	≥2 to <3	1 (8)	6 (50)	3 (21)	4 (33)
	≥3 to <4	6 (46)	2 (17)	8 (57)	7 (58)
	≥4	2 (15)	1 (8)	0	1 (8)
HBeAg negative, n (%)		13 (100)	11 (92)	14 (100)	11 (92)

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LDV, ledipasvir; NIVO, nivolumab; Q, quartile; SLGN, selgantolimod; SOF, sofosbuvir.

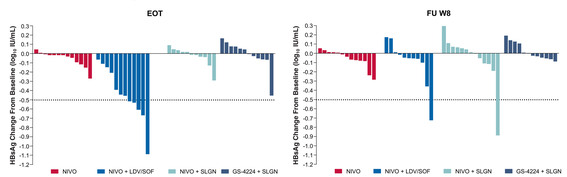
HBsAg Change From Baseline on Treatment and During FU



Only the NIVO + LDV/SOF group had visits at W14 through W24. EOT for the NIVO, NIVO + SLGN, and GS-4224 + SLGN cohorts was W12, and these participants entered FU immediately.
BL, baseline; EOT, end of treatment; FU, follow-up; HBsAg, hepatitis B surface antigen; LDV, ledipasvir; NIVO, nivolumab; SLGN, selgantolimod; SOF, sofosbuvir; W, week.

- No treatment group had a sustained decline in HBsAg
- The group receiving NIVO + LDV/SOF showed a modest HBsAg decline during treatment, but experienced a rebound during follow-up

Individual HBsAg Decline From Baseline

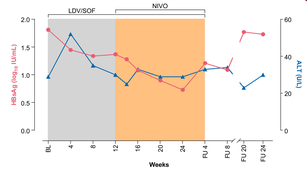


EOT, end of treatment; FU, follow-up; HBsAg, hepatitis B surface antigen; LDV, ledipasvir; NIVO, nivolumab; SLGN, selgantolimod; SOF, sofosbuvir; W, week.

- Two patients (1 each in the NIVO + LDV/SOF and NIVO + SLGN groups) experienced ≥0.5 $\log_{10}$ IU/mL decline from baseline in HBsAg at FU W8 (primary endpoint)
- No patient achieved HBsAg loss

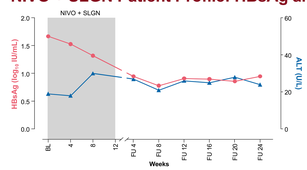
Two Patients With ≥0.5 $\log_{10}$ IU/mL Decline From Baseline in HBsAg at FU W8

NIVO + LDV/SOF Patient Profile: HBsAg and ALT Levels



Baseline:
- 50-year-old Asian male
- HBeAg negative/HBeAb positive
- HBsAg = 1.81 $\log_{10}$ IU/mL
- ALT = 29 U/L

NIVO + SLGN Patient Profile: HBsAg and ALT Levels



Baseline:
- 48-year-old Asian male
- HBeAg negative/HBeAb positive
- HBsAg = 1.67 $\log_{10}$ IU/mL
- ALT = 19 U/L

For the patient on NIVO + LDV/SOF (top), FU W12 and W16 data were unavailable due to missed or virtual visits; HBV DNA was TND at all visits. For the patient on NIVO + SLGN (bottom), W12 data were unavailable due to a COVID-19 virtual visit, and W16, W20, and W24 visits were not applicable; HBV DNA was <LLOQ at W4 and W8 and TND at BL and all FU visits.
ALT, alanine aminotransferase; BL, baseline; FU, follow-up; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LDV, ledipasvir; LLOQ, lower limit of quantitation; NIVO, nivolumab; SLGN, selgantolimod; SOF, sofosbuvir; TND, target not detected; W, week.

- One patient (NIVO + LDV/SOF; top) experienced an HBsAg decline during treatment, which was maintained through FU W8 with rebound observed at FU W24
- One patient (NIVO + SLGN; bottom) experienced an HBsAg decline during treatment, which was sustained through FU W24

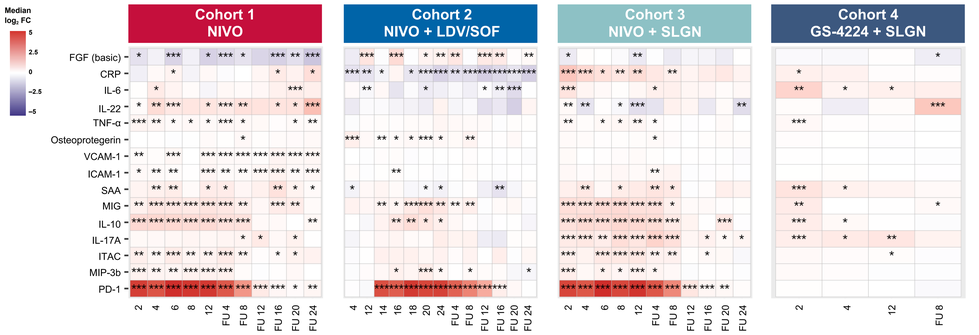
Safety Parameters

Patients, n (%)	NIVO n = 13	NIVO + LDV/SOF n = 12		NIVO + SLGN n = 14		GS-4224 + SLGN n = 12	
Any TEAE	12 (92)	10 (83)		13 (93)		9 (75)	
TEAE related to study drug	2 (15)	LDV/SOF	5 (42)	SLGN	5 (42)	SLGN	5 (42)
		NIVO	0	NIVO	4 (29)	GS-4224	7 (58)
TEAE Grade ≥3	0	0		0		1 (8)[a]	
TEAE Grade ≥3 related to study drug	0	0		0		0	
TE SAE	1 (8)	1 (8)		0		1 (8)	
TE SAE related to study drug	0	0		0		0	
TEAE leading to discontinuation							
SLGN	NA	NA		0		1 (8)[b]	
NIVO	0	0		0		NA	
GS-4224	NA	NA		NA		1 (8)[b]	
LDV/SOF	NA	0		NA		NA	
Death	0	0		0		0	

[a]Grade 3 anemia TEAE.
[b]One patient in the SLGN + GS-4224 group prematurely discontinued study treatment due to multiple gastrointestinal AEs (all Grade 1).
AE, adverse event; LDV, ledipasvir; NA, not applicable; NIVO, nivolumab; SAE, serious adverse event; SLGN, selgantolimod; SOF, sofosbuvir; TE, treatment emergent; TEAE, treatment-emergent adverse event.

- No patient experienced an immune-related AE related to NIVO

Induction of Peripheral Inflammatory Response With Combination Treatment



A paired Wilcoxon rank-sum test was used to test changes from baseline (day 1). *P <.05; ** P <.01; ***P <.001.
CRP, C-reactive protein; FC, fold change; FGF, fibroblast growth factor; FU, follow-up; ICAM, intercellular adhesion molecule; IL, interleukin; ITAC, interferon-inducible T-cell alpha chemoattractant; LDV, ledipasvir; MIG, monokine induced by interferon-gamma; MIP, molecularly imprinted polymer; NIVO, nivolumab; PD-1, programmed cell death protein 1; SAA, serum amyloid A; SLGN, selgantolimod; SOF, sofosbuvir; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; W, week.

- Peripheral inflammatory cytokines and chemokines were significantly elevated from baseline in all cohorts, notably MIG (CXCL-9) and ITAC (CXCL-11)
  - A sustained elevation over time of inflammatory cytokines and chemokines was observed for cohorts 1 (NIVO) and 3 (NIVO + SLGN)
- As expected, robust increases in soluble PD-1 were seen in all cohorts receiving NIVO treatment