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Safety, pharmacokinetics, and pharmacodynamics of the oral TLR8 agonist selgantolimod in chronic hepatitis B

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Abbreviations: CCL, chemokine ligand; CD8+, cluster of differentiation 8 positive; CHB, chronic hepatitis B; CRP, C-reactive protein; CXCL, C-X-C motif chemokine ligand; HBeAg, hepatitis B e antigen, HBsAg, hepatitis B virus S antigen; HBV, hepatitis B virus; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; OAV, oral antiviral; PD, pharmacodynamic; PK, pharmacokinetic; PTM, placebo-to-match; SAA, serum amyloid A; TLR, toll-like receptor

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Abstract [252/275 words]

Background & Aims: In patients with chronic hepatitis B (CHB) infection, activation of toll-like receptor 8 (TLR8) may induce antiviral immunity and drive functional cure. Selgantolimod, a novel TLR8 agonist, was evaluated in CHB patients who were virally suppressed on oral antiviral treatment (OAV) or viremic not on OAV.

Approach & Results: In this Phase 1b study, patients were randomized 4:1 to receive either selgantolimod or placebo once-weekly. Virally suppressed patients received either 1.5 mg (for two weeks) or 3 mg (for two weeks or four weeks). Viremic patients received 3 mg for two weeks. The primary endpoint was safety as assessed by adverse events (AEs), laboratory abnormalities, and vital sign examination. Pharmacokinetic and pharmacodynamic parameters were assessed by plasma analysis. A total of 38 patients (28 virally suppressed, 10 viremic) were enrolled from 6 sites in Australia, New Zealand, and South Korea. Twenty patients (53%) experienced an AE and 32 (84%) had laboratory abnormalities, all of which were mild or moderate in severity. The most common AEs were headache (32%), nausea (24%) and dizziness (13%). With a half-life of 5 hours, no accumulation of selgantolimod was observed with multiple-dosing. Selgantolimod induced transient dose-dependent increases in serum cytokines, including IL-12p40 and IL-1RA, that are important for the expansion and activity of multiple T-cell subsets and innate immunity.

Conclusion: Selgantolimod was safe and well-tolerated in virally suppressed and viremic CHB patients and elicited cytokine responses consistent with target engagement. Further studies with longer durations of selgantolimod treatment are required to evaluate efficacy.

INTRODUCTION

Chronic hepatitis B (CHB) is one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma and represents a global public health concern. Nucleos(t)ide analogs are the current standard-of-care for CHB, and long-term treatment provides durable suppression of viral replication that results in clinical benefits and reduced risk of liver complications (1-3). However, treatment with nucleos(t)ide analogs rarely results in clearance of hepatitis B virus S antigen (HBsAg) and seroconversion to anti-HBsAg (4), the accepted functional cure of CHB that allows for cessation of therapy (5-9). New treatment options that enhance rates of HBsAg

clearance and seroconversion will allow patients to discontinue life-long oral antiviral therapy and provide finite-duration treatment to attain functional cure.

Toll-like receptors (TLRs) are a family of membrane-bound pattern recognition receptors that play a central role in both innate and adaptive immunity by recognition of pathogen-associated molecular patterns from microorganisms (10). TLR8, a transmembrane receptor located in the endosomal membrane of a subset of immune cells that recognizes single-strand RNA, activates effector cell immune responses (11-16). Activation of TLR8 by a selective, small-molecule agonist may induce antiviral immunity in CHB patients and drive functional cure.

Selgantolimod (formerly GS-9688) is a potent, selective, oral, small-molecule agonist of TLR8. In vitro, selgantolimod induced the cellular immune mediators interleukin (IL)-12 and IL-18 and the antiviral cytokines tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) in human peripheral blood mononuclear cells (17). Additionally, selgantolimod activated natural-killer cells and mucosal-associated invariant T cells, stimulated cluster of differentiation 8 positive (CD8+) T-cell proliferation, and increased IFN-γ production, while reducing expression of the inhibitory receptor programmed cell death protein 1 by hepatitis B virus (HBV)-specific CD8+ T cells. In HBV-infected primary human hepatocytes, selgantolimod-induced cytokines reduced HBV DNA, RNA, and antigen levels. In vivo, once-weekly dosing of oral selgantolimod induced dose-dependent increases in serum IL-12p40 and IL-1 receptor antagonist (IL-1RA) in cynomolgus monkeys and induced functional cure in 40% of animals in the woodchuck model of CHB. In healthy volunteers, selgantolimod also induced a dose-dependent elevation of serum IL-12p40 and IL-1RA which reached maximum levels at 4 h post dosing and returned to baseline by 24 h (18). These data suggest that immunity induced by activation of TLR8 with selgantolimod may have the potential to suppress HBV. Here, we describe the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles of selgantolimod following multiple-dose administration to virally suppressed and viremic patients with CHB.

METHODS

Study Design & Patients

This was a Phase 1b, randomized, blinded, placebo-controlled, multicenter study (Australian New Zealand Clinical Trials Registry, ACTRN Identifier: 12617000235303) evaluating selgantolimod in patients with CHB. Patients were enrolled into 1 prespecified and 3 adaptive cohorts with dosing governed by review of safety, pharmacokinetic, and pharmacodynamic data: 1) Cohort 1: virally suppressed patients who received once weekly selgantolimod 1.5 mg or placebo-to-match (PTM) for two weeks, 2) Cohort 2: virally suppressed patients who received once weekly selgantolimod 3 mg or PTM for two weeks, 3) Cohort 4: viremic patients who received once weekly selgantolimod 3 mg or PTM for two weeks, and 4) Cohort 5: virally suppressed patients who received once weekly selgantolimod 3 mg or PTM for four weeks (**Table 1**). Two additional adaptive cohorts (Cohorts 3 and 6) were prespecified to study higher doses of selgantolimod up to 30 mg but were not enrolled based on safety, pharmacokinetic, and pharmacodynamic data from the Phase 1a study of selgantolimod (Australian New Zealand Clinical Trials Registry, ACTRN Identifier: 12616001646437).

All the treatments were administered in the fasted state. Virally suppressed patients who were on prescribed HBV OAV therapy continued their treatment for the entire duration of study. Post-treatment follow-up visits were conducted 28 days after the patients received their last selgantolimod dose.

Patients were 18 to 65 years of age with documented evidence of chronic HBV infection (HBsAg positive for > 6 months with detectable HBsAg). Virally suppressed patients had HBV DNA < 20 IU/mL and were on stable oral antiviral treatment (OAV) for ≥ 3 months; viremic patients had HBV DNA ≥ 2000 IU/mL and had not received antiviral treatment for HBV for ≥ 3 months. Patients with extensive bridging fibrosis or cirrhosis (defined clinically, by imaging, Metavir ≥3 or Ishak ≥4 by a liver biopsy within 5 years, FibroTest score >0.48 and APRI >1, or a historic FibroScan >9 kPa within the last 6 months), hepatocellular carcinoma, HIV/HCV/HDV coinfection, malignancy, autoimmune disease, or who received prolonged therapy with immunomodulators or biologics within 3 months of screening were not eligible for participation. Complete inclusion and exclusion criteria are provided in the **Supplemental Appendix**. Eligible patients were randomized 4:4:1 to receive selgantolimod 1.5 mg, 3 mg, or PTM oral tablets.

The study could be stopped due to safety concerns following a review of available data if, in three or more patients of any cohort, the same or similar Grade 3 or 4 treatment-emergent adverse event or laboratory abnormality occurred without clear physiologic explanation.

The study protocol was approved by the review board or ethics committee for each study site prior to study initiation. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to undergoing any study procedures.

Safety Evaluations

Safety assessments included monitoring of adverse events, clinical laboratory tests, 12-lead electrocardiograms, vital sign measurements, and physical examinations. Ophthalmic examinations were also included as a precaution based on preclinical studies of selgantolimod in monkeys. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 21.0.

Pharmacokinetics and Pharmacodynamics Evaluations

To assess pharmacokinetic (PK) and pharmacodynamic (PD) parameters of selgantolimod, blood samples were collected over a 24-hour period on dosing Days 1 and 8 (i.e., at predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, and 24 hours postdose relative to selgantolimod dosing). Plasma concentrations of selgantolimod were analyzed by using a fully validated high-performance liquid chromatography-tandem mass spectroscopy method (Frontage Laboratories, Incl, Exton, PA, USA). Non-compartmental analysis of individual plasma concentration-time data was performed using Phoenix WinNonlin 6.4 (Princeton, NJ, USA).

Blood samples collected on Days 1, 2, 4, 8, 9, 11, and 15 (and Days 22, 23, and 29 for patients in Cohort 5) were used to determine serum concentrations of IL-12p40, IL-1RA (Covance Central Laboratory, Indianapolis, IN, USA) for pharmacodynamic analyses. IL-12p40 and IL-1RA concentration ratios (i.e., postbaseline value / baseline value) were evaluated at each time point The serum levels of additional cytokines (IL-12p70, IFN-γ and TNF-α), chemokines (C-C motif chemokine ligand [CCL] 2 [MCP-1], CCL4 [MIP-1β], CCL8 [MCP-2], CCL11 [Eotaxin-1],

CCL20 [MIP-3α] C-X-C motif chemokine ligand [CXCL] 8 [IL-8], CXCL9 [MIG], and CXCL10 [IP-10]), and acute phase proteins (C-reactive protein [CRP] and serum amyloid A [SAA]) were also analyzed across longitudinal samples using standard Myriad RBM multiplex cytokine panels.

Efficacy Evaluations

Efficacy of selgantolimod on HBV in CHB subjects was evaluated as the proportion change from baseline in serum HBsAg levels. Changes in baseline HBV DNA levels were also assessed in viremic patients. Blood samples were collected on Days 1, 4, 8, 15, 22, and 36 (and Days 29 and 50 for patients in Cohort 5) to determine HBsAg and HBV DNA levels. Serum levels of HBsAg were quantified using the Architect HBsAg Assay (Abbott Laboratories, Abbott Park, IL, USA) and HBV DNA levels with the COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0 assay (Roche Diagnostics, Mannheim, Germany).

Endpoints

The primary endpoint was the safety and tolerability of selgantolimod as assessed by the incidences of adverse events, laboratory abnormalities, vital sign assessments, and ECG measurements. Secondary endpoints were the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} of selgantolimod. Exploratory endpoints included the change from baseline in HBsAg log10 IU/mL, PD and biomarker levels of selgantolimod, immunologic changes after treatment, and changes in viral parameters.

Statistical Analysis

A sample size of approximately 60 patients in 6 cohorts was selected to provide adequate characterization of the safety profile and descriptive PK and PD analyses. Cohorts 3 and 6, which included evaluations of higher doses up to 30 mg, were not initiated based on a review of available safety, PK, and PD data. All patients randomized into the study who received at least one dose of study drug were included in the safety and efficacy analyses. Patients who also had at least 1 evaluable postdose concentration value available for each analyte were included in the PK analysis, and those with at least one evaluable PD value were included in the PD analysis.

Safety, efficacy, and plasma PK concentrations and parameters were summarized descriptively. Dose proportionality was assessed across evaluated dose levels by an analysis of variance (ANOVA) model based on AUC_{last}, AUC_{inf}, and C_{max} values obtained on Day 1 compared with Day 8 applying dose as a fixed effect (PK parameters were dose-normalized to 1.5 mg).

Results

Baseline Characteristics

Fifty-three patients with CHB were screened from May 2, 2017 to May 28, 2018 at 6 sites in Australia, New Zealand, and South Korea. Thirty-eight patients were randomized and received study treatment, including 28 (74%) virally suppressed patients and 10 (26%) viremic patients (**Supplemental Figure 1**). Of the 15 patients who were screened and not enrolled, 12 patients did not meet eligibility criteria, and 3 patients met the eligibility criteria but withdrew consent for study participation. Patient demographics were similar for patients in the virally suppressed and viremic treatment groups (**Table 2**). The median age of patients was 48 years (range 30 – 63 years), 79% of patients were male, 79% were Asian, and 32% were hepatitis B e antigen (HBeAg) positive. The majority of patients (53%) were infected via vertical transmission, and 42% of patients had an unknown mode of HBV infection.

All enrolled patients completed study treatment. Baseline levels of serum HBsAg were comparable across virally suppressed and viremic patients. With the exception of 1 patient with a plasma HBV DNA level of 1.32 $\log_{10}$ IU/mL at baseline, all virally suppressed patients had baseline HBV DNA levels less than the lower limit of quantitation. All viremic patients with available HBV genotype data had genotype C virus (**Table 2**).

Safety

Selgantolimod was well-tolerated at the evaluated dose levels. No notable abnormalities in vital signs, electrocardiograms, or ophthalmic examinations were reported for any patient, and there were no serious adverse events, discontinuations due to adverse events, or deaths during the study. Twenty patients (53%) experienced an adverse event. All adverse events were mild or moderate in severity. Rates of adverse events were higher in the selgantolimod 3 mg groups compared with the selgantolimod 1.5 mg and placebo groups. The most common adverse events

(reported for at least 2 patients in any treatment group) were headache (32% of patients), nausea (24%), dizziness (13%), chills (8%), decreased appetite (5%), and pyrexia (5%) (**Table 3**).

Thirty-two patients (84%) had at least 1 treatment-emergent laboratory abnormality. Fourteen patients (37%) had a Grade 2 laboratory abnormality, all of which were transient, and none were associated with adverse events. The only Grade 2 laboratory abnormalities reported for more than 1 patient in any treatment group were increased low-density lipoprotein cholesterol (5 patients, 13%) and increased serum glucose (5 patients, 13%).

Pharmacokinetics

Pharmacokinetic data from 31 selgantolimod-treated patients were evaluated. Selgantolimod exhibited rapid absorption following single- or multiple-dose oral administration of selgantolimod 1.5- or 3-mg on Day 1 and Day 8 in all treatment groups. The median times at which peak selgantolimod plasma concentration was achieved (T_{max}) ranged from 0.38 hours to 1.00 hour postdose on Day 1 and was 0.5 hours postdose on Day 8. The median selgantolimod half-life ($t_{1/2}$) was approximately 5 hours across treatment groups on Day 1 and Day 8 **(Figure 1** and **Table 4)**. Detectable concentrations were observed at 24 hours postdose in all but 2 patients (95%). Across all treatment groups, dose levels, and dosing day, selgantolimod PK parameter estimates were fairly variable due to interpatient variability and ranged from 36% to 77% coefficient of variance for AUC and 32% to 132% coefficient of variance for C_{max}.

Although the mean concentrations in the virally suppressed patients receiving 2 weekly doses of 3 mg were on an average lower compared with the other two cohorts receiving 3 mg doses, this difference in mean exposure was driven by outliers in each cohort. As such, selgantolimod PK was generally comparable in virally suppressed and viremic subjects with CHB. Consistent with the half-life of selgantolimod, no clinically relevant changes in PK parameters were observed after repeated dosing as reflected by the observed accumulation ratios.

A dose proportionality assessment with pooled data for the 3 mg treatment groups demonstrated that selgantolimod exposure, measured by AUC_{last}, AUC_{inf}, and C_{max}, increased in an approximately dose-proportional manner in virally suppressed and viremic patients who received selgantolimod 1.5 or 3 mg on Days 1 and 8.

Pharmacodynamics

The biological activity of selgantolimod was evaluated by serum concentrations of IL-12p40 and IL-1RA, immunomodulatory cytokines that are upregulated by TLR8 activation. Across treatment groups, peak concentrations of IL-12p40 and IL-1RA occurred approximately 4 hours after each dose of selgantolimod and decreased to near predose levels by the 24-h timepoint, with higher serum concentration ratios observed following selgantolimod 3 mg compared with selgantolimod 1.5 mg (**Figure 2**). The magnitude of IL-12p40 and IL-1RA PD responses were similar for successive doses, indicating a lack of tachyphylaxis.

To further explore the breadth of the PD response, we measured serum levels of a broader panel of cytokines, chemokines and acute phase proteins (**Figure 3, Supplemental Table 1, and Supplemental Figures 2-16**). There was a clear selgantolimod dose-dependent increase in the median fold changes from baseline in serum concentration of IL-12p70, IFN-γ, CCL2, CCL4, CCL8, CCL11, CCL20, CXCL8, CXCL9, CXCL10, CRP and SAA . Notably, the kinetics of induction varied across this panel of biomarkers. The maximum fold change from baseline for most biomarkers, including IL-12p70, IFN-γ, CCL2, CCL4, CCL8, CCL11, CCL20, CXCL8, IL1RA and CXCL10, peaked at 4-h postdose. In contrast, CXCL9 reached a maximal induction at 8-h postdose. Finally, the acute phase proteins CRP and SAA exhibited a substantially distinct profile and reached maximum levels at 24-h postdose. No significant differences were detected in cytokines at baseline or on-treatment between virally suppressed and viremic subjects.

EFFICACY

Two or four weekly doses of selgantolimod 1.5 mg or 3 mg in virally suppressed and viremic CHB patients did not result in declines from baseline in HBsAg or HBV DNA. Across selgantolimod treatment groups, for all time points evaluated, median changes from baseline in HBsAg ranged from −0.04 to 0.01 $\log_{10}$ IU/mL compared with −0.11 to 0.26 $\log_{10}$ IU/mL in the placebo groups; median changes from baseline in HBV DNA ranged from −0.06 to 0.0 $\log_{10}$ IU/mL compared with −0.35 to 0.0 $\log_{10}$ IU/mL in the placebo groups (**Figure 4**).

Discussion

This Phase 1b study describes the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of a novel TLR-8 agonist selgantolimod in patients with CHB. Overall, multiple weekly doses of selgantolimod was safe and well tolerated in virally suppressed and viremic CHB patients. Adverse events were mild or moderate in severity, with no observed serious adverse events or discontinuations due to adverse events. Similarly, all graded laboratory abnormalities were mild or moderate and none were associated with adverse events.

The plasma pharmacokinetics of selgantolimod was investigated over a 24-hour period postdose on Days 1 and 8. The results indicate that selgantolimod is rapidly absorbed following single or once weekly oral administration of 1.5 or 3 mg, with mean plasma concentrations and exposure increasing with increasing dose. While the average exposure in the virally suppressed cohort that received two doses of selgantolimod 3 mg was lower than the other two cohorts that received doses of 3 mg, this difference was driven by outliers in each of those cohorts. Thus, all 3-mg cohorts were pooled in the dose-proportionality evaluation. Analysis using the ANOVA model indicated that selgantolimod exposure was approximately dose-proportional over the dose range studied. Despite interpatient variability, selgantolimod pharmacokinetic parameters were generally similar between virally suppressed and viremic CHB patients, suggesting the potential for a single dosing strategy in both populations.

Selgantolimod had an immunomodulatory effect in CHB patients, measured by postdose increases in multiple cytokines. Peak concentrations of IL-12p40 and IL-1RA occurred 4 hours after selgantolimod dosing and returned to baseline levels approximately 24 hours postdose. Most of the other cytokines measured showed similar kinetics with the exception of CXCL9, SAA and CRP which peaked at 8 and 24 hours postdose, respectively (18). The magnitude of the IL-12p40 and IL-1RA induction was comparable following single- and multiple-dose administration, indicating that the responses were not augmented upon repeat dosing. It also suggests that tachyphylaxis will not present a complication for multidose selgantolimod regimens. These findings in combination with the pharmacokinetic data demonstrating a shorter half-life of selgantolimod (median $t_{1/2}$ of ~5 h), that led to no apparent accumulation upon once-weekly administration, further substantiates once-weekly dosing of selgantolimod for longer duration in the Phase II studies.

Overall, the pharmacokinetic and pharmacodynamic findings are consistent with those observed in prior studies on selgantolimod. In a first-in-human, randomized, blinded, placebo-controlled, single ascending dose study of selgantolimod in healthy male and female subjects (GS-US-389-2021), oral selgantolimod was found to be absorbed quickly with dose proportional pharmacokinetics for the doses ranging from 1.5 to 5 mg (18). Notably, selgantolimod levels in patients with CHB were numerically higher than exposures observed following dosing in these healthy volunteers. Additional studies are being conducted to further understand these differences in exposures in CHB patients. The magnitude and kinetics of the IL-12p40, IL-1RA, and other cytokine responses were comparable to those observed in healthy volunteers. These findings suggest selgantolimod is effective at activating local immune response, including monocytes, dendritic cells, natural killers to increase IL-12 and IFNγ production and other inflammatory mediators to promote T helper 1 (Th1) immune cell activation and trafficking in CHB patients. The cytokine response elicited by selgantolimond may activate antigen-presenting cells, thereby inducing HBV-specific T cell response. Analyses of HBV-specific T cell responses and shifts in peripheral immune cell subsets are currently ongoing for the phase 2 study.

In the current study, 2 or 4 doses of selgantolimod were not associated with declines in HBsAg or HBV DNA. This could be attributed to the short duration of dosing which may have resulted in limited exposures to TLR-8- dependent mediators, particularly in the liver. As such, the efficacy response observed in this study was not unexpected and suggests that longer duration therapy beyond 2-4 doses will be required to induce an antiviral efficacy response. To that end, phase 2 studies evaluating selgantolimod safety and efficacy with longer term weekly selgantolimod dosing are underway.

In summary, selgantolimod was found to be safe and tolerable in CHB patients and has pharmacokinetic and pharmacodynamic properties consistent with early phase 1 studies. The dose-dependent cytokine responses indicate target engagement of this oral TLR-8 agonist. TLR8 activation with selgantolimod may be a therapeutic option, either alone or in combination with other emerging therapies, for the clearance of HBV in CHB patients. Collectively, the data obtained in the current study supports the continued development of selgantolimod as a potential treatment for CHB infection.

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Bolded names indicate equal first co-authors.

TABLE 1. Treatment groups and dosing regimens

Cohort	Patients	Weekly Dose	Dosing Week (day) 1 (1)	2 (8)	3 (15)	4 (22)
1	Virally Suppressed (n = 10)	Selgantolimod 1.5 mg (n = 8)	**X**	**X**	—	—
		Placebo (n = 2)	**X**	**X**	—	—
2	Virally Suppressed (n = 9)	Selgantolimod 3 mg (n = 7)	**X**	**X**	—	—
		Placebo (n = 2)	**X**	**X**	—	—
4	Viremic (n = 10)	Selgantolimod 3 mg (n = 8)	**X**	**X**	—	—
		Placebo (n = 2)	**X**	**X**	—	—
5	Virally Suppressed (n = 9)	Selgantolimod 3 mg (n = 8)	**X**	**X**	**X**	**X**
		Placebo (n = 1)	**X**	**X**	**X**	**X**

TABLE 2. Patient Demographics and Baseline Disease Characteristics

	Virally Suppressed on OAV					Viremic		
	Cohort 1	Cohort 2	Cohorts 1 and 2[a]	Cohort 5		Cohort 4		Total
	Selgantolimod 1.5 mg (N = 8)	Selgantolimod 3 mg (N = 7)	Placebo (N = 4)	Selgantolimod 3 mg (N = 8)	Placebo (N = 1)	Selgantolimod 3 mg (N = 8)	Placebo (N = 2)	Total (N = 38)
Median (range) age in years	39 (31-49)	46 (32-62)	36 (30-55)	54 (44-62)	48 (48-48)	48 (33-56)	58 (53-63)	48 (30-63)
Male, n (%)	7 (88)	6 (86)	3 (75)	6 (75)	0	6 (75)	2 (100)	30 (79)
Asian, n (%)	5 (63)	5 (71)	3 (75)	8 (100)	0	7 (88)	2 (100)	30 (79)
Median (range) BMI (kg/m^2)	28 (21-34)	27 (21-34)	22 (20-30)	24 (21-34)	28 (28-28)	24 (22-27)	25 (21-28)	25 (20-34)
Median (range) HBsAg (log_{10} IU/mL)	3.2 (2.7-3.8)	2.9 (1.4-4.3)	3.5 (3.2-4.3)	3.2 (1.7-3.8)	4.0 (4.0-4.0)	3.8 (3.0-5.0)	2.3 (2.2-2.3)	3.3 (1.4-5.0)
HBV DNA category, n (%)								
< LLOQ	7 (88)	7 (100)	4 (100)	8 (100)	1 (100)	0	0	27 (71)
≥ LLOQ	1 (13)	0	0	0	0	8 (100)	2 (100)	11 (29)
Median (range) HBV DNA (IU//mL)	--	--	--	--	--	4.5 (3.1-8.7)	4.2 (3.4-5.0)	--
HBeAg status, n (%)								
Positive	4 (50)	2 (29)	1 (25)	2 (25)	0	3 (38)	0	12 (32)
Negative	4 (50)	5 (71)	3 (75)	6 (75)	1 (100)	5 (63)	2 (100)	26 (68)
ALT level based on AASLD normal range[b], n (%)								
≤ ULN	6 (75)	5 (71)	4 (100)	7 (88)	1 (100)	5 (63)	1 (50)	29 (76)
> ULN	2 (25)	2 (29)	0	1 (13)	0	3 (38)	1 (50)	9 (24)

Median (range) eGFR (Cockcroft-Gault) (mL/min)	135 (108-150)	116 (103-190)	123 (117-162)	94 (76-116)	132 (132-132)	103 (91-135)	108 (100-116)	116 (76-190)
HBV Genotype C, n (%)	0	0	0	0	0	6 (100)	1 (100)	7 (100)
Median (range) years of being HBV positive	17 (4-32)	14 (13-23)	21 (12-31)	14 (7-35)	22 (22-22)	5 (1-36)	29 (19-39)	15 (1-39)
Mode of HBV infection, n (%)								
Vertical Transmission	5 (63)	4 (57)	2 (50)	4 (50)	1 (100)	3 (38)	1 (50)	20 (53)
Blood Product Transfusion	1 (13)	0	0	0	0	0	0	1 (3)
Contact with Infected Individual	0	0	0	0	0	1 (13)	0	1 (3)
Unknown	2 (25)	3 (43)	2 (50)	4 (50)	0	4 (50)	1 (50)	16 (42)

a Patients who received placebo in Cohorts 1 and 2 were combined for analysis.

b. AASLD normal range for ALT: Males, 29 to 33 IU/I and females, 19 to 25 IU/I

Abbreviations: OAV, oral antiviral; BMI, body mass index; LLOQ, lower limit of quantitation

TABLE 3. **Adverse Events and Laboratory Abnormalities**

	Virally Suppressed (2 Doses)			Virally Suppressed (4 Doses)		Viremic (2 Doses)	
	Cohort 1	Cohort 2	Cohorts 1 and 2	Cohort 5		Cohort 4	
	Selgantolimod 1.5 mg (N = 8)	Selgantolimod 3 mg (N = 7)	Placebo (N = 4)	Selgantolimod 3 mg (N = 8)	Placebo (N = 1)	Selgantolimod 3 mg (N = 8)	Placebo (N = 2)
No. (%) of patient with any adverse event	3 (38)	5 (71)	1 (25)	7 (88)	1 (100)	3 (38)	0
No. (%) of grade 2 or higher adverse events	0	0	1 (25)	3 (38)	1 (100)	0	0
No. of serious adverse events	0	0	0	0	0	0	0
No. of adverse events leading to discontinuation	0	0	0	0	0	0	0
No. of deaths	0	0	0	0	0	0	0
Adverse events reported in ≥ 2 patients, n (%)	1 (13)	5 (71)	1 (25)	5 (63)	1 (100)	3 (38)	0
Headache	1 (13)	4 (57)	1 (25)	4 (50)	1 (100)	1 (13)	0
Nausea	0	3 (43)	0	4 (50)	1 (100)	1 (13)	0
Dizziness	0	2 (29)	0	2 (25)	0	1 (13)	0
Chills	0	0	0	2 (25)	0	1 (13)	0
Decreased appetite	0	0	0	2 (25)	0	0	0
Pyrexia	0	0	0	0	0	2 (25)	0
No. (%) of patients with any postbaseline laboratory abnormality	6 (75)	5 (71)	3 (75)	8 (100)	1 (100)	8 (100)	1 (50)

	Virally Suppressed (2 Doses)			Virally Suppressed (4 Doses)		Viremic (2 Doses)	
	Cohort 1	Cohort 2	Cohorts 1 and 2	Cohort 5		Cohort 4	
	Selgantolimod 1.5 mg (N = 8)	Selgantolimod 3 mg (N = 7)	Placebo (N = 4)	Selgantolimod 3 mg (N = 8)	Placebo (N = 1)	Selgantolimod 3 mg (N = 8)	Placebo (N = 2)
No. (%) of patients with a grade 2 or higher laboratory abnormality	3 (38)	2 (29)	2 (50)	1 (13)	1 (100)	4 (50)	1 (50)
Grade 2 or above laboratory abnormalities in ≥ 2 patients, n (%)							
Increased low-density lipoprotein cholesterol	2 (25)	1 (14)	0	0	0	1 (13)	1 (50)
Hyperglycemia	0	0	0	1(13)	0	3 (38)	1 (50)

TABLE 4. Summary Statistics of Selgantolimod Plasma Pharmacokinetic Parameters by Treatment Following Single- or Multiple-Dose (2 or 4 Weekly Doses) Administration of Selgantolimod

Selgantolimod PK Parameter	Mean (%CV)			
	Virally Suppressed (2 Doses)		Virally Suppressed (4 Doses)	Viremic (2 Doses)
	Cohort 1	Cohort 2	Cohort 5	Cohort 4
	Selgantolimod 1.5 mg (N = 8)	Selgantolimod 3 mg (N = 7)	Selgantolimod 3 mg (N = 8)	Selgantolimod 3 mg (N = 8)
Day 1				
AUC_{last} (h•pg/mL)	305 (35.8)	625 (76.5)	932 (53.0)	944 (65.1)

Selgantolimod PK Parameter	Mean (%CV)			
	Virally Suppressed (2 Doses)		Virally Suppressed (4 Doses)	Viremic (2 Doses)
	Cohort 1	Cohort 2	Cohort 5	Cohort 4
	Selgantolimod 1.5 mg (N = 8)	Selgantolimod 3 mg (N = 7)	Selgantolimod 3 mg (N = 8)	Selgantolimod 3 mg (N = 8)
AUC_{inf} (h•pg/mL)	316 (36.1)	642 (74.2)	950 (52.5)	960 (64.5)
C_{max} (pg/mL)	105 (32.2)	267 (83.2)	628 (84.7)	627 (132)
T_{max} (h)[a]	1.00 (0.75, 1.00)	0.50 (0.25, 2.00)	0.75 (0.50, 1.00)	0.38 (0.25, 1.00)
$t_{1/2}$ (h)[a]	5.63 (5.16, 6.11)	5.26 (3.86, 6.19)	4.77 (3.96, 5.73)	4.59 (4.15, 5.05)
CL/F (L/h)	5260 (32.4)	8330 (101)	3790 (39.8)	4020 (45.7)
Day 8				
AUC_{last} (h•pg/mL)	351 (37.7)	434 (44.0)	967 (61.1)	900 (61.2)
AUC_{inf} (h•pg/mL)	365 (38.1)	445 (43.5)	986 (60.8)	919 (60.9)
C_{max} (pg/mL)	140 (34.2)	235 (68.3)	621 (71.0)	433 (79.1)
T_{max} (h)[a]	0.50 (0.50, 1.00)	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)	0.50 (0.50, 1.50)
$t_{1/2}$ (h)[a]	5.54 (4.64, 6.26)	5.32 (4.60, 6.05)	5.76 (4.69, 6.00)	4.98 (4.60, 5.95)
CL/F (L/h)	4810 (45.3)	8410 (60.2)	4000 (48.3)	4890 (81.4)
	Accumulation Ratios (Day 8 / Day 1)			
Ratio $AUC_{0\text{-}24}$	1.15 (19.0)	0.87 (35.9)	1.01 (26.4)	0.96 (31.5)
Ratio C_{24}	1.11 (16.5)[c]	0.74 (48.5)[b]	1.22 (43.0)[c]	1.22 (48.6)
Ratio C_{max}	1.41 (31.3)	1.10 (33.6)	1.21 (44.8)	0.93 (52.9)
	ANOVA Analysis %GLSM Ratio (Dose/1.5 mg[d]) (90%CI)			
	Day 1		Day 8	
AUC_{last} (h•pg/mL)	121.0 (80.4, 183.0)		97.6 (63.7, 150.0)	

Selgantolimod PK Parameter	Mean (%CV)			
	Virally Suppressed (2 Doses)		Virally Suppressed (4 Doses)	Viremic (2 Doses)
	Cohort 1	Cohort 2	Cohort 5	Cohort 4
	Selgantolimod 1.5 mg (N = 8)	Selgantolimod 3 mg (N = 7)	Selgantolimod 3 mg (N = 8)	Selgantolimod 3 mg (N = 8)
AUC_{inf} (h•pg/mL)	120.0 (80.3, 180.0)		96.4 (63.1, 147.0)	
C_{max} (pg/mL)	168.0 (90.4, 312.0)		119.0 (69.0, 207.0)	

a Values are presented as median (Q1, Q3).

b. N= 6.

c N= 7.

d. PK parameter estimates were dose-normalized to 1.5 mg.

Data presented to 3 significant digits.

Abbreviations: GLSM, geometric least-squares mean; CI, confidence interval

FIGURE LEGENDS

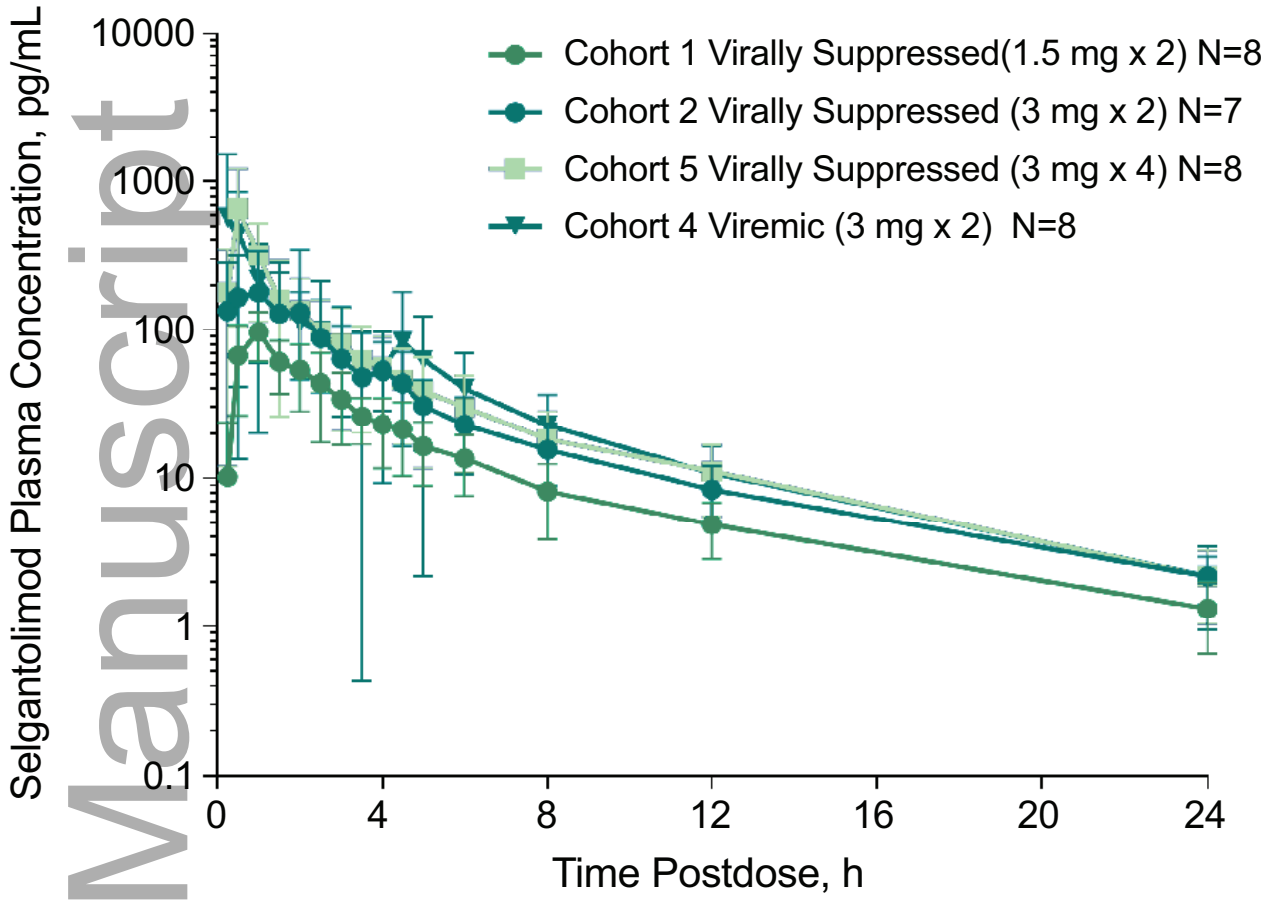
Figure 1. Mean (SD) selgantolimod plasma concentration versus time curves by treatment on (A) Day 1 and (B) Day 8

Figure 2. (A) IL-12p40 and (B) IL-1RA concentration ratios versus time

Figure 3. Cytokine Fold Change Across Different Timepoints Post-Dose. FC, fold change.

Figure 4. Efficacy. (A) Median (Q1, Q3) Change from Baseline in HBsAg (log_{10} IU/mL) by Treatment Group and (B) Median (Q1, Q3) Change from Baseline in HBV DNA (log_{10} IU/mL) by Viremic Treatment (Viremic cohorts only)

A



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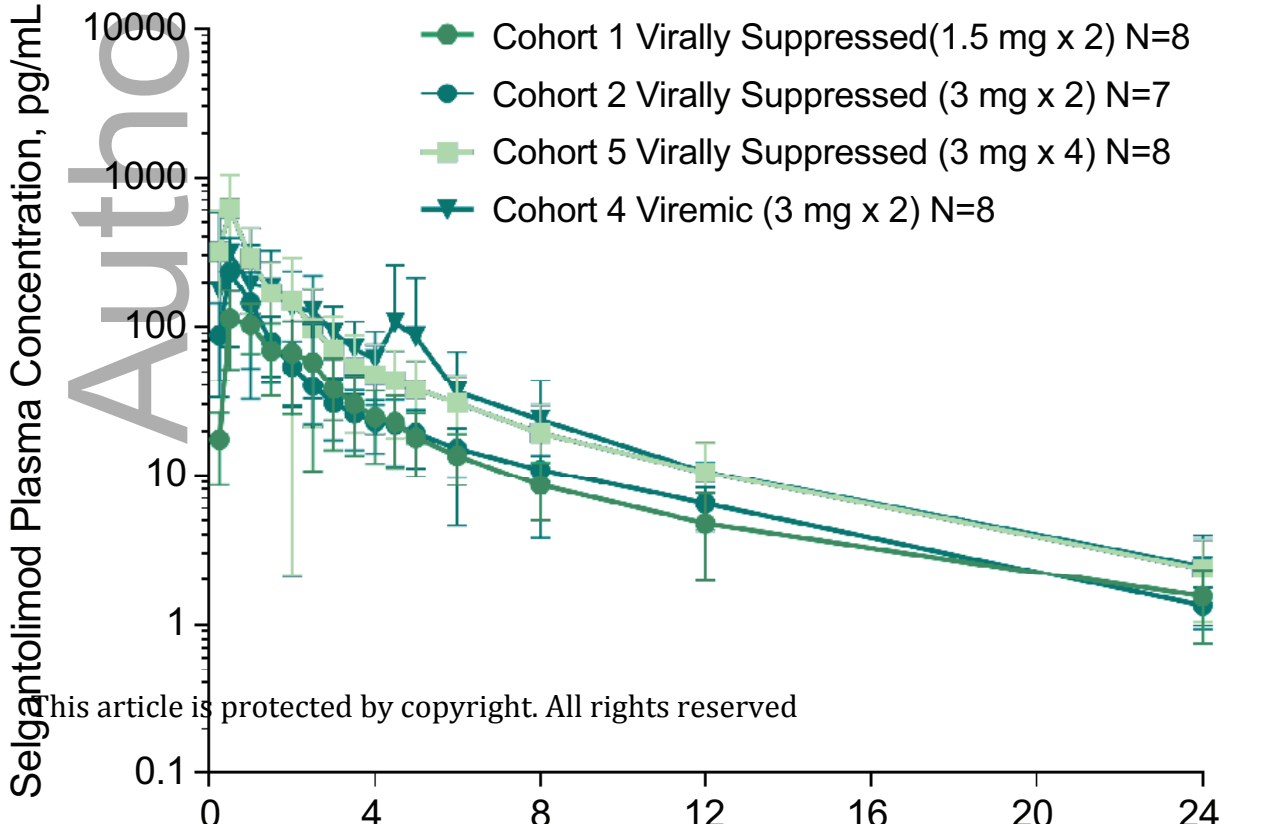

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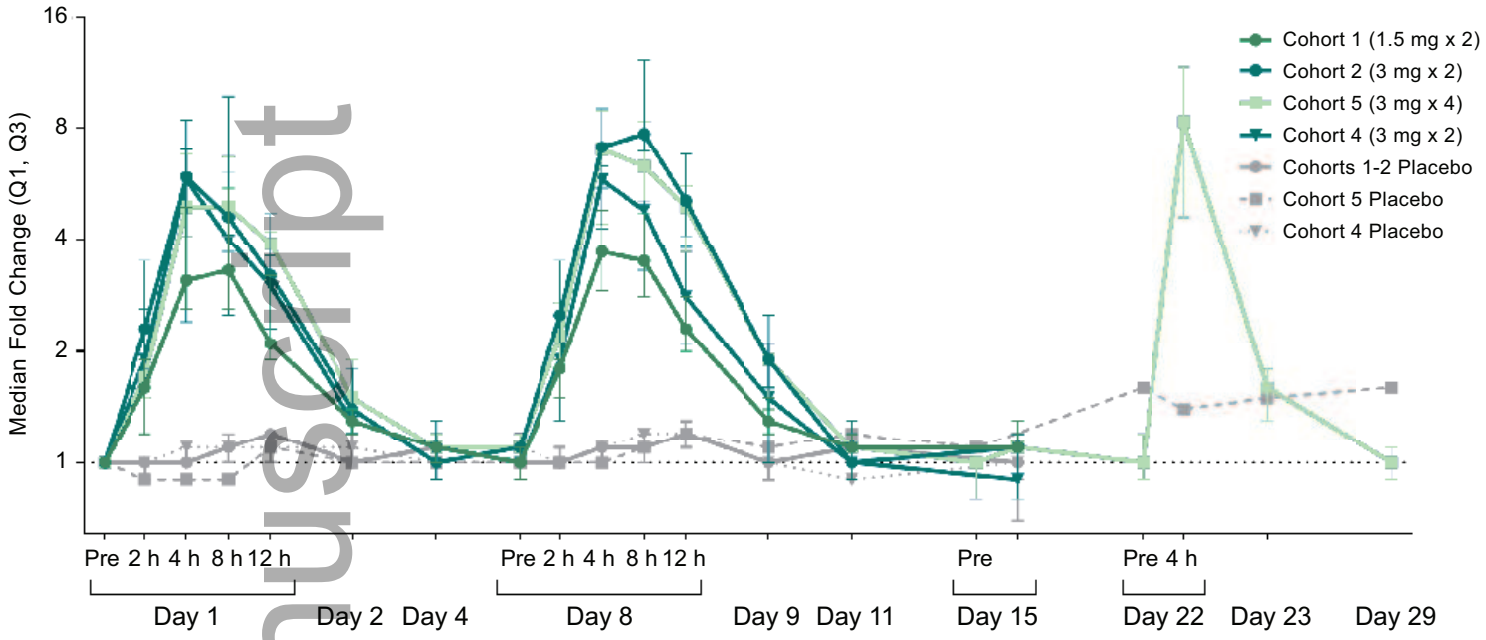

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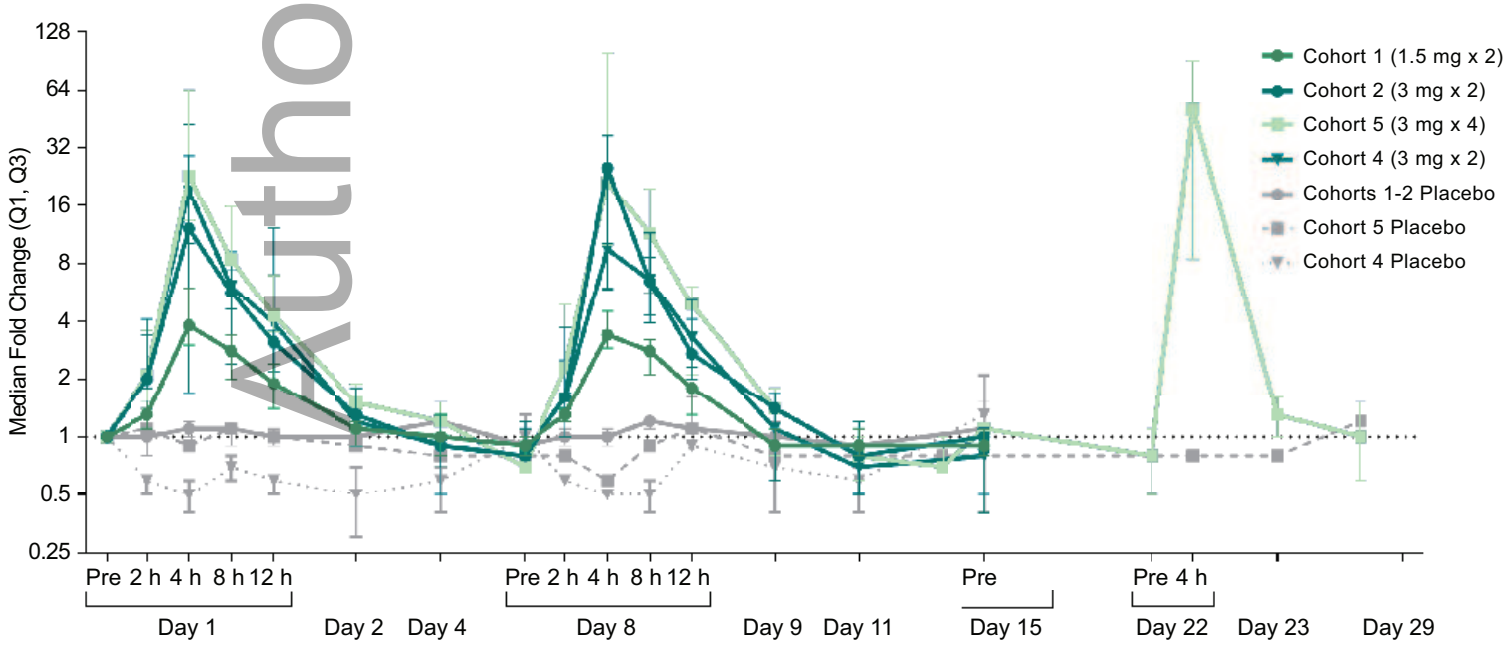

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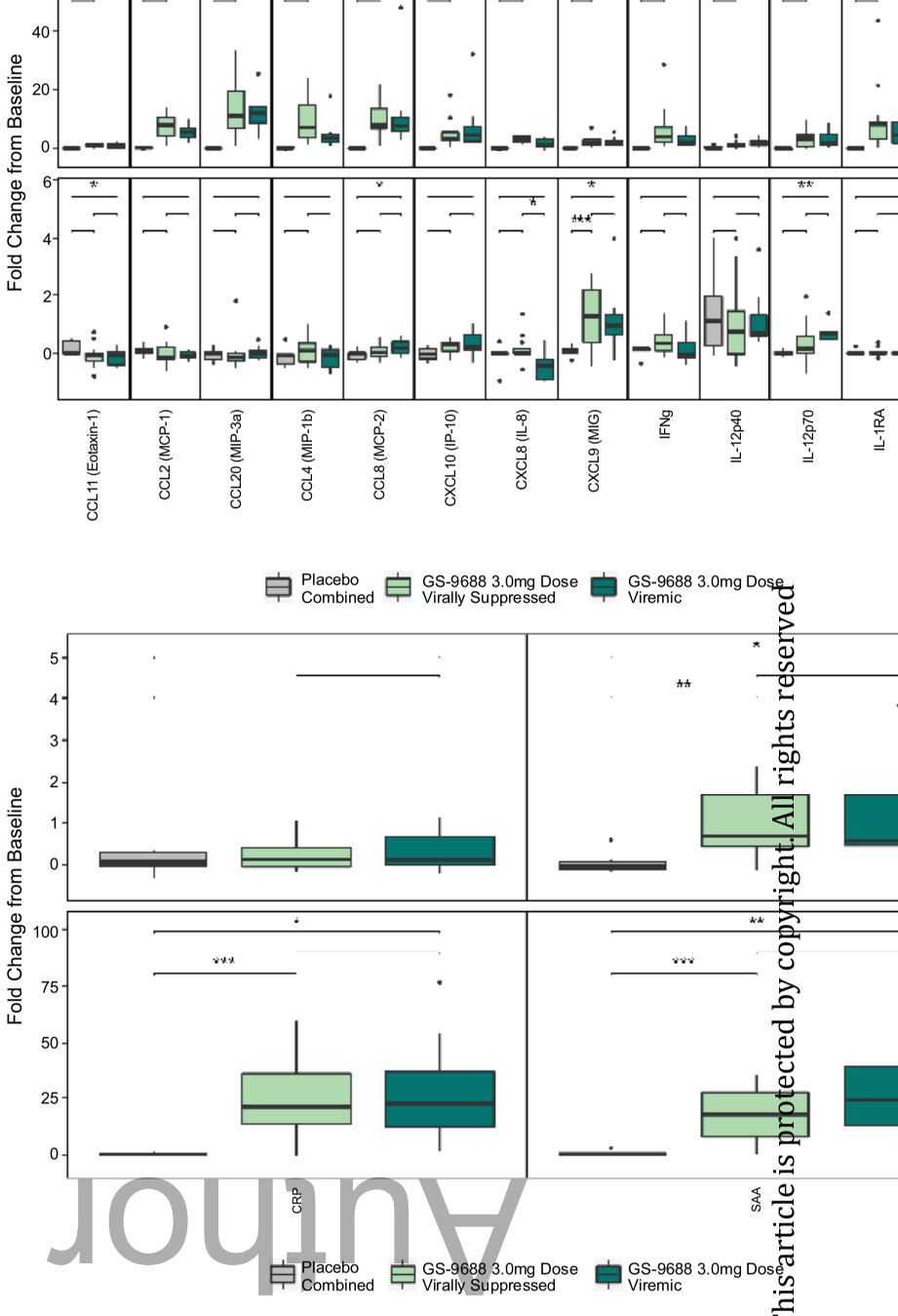

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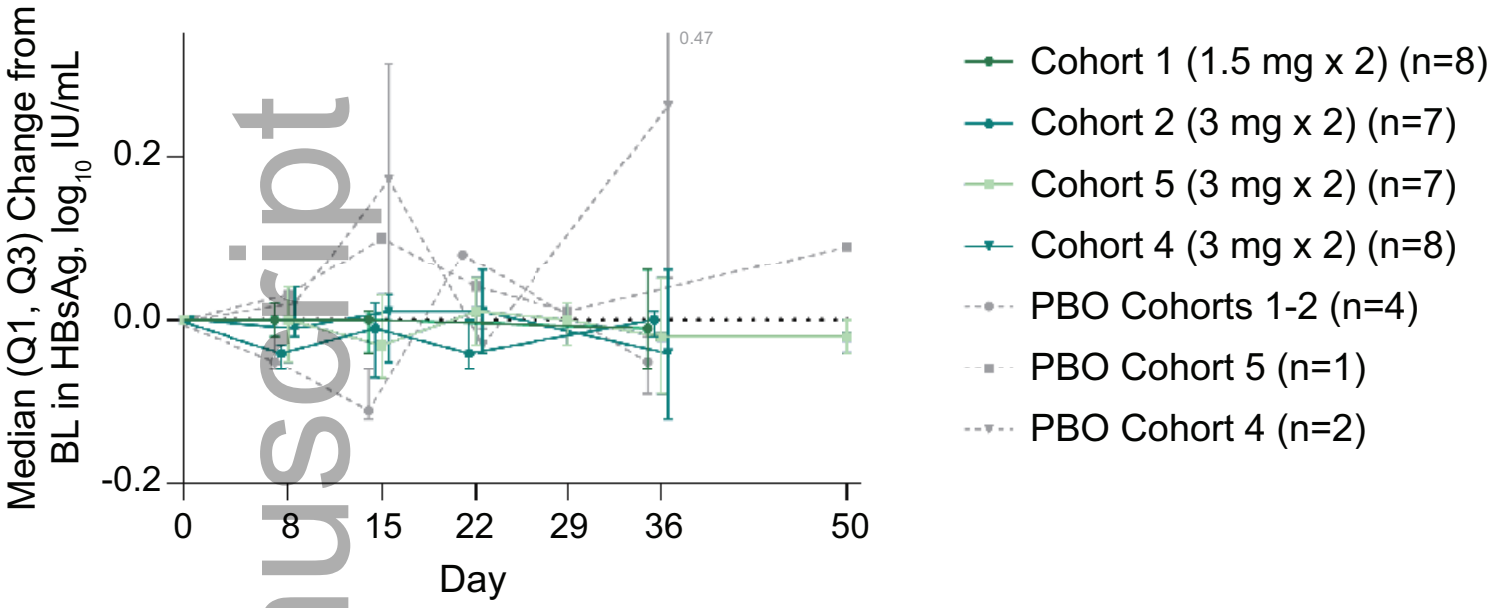

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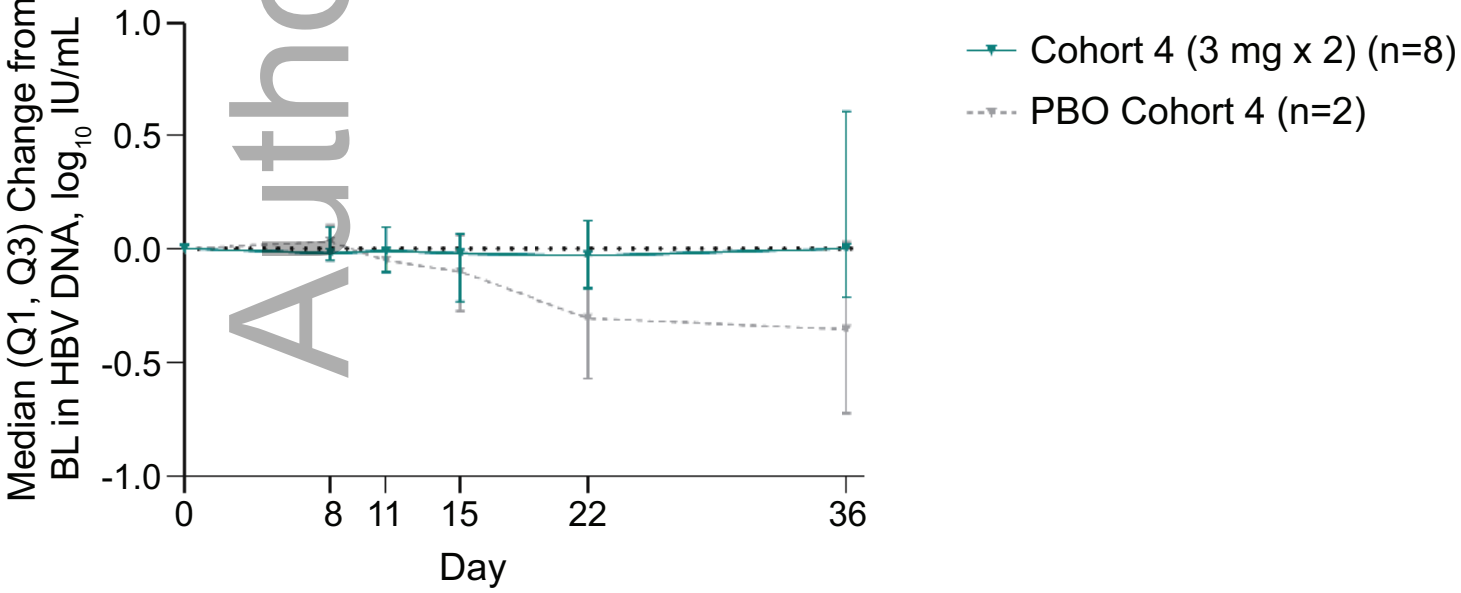

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