Safety and Efficacy of Oral TLR8 Agonist Selgantolimod in Viremic Adult Patients With Chronic Hepatitis B

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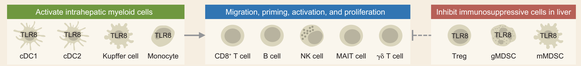
Introduction

- Selgantolimod (GS-9688; SLGN) is a potent, selective, oral, small-molecule agonist of toll-like receptor 8 (TLR8) in clinical development for the treatment of chronic hepatitis B (CHB)

SLGN Has Potential to Induce Intrahepatic HBV Immunity



CD8, cluster of differentiation-8; cDC, conventional (myeloid) dendritic cell; gMDSC, granulocytic myeloid-derived suppressor cell; HBV, hepatitis B virus; MAIT, mucosal-associated invariant T cell; mMDSC, monocytic MDSC; NK, natural killer; Treg, regulatory T cell.

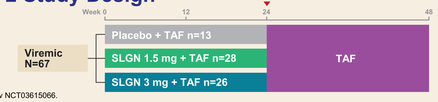
- SLGN has the potential to induce intrahepatic hepatitis B virus (HBV) immunity through the migration, activation, and proliferation of intrahepatic CD8+ T, B, NK, and MAIT cells[1]
- In a Phase 2 study of virally suppressed patients, oral SLGN was safe and well tolerated; 5% (2/39) achieved hepatitis B surface antigen (HBsAg) loss and 16% (3/19) achieved hepatitis B e antigen (HBeAg) loss by Week 48, while no placebo patients achieved HBsAg or HBeAg loss during the study[2]

Objectives

- To evaluate the safety and efficacy of 24 weeks of SLGN with tenofovir alafenamide (TAF) in viremic CHB patients through 48 weeks

Methods

Phase 2 Study Design*



*ClinicalTrials.gov NCT03615066.

- Phase 2, randomized, double-blind, placebo-controlled study
- Weekly, oral dosing of SLGN for 24 weeks with daily TAF, followed by TAF for an additional 24 weeks
- Primary endpoints:
  - Safety and tolerability of SLGN at Week 24
  - Proportion of patients with HBsAg decline ≥1 $\log_{10}$ IU/mL from baseline at Week 24
- Secondary and exploratory endpoints:
  - Proportions of patients with HBsAg and HBeAg loss through Week 48
  - Proportions of patients with HBV DNA <20 IU/mL through Week 48
  - Changes from baseline in quantitative HBeAg, hepatitis B core-related antigen (HBcrAg), and HBV RNA
  - Changes in pharmacodynamic marker (interleukin [IL]-12p40, IL-1-receptor antagonist [IL-1RA], and interferon [IFN]-γ) induction
  - Changes in immune cell population and cell phenotype in peripheral blood

Results

Baseline Demographics and Disease Characteristics

	TAF 25 mg +		
	Placebo n=13	SLGN 1.5 mg n=28	SLGN 3 mg n=26
Mean age, y (range)	46 (27–65)	44 (19–65)	46 (24–62)
Men, n (%)	9 (69)	15 (54)	15 (58)
Asian, n (%)	13 (100)	28 (100)	25 (96)
Mean FibroTest™* score (SD)	0.24 (0.2)	0.20 (0.2)	0.29 (0.2)
HBV GT, n (%)			
B	8 (67)	9 (36)	9 (39)
C	4 (33)	14 (56)	13 (57)
D	0 (0)	2 (8)	1 (4)
HBeAg-negative, n (%)	6 (46)	10 (36)	12 (46)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)†	6.8 (1.8)	7.0 (1.8)	6.5 (1.8)
Mean HBsAg, $\log_{10}$ IU/mL (SD)	4.0 (0.7)	4.2 (0.8)	3.8 (0.9)
Mean HBeAg, $\log_{10}$ IU/mL (SD)†	2.9 (0.4)	2.8 (0.4)	2.6 (0.8)
Mean HBV RNA, $\log_{10}$ IU/mL (SD)	5.6 (1.7)	5.8 (1.8)	5.2 (1.7)
Mean HBcrAg, $\log_{10}$ IU/mL (SD)	6.6 (2.2)	6.9 (2.3)	6.5 (2.1)
Mean ALT, U/L (SD)	34 (17)	42 (35)	56 (67)

*BioPredictive S.A.S, Paris, France; †HBV DNA <20 IU/mL (lower limit of quantitation) values were imputed as 1.3 $\log_{10}$ IU/mL; ‡HBeAg positive at baseline only. ALT, alanine aminotransferase; GT, genotype; SD, standard deviation.

Overall Safety

	TAF 25 mg +		
Patients, n (%)	Placebo n=13	SLGN 1.5 mg n=28	SLGN 3 mg n=26
TEAE	10 (77)	19 (68)	23 (89)
Grade ≥3 TEAE	1 (8)	0	0
Serious TEAE	0	0	1 (4)*
TEAE leading to premature discontinuation of SLGN	0	0	1 (4)†
TEAEs >10% of SLGN-treated patients by preferred term			
Nausea	0	6 (21)	8 (31)
Headache	2 (15)	5 (18)	3 (12)
Vomiting	0	3 (11)	6 (23)
Fatigue	0	3 (11)	5 (19)
Dizziness	0	1 (4)	5 (20)
Diarrhea	2 (15)	1 (4)	3 (12)
Nasopharyngitis	1 (8)	3 (11)	2 (8)
Upper abdominal pain	0	3 (11)	1 (4)
Chills	0	0	4 (15)
Palpitations	1 (8)	0	3 (12)
Pruritus	0	0	3 (12)
Urinary tract infection	0	3 (11)	0

*Serious treatment-emergent adverse event (TEAE) of Grade 1 limb injury not related to study treatment; †TEAE of vomiting and abdominal pain.

- SLGN was generally safe and well tolerated
- Nausea and vomiting occurred infrequently (1–3 episodes during treatment); most events were mild (Grade 1)

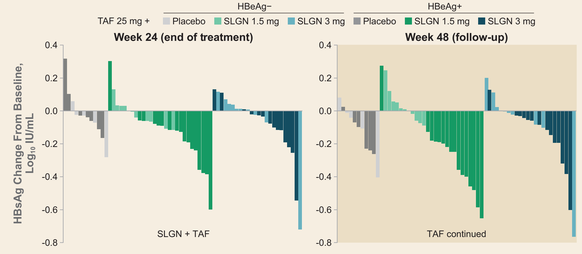
Mild ALT Elevations Seen With SLGN Treatment

	TAF 25 mg +								
	Placebo			SLGN 1.5 mg			SLGN 3 mg		
Patients, n or n/n (%)	HBeAg+ n=2	HBeAg− n=6	Total n=15	HBeAg+ n=18	HBeAg− n=10	Total n=28	HBeAg+ n=14	HBeAg− n=12	Total n=26
Any ALT elevation	1 (14)	1 (17)	2 (15)	4 (22)	1 (10)	5 (18)	1 (7)	2 (17)	3 (12)
≥2x baseline	1/1 (100)	1/1 (100)	2/2 (100)	3/4 (75)	0	3/5 (60)	1/1 (100)	0	1/3 (33)
≥2.5x–<5x ULN	0	0	0	1/4 (25)	1/1 (100)	2/5 (40)	1/1 (100)	1/2 (50)	2/3 (67)
≥5x ULN	0	0	0	0	0	0	0	1/2 (50)*	1/3 (33)

*Baseline ALT of 342 IU/mL; peak ALT of 380 IU/mL at Week 2. ULN, upper limit of normal.

- No patient met ALT flare criteria (ALT >2x baseline and ≥5x ULN)

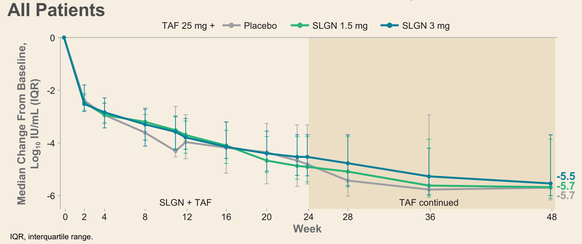
Individual HBsAg Changes From Baseline at Weeks 24 and 48



- No patient achieved the primary endpoint of HBsAg decline ≥1 $\log_{10}$ IU/mL at Week 48
- HBsAg decline ≥0.5 $\log_{10}$ IU/mL was observed only in SLGN-treated patients; at Week 48, 4 patients (7%) treated with SLGN vs 0 in the placebo group achieved HBsAg decline ≥0.5 $\log_{10}$ IU/mL
- In SLGN-treated patients, HBsAg declines were sustained or continued to decline during the 24 weeks of follow-up
- No patients achieved HBsAg or HBeAg loss through Week 48

Declines in HBV DNA Levels Over Time by Treatment

All Patients

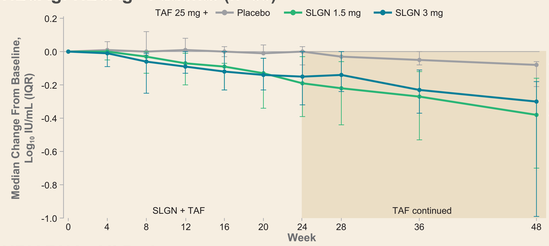


IQR, interquartile range.

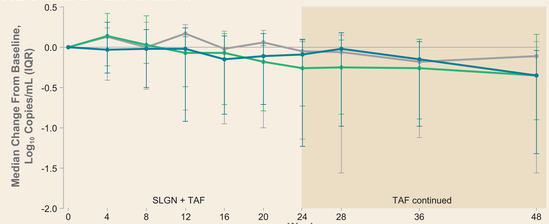
- The proportions of patients with HBV DNA <20 IU/mL were similar between groups (SLGN 3 mg: 50%; SLGN 1.5 mg: 44%; and placebo: 46%) at Week 48

Declines in HBeAg, HBV RNA, and HBcrAg Levels Over Time With SLGN

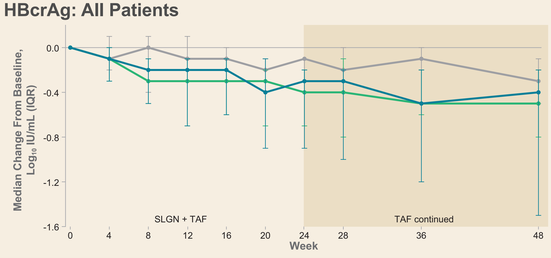
HBeAg: HBeAg+ Patients (n=39)



HBV RNA: All Patients



HBcrAg: All Patients



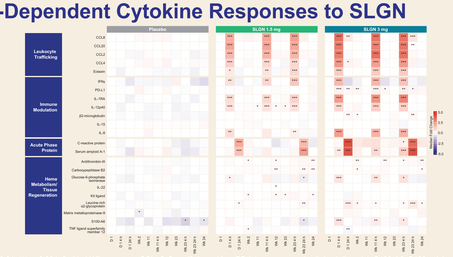
- HBeAg, HBV RNA, and HBcrAg declines to Week 48 were similar between SLGN-treated groups and placebo

HBeAg, HBV RNA, and HBcrAg Declines in HBeAg+ Patients: Week 48

	TAF 25 mg +	
Patients, n/n (%)	Placebo	SLGN Total
HBeAg decline ≥0.5 $\log_{10}$ IU/mL	0/6	5/31 (16)
HBV RNA decline ≥1.0 $\log_{10}$ copies/mL	0/6	6/31 (19)
HBcrAg decline ≥1.0 $\log_{10}$ IU/mL	0/6	6/31 (19)

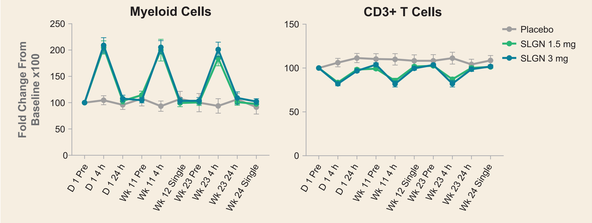
- Among HBeAg+ patients, a greater proportion in the SLGN-treated groups achieved declines in HBeAg, HBV RNA, and HBcrAg

Dose-Dependent Cytokine Responses to SLGN



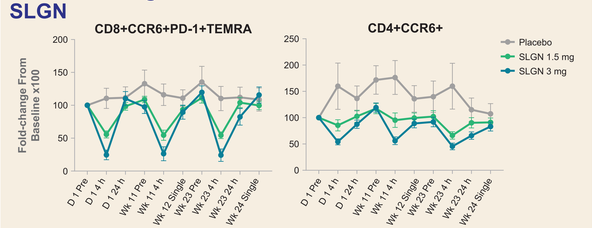
*p <0.05; **p <0.01; ***p <0.001; 2-sided Wilcoxon test. CCL, C-C motif chemokine; PD-L1, programmed cell death ligand 1; S100-A6, S100 calcium binding protein A6; TNF, tumor necrosis factor.

Redistribution of Immune-Cell Population in Peripheral Blood With SLGN



- Most SLGN-treated patients demonstrated loss of CD3+ lymphocytes from the circulation 4 hours after dosing, which resulted in apparent shifts in myeloid-cell populations
- B-cell populations did not display any notable redistributions following dosing

Profound Marginalization of CCR6+ T-Cell Subsets With SLGN



CCR6, chemokine receptor-6; PD-1, programmed death 1; TEMRA, terminally differentiated effector memory T cells.

- Some immune populations such as CCR6+PD-1+CD8 TEMRA and CCR6+ CD4 T-cell subsets exhibited profound marginalization at each 4-hour dose

Summary

- SLGN induced cytokines and chemokines important for the expansion and activity of multiple T-cell subsets, and innate immunity in viremic CHB patients
- No tachyphylaxis in immune response to SLGN was observed with weekly dosing
- Declines in immune-cell subsets in the circulation 4 hours after dosing were observed concurrently with increases in IL-12p40 and IL-1RA; these parameters reverted to baseline values at 24 hours postdosing
- The data suggest SLGN induces rapid redistribution of immune-cell subsets from the circulation, possibly into the liver or other tissues

Conclusions

- Oral SLGN up to 3 mg once weekly for 24 weeks was safe and well tolerated
- SLGN + TAF induced sustained HBsAg declines ≥0.5 $\log_{10}$ IU/mL in some patients out to Week 48
- Similar to data observed in virally suppressed CHB patients,[2,3] greater HBsAg declines were observed with SLGN vs placebo in viremic CHB patients; HBsAg levels were sustained or continued to decline during the 24 weeks of follow-up
- SLGN also induced cytokines important for the expansion and activity of multiple T-cell subsets, and innate immunity in viremic CHB patients[4,5]
- Further evaluation of SLGN in combination with novel immunomodulatory and antiviral agents is planned

References: **1.** Amin OE, et al. Hepatology 2020 Dec 25; **2.** Gane E, et al. AASLD 2019, poster 697; **3.** Gane E, et al. EASL 2020, abstr 71; **4.** Chen DY, et al. AASLD 2020, poster 0721; **5.** Chen DY, et al. EASL 2020, poster FRI350. **Acknowledgments:** We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc.

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