Results of a Phase 1b, Open-label, Multicenter Study of Selgantolimod (GS-9688) in Special Populations of Patients With Chronic Hepatitis B

SAT-182

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Key Findings

- The majority of TEAEs were Grade 1 or 2, and no TEAEs led to premature SLGN discontinuation
- ALT elevations (predominantly Grade 1 or 2) occurred in a subset of patients
- No patients achieved ≥1 $\log_{10}$ IU/mL decline in HBsAg
- In the HBV/HDV cohort, 2 patients achieved a >0.5 $\log_{10}$ IU/mL decline in HDV RNA, with 1 patient achieving HDV RNA <LLOQ

Conclusions

In this Phase 1b study, SLGN was generally safe and well tolerated in 3 subpopulations with CHB (immunotolerant, inactive, and HBV/HDV)

No patient met the primary endpoint of ≥1 $\log_{10}$ IU/mL decline in HBsAg or >2 $\log_{10}$ IU/mL decline in HDV RNA at week 24

SLGN may have a modest effect on HDV RNA in a subset of HBV/HDV coinfected patients

References: **1.** World Health Organization. Hepatitis B. 2022. URL: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b; **2.** Amin OE, et al. *Hepatology*. 2021;74 (1):55-74; **3.** Ayithan N, et al. *Viruses*. 2021;13(12):2400; **4.** Gane EJ, et al. *J Hepatol*. 2023;78(3):513-523; **5.** Janssen HLA, et al. *J Hepatol*. 2021;75(Suppl 2):S757-S758.

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Introduction

- Globally, 296 million people are living with chronic hepatitis B (CHB) infection, making it the most prevalent viral hepatitis worldwide[1]
- Selgantolimod (SLGN; GS-9688) is a potent, selective, oral, small-molecule agonist of toll-like receptor 8 in clinical development for the treatment of CHB
- SLGN has the potential to induce intrahepatic hepatitis B virus (HBV) immunity through the migration, activation, and proliferation of intrahepatic $CD8^+$ T, B, natural killer, and mucosal-associated invariant T cells[2,3]
- In prior Phase 2 studies, oral SLGN was well tolerated in immune-active hepatitis B e antigen (HBeAg)-positive or -negative patients with CHB[4,5]

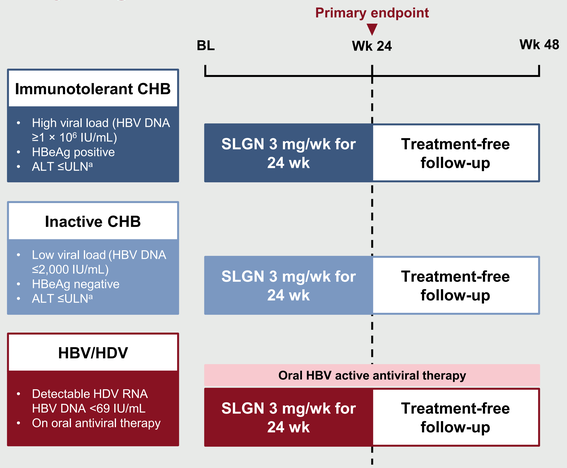
Objective

- To evaluate the safety and tolerability of multiple oral doses of SLGN at week 24 in 3 subpopulations of patients with CHB

Methods

- This Phase 1b open-label study assessed 3 subpopulations of adults with CHB

Study design



[a]AASLD criteria: an ULN for ALT of 35 U/L for males and 25 U/L for females. AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; BL, baseline; HBeAg, hepatitis B e antigen; ULN, upper limit of normal.

- Hepatitis B surface antigen (HBsAg) levels were determined by the ARCHITECT® i2000SR (Abbott)
  - Lower limit of detection (LLOD) is 0.026 IU/mL (reportable range 0.05–124,925.00 IU/mL)
- Hepatitis delta virus (HDV) RNA levels were determined by RT-qPCR using the RoboGene® HDV RNA Quantification Kit 2.0
  - Lower limit of quantification (LLOQ) and LLOD were 63 IU/mL and 14 IU/mL, respectively

Results

Baseline demographics and disease characteristics

	Immunotolerant CHB n = 5	Inactive CHB n = 14	HBV/HDV[a] n = 6
Age, years, median (range)	38 (20–55)	46 (36–64)	46 (35–64)
Male sex at birth, n (%)	2 (40)	7 (50)	5 (84)
Race, n (%)			
Asian	5 (100)	12 (86)	1 (17)
Black or African	0	1 (7.1)	4 (66.7)
White	0	1 (7.1)	1 (16.7)
FibroTest score, median (IQR)	0.1 (0.1, 0.1)	0.2 (0.1, 0.2)	0.5 (0.2, 0.8)
ALT, U/L, mean (SD)	20 (7.1)	22 (5.0)	56 (48.8)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	8.0 (0.9)	2.4 (0.8)	1.3 (0.0)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	NA	NA	3.5 (1.3)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	4.5 (0.5)	2.8 (0.9)	3.5 (1.2)
HBeAg positive, n (%)	5 (100)	0 (0)	0 (0)
HBV genotype, n (%)			
A	0	0	3 (50)
B	2 (40)	7 (50)	0
C	3 (60)	3 (22)	0
Other/unknown	0	4 (23)	3 (50)

[a]3/6 patients had HDV genotype 5 infection, and most patients (83%) were on entecavir-based regimens. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NA, not applicable.

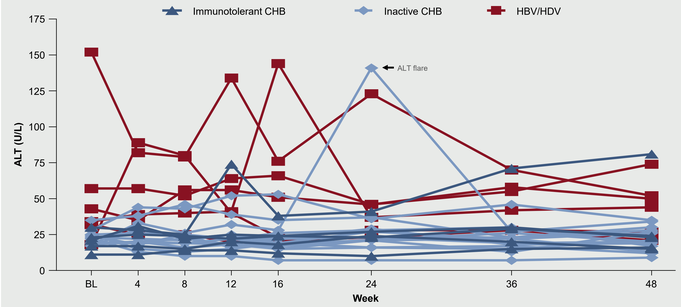
Overall safety

Patients, n (%)	Immunotolerant CHB n = 5	Inactive CHB n = 14	HBV/HDV n = 6
Any TEAE[a]	5 (100)	14 (100)	6 (100)
Grade 3 or 4 treatment-related TEAEs	0	0	1 (16.7)
Any SAE[b]	0	0	1 (16.7)
Treatment-related SAEs	0	0	1 (16.7)
TEAEs leading to premature discontinuation	0	0	0
Grade ≥1 lab abnormalities[c]	5 (100.0)	13 (92.9)	5 (83.3)
Grade 3 or 4 lab abnormalities	0	3 (21.4)	1 (16.7)

[a]TEAEs in >5% of patients included palpitations, nausea, vomiting, gastroesophageal reflex disorder, feeling cold, chills, headache, dizziness, insomnia, and cough. [b]Only SAE was Grade 4 nausea and vomiting requiring hospitalization and intravenous hydration in an HBV/HDV cohort patient. [c]No single lab abnormality occurred in more than 1 patient, including increased creatine kinase, increased lipase, hyponatremia, occult blood, and hematuria. AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

- No adverse event led to SLGN interruption or withdrawal

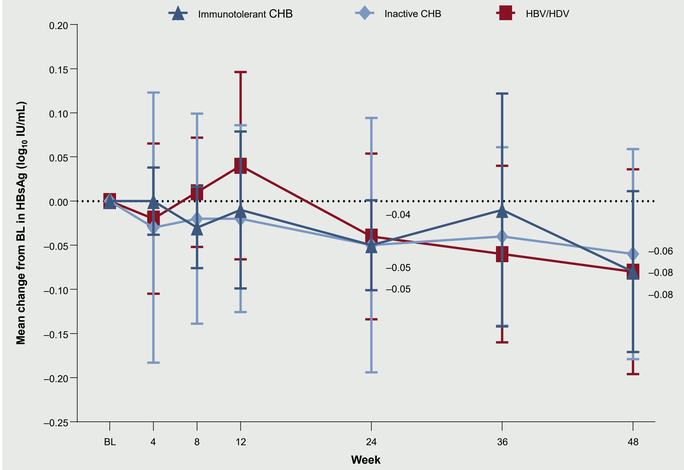
ALT levels over time



ALT elevations were based on Division of Aids AE criteria >1.25 × ULN. AE, adverse event; ALT, alanine aminotransferase; BL, baseline; ULN, upper limit of normal.

- All ALT elevations were Grade 1 or 2 across cohorts
- 8/25 (32%) patients had AASLD ALT elevations: 1 immunotolerant CHB, 3 inactive CHB, and 4 HBV/HDV
- 1 patient (see arrow) met ALT flare criteria per study protocol (ALT >2× BL and ≥5× ULN) in the setting of HBV reactivation (patient was not on HBV oral antiviral therapy). There were no signs of hepatic dysfunction and flare self-resolved without starting HBV oral antiviral therapy

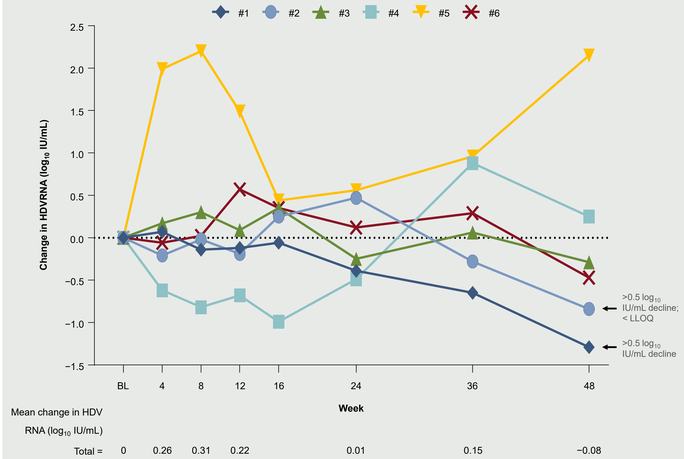
Mean HBsAg decline from baseline



BL, baseline; HBsAg, hepatitis B surface antigen.

- Modest declines in HBsAg levels were seen in all cohorts
- No patients met the primary endpoint of ≥1 $\log_{10}$ IU/mL decline in HBsAg

HDV RNA change from baseline



LLOQ is 1.14 $\log_{10}$ IU/mL. BL, baseline; LLOQ, lower limit of quantitation.

- Modest decline in HDV RNA was seen in some HBV/HDV patients over time
- 2 patients had >0.5 $\log_{10}$ IU/mL decline in HDV RNA (see arrows), 1 of whom had an HDV RNA <LLOQ at week 48