

Association of Baseline Characteristics and Plasma ALG-001075 to HBsAg Responses in HBeAg+ CHB subjects following ALG-000184±ETV treatment



WED-378

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Introduction

- ALG-000184 is a prodrug of ALG-001075, a potent chronic hepatitis B (CHB) capsid assembly modulator-empty that inhibits viral replication and cccDNA establishment in vitro.
- The potent antiviral effects and favorable safety profile in HBeAg+ CHB subjects receiving 300 mg ALG-000184 ± Entecavir (ETV) ≤72 weeks and in HBeAg- CHB subjects receiving 300 mg ALG-000184 monotherapy ≤60 weeks from an ongoing study ALG-000184-201 are reported in poster WED-365 and WED-361, EASL 2024.¹
- Functional cure, defined as sustained hepatitis B surface antigen (HBsAg) loss with virologic suppression after a finite treatment course, is one of the desired outcomes for new treatment approaches for the management of chronic hepatitis B (CHB).²
- Substantial reductions in HBsAg has been shown for ALG-000184 ± ETV in HBeAg+ CHB subjects.³
- Identifying factors associated with HBsAg reductions would be critical to patient identification and understanding of mechanism of action of ALG-000184 in CHB subjects.

Aim

To evaluate whether there is an association between baseline characteristics including demographics, baseline viral antigens, and plasma ALG-001075 exposures to HBsAg responses in HBeAg+ CHB subjects following ALG-000184 ± ETV treatment

Method

ALG-000184-201 is a multi-part, multi-center, double-blind, randomized, placebo-controlled study (NCT04536337). In Part 4, eligible treatment naïve or currently-not-treated HBeAg+ CHB subjects that enrolled in Cohorts 1 and 2 were randomly assigned (3:1) to receive oral daily doses of 100 and 300 mg ALG-000184, respectively or placebo in combination with entecavir (ETV) x 12 weeks followed by open-label treatment with 100 mg ALG-000184 + ETV x ≤ 12 weeks and 300 mg ALG-000184 + ETV x ≤ 96 weeks, respectively. Those enrolled in Cohort B received open-label daily doses of 300 mg ALG-000184 alone x ≤ 96 weeks.

A total of 22 subjects (n= 4, 9, and 9 in Cohorts 1, 2 and B, respectively) with ≥ 24 weeks of ALG-000184 dosing were included in the analysis.

Baseline participant characteristics, including age, sex, ethnicity, body weight, BMI, HBV genotype, HBsAg, HBeAg, HBcrAg and steady state plasma ALG-001075 exposures were included in the analysis. For baseline HBsAg, both continuous and categorical (stratified by < or ≥ 4 log₁₀IU/mL) was examined.

Linear univariate and multiple regression models were used to determine associations between selected baseline variables, plasma ALG-001075 exposures and HBsAg reduction. The level of significance was set to a 2-sided P < 0.05. Association was also shown in graphical form.

References

¹MF Yuen et al. and Kosh A. et al., EASL 2024; ²Lok et al., Hepatology 2017; ³Hou, et. al, Poster 2023 EASL Conference

Results

- Baseline patient characteristics were similar for those stratified by HBsAg < or ≥ 4 log₁₀ IU/mL and overall population (Table 1).
- In the univariate regression model, baseline HBsAg continuous and categorical (< or ≥ 4 log₁₀ IU/mL) variables were shown to have a statistically significant association with the change from baseline in HBsAg at Week 24 (Table 2a, Figure 1).
- In the multiple regression model, baseline HBsAg (< or ≥ 4 log₁₀ IU/mL) and steady state plasma ALG-001075 exposure (AUC) were shown to have a statistically significant association with the change from baseline in HBsAg at Week 24 (Table 2b).
- Plasma ALG-001075 exposures did not show statistical significance in the univariate model but after adjustment for baseline HBsAg, higher plasma ALG-001075 exposures added statistical significance to the prediction (p=0.00416) (Table 2, Figures 2a and 2b).
- Subjects with baseline HBsAg of < 4 log₁₀ IU/mL did not show significant reduction in HBsAg regardless of plasma ALG-001075 exposure (Figure 2a).
- No statistically significant associations were found between age, sex, ethnicity, HBV genotype, baseline HBeAg, HBcrAg or ALT and change from baseline in HBsAg in either univariate or multiple regression models (Tables 2a and 2b).
- Baseline HBV DNA and HBV RNA showed significant association with maximum change from baseline in HBsAg at Week 24 but the association was not statistically significant after adjustment for baseline HBsAg (Table 2b).
- Similar results were observed at longer time points of Weeks 36 and 48 (data not shown).
- HBeAg+ CHB subjects had exposure related decreases in HBeAg and HBcrAg irrespective of their baseline (Figures 3).

Figure 1: Maximum HBsAg Change from Baseline vs. HBsAg Baseline

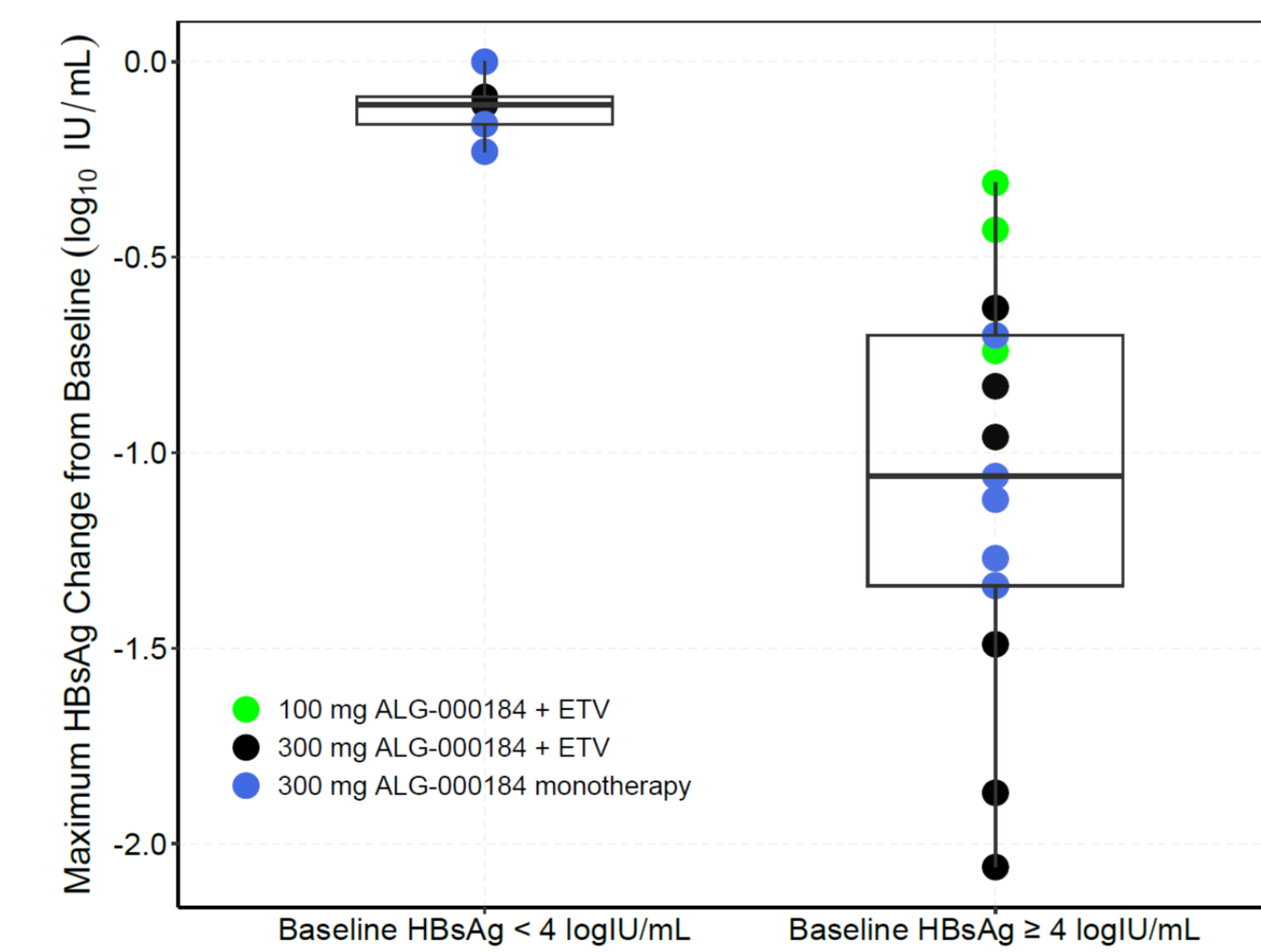


Figure 2: Linear Regression Model HBsAg Change from Baseline vs. Plasma ALG-001075 Exposure

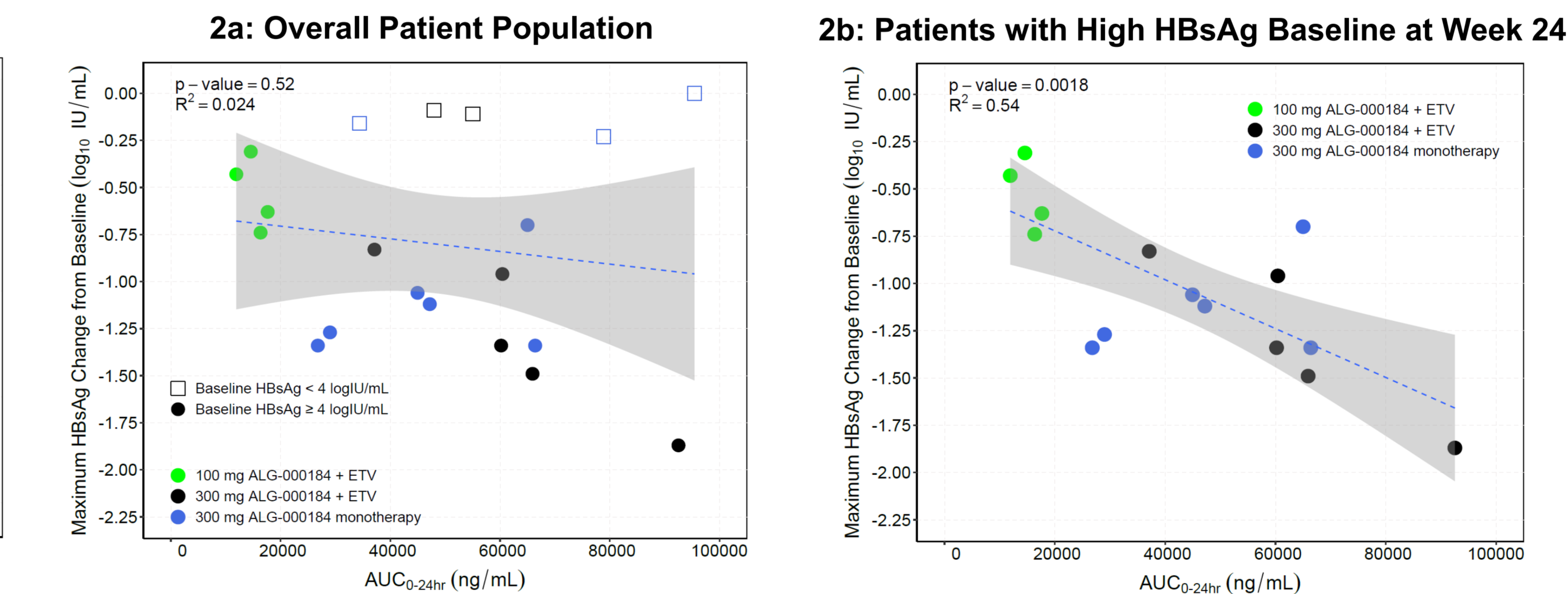
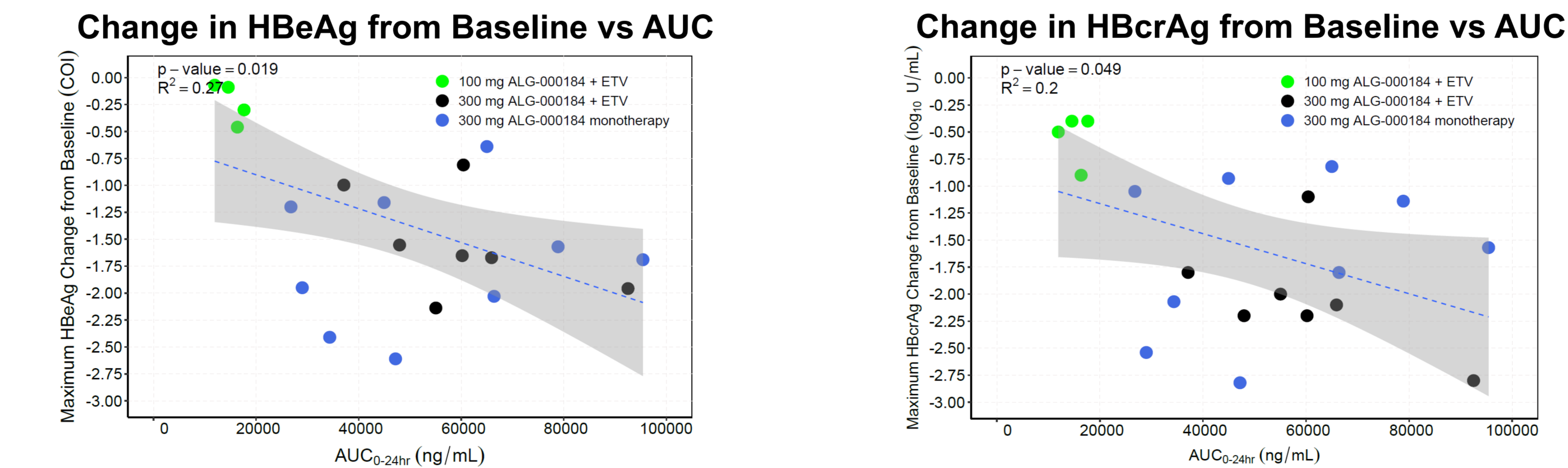


Figure 3: Linear Regression Model HBV Antigen Change from Baseline and Plasma ALG-001075 Exposure



Conclusions

Multi-log reduction in HBV antigens appears to be mediated by ALG-000184 secondary mode of action to lower cccDNA. Higher baseline HBsAg (≥4 log₁₀ IU/mL) and plasma ALG-001075 levels were predictors of HBsAg response to ALG-000184 treatment. Plasma ALG-001075 was associated with HBeAg and HBcrAg reduction.

Table 1: Baseline Patient Characteristics

	Baseline HBsAg		Overall (n=22)
	<4 log ₁₀ IU/mL (n=5)	≥4 log ₁₀ IU/mL (n=17)	
Age, years, mean (SEM)	40.0 (5.2)	32.4 (2.0)	34.1 (2.0)
Male, n (%)	4 (80%)	9(53%)	12 55%
Asian, n (%)	5 (100%)	16 (95%)	21(95%)
Body Weight, kg, mean (SEM)	68.1(5.5)	59.3 (2.7)	61.2 (2.5)
BMI, kg/m ² , mean (SEM)	21.6(0.6)	22.0 (0.5)	22.0 (0.5)
HBV Genotype	B (1, 20%) C (4, 80%)	B (8/17, 47%) C (8/17, 47%) D (1/17, 5.9%)	B (9/22, 41%) C (12/22, 55%) D (1/22, 4.5%)
HBV DNA, log ₁₀ IU/mL, mean (SEM)	7.0 (0.3)	8.4 (0.1)	8.0 (0.16)
HBV RNA, log ₁₀ copies/mL, mean (SEM)	4.8 (0.56)	6.6 (0.27)	6.2 (0.29)
HBsAg, log ₁₀ IU/mL, mean (SEM)	3.5 (0.25)	4.7 (0.05)	4.4 (0.13)
HBeAg, log ₁₀ COI, mean (SEM)	2.1(0.34)	2.7(0.13)	2.6 (0.13)
HBcrAg, log ₁₀ U/mL, mean (SEM)	6.0±0.82 log ₁₀ U/mL	7.5±0.36 log ₁₀ U/mL	7.1±0.36 log ₁₀ U/mL
ALT, U/L, mean (SEM)	47(7.0)	43 (7.4)	62 (17)

Table 2: Association of Patient Characteristics and Plasma ALG-001075 Exposure to HBsAg Change from Baseline

2a: Univariate Model

	Maximum Change from Baseline in HBsAg at Week 24	
Age	0.02373 (0.01297)	0.08234
Sex	Male 0.2668 (0.2508)	0.3
Ethnicity	White -0.2824 (0.6129)	0.65
Body Weight	0.01576 (0.01069)	0.1561
BMI	0.06121 (0.05035)	0.2382
HBV Genotype	C 0.478611 (0.247667) D -0.008889 (0.592038)	0.1645
Baseline HBV DNA	-0.5095 (0.1291)	0.000797
Baseline HBV RNA	-0.22511 (0.08135)	0.0119
Baseline HBsAg	-0.5761 (0.1732)	0.003364
Baseline HBsAg (≥ 4 log ₁₀ IU/mL)	-0.9479 (0.2211)	0.000359
Baseline HBeAg	-0.08256 (0.20702)	0.6943
Baseline HBcrAg	-0.07826 (0.07692)	0.3211
Baseline ALT	0.001126 (0.004007)	0.7815
AUC ₀₋₂₄	-3.361e-06 (5.081e-06)	0.5167
C _{trough} (24hr)	1.816e-05 (1.692e-04)	0.9157
Age	0.02373 (0.01297)	0.08234
Sex	Male 0.2668 (0.2508)	0.3

2b: Multiple Regression Model

	Maximum Change from Baseline in HBsAg at Week 24	
Baseline HBsAg (≥ 4 log ₁₀ IU/mL)	Coefficient (Standard Error)	P-value
After Adjustment for Baseline HBsAg	-0.9479 (0.2211)	0.000359
Age	0.009852 (0.010836)	0.37465
Sex	Male 0.04946 (0.19836)	0.805756
Ethnicity	White -0.0575 (0.4594)	0.901701
Body Weight	0.004962 (0.008744)	0.57700
BMI	0.01429 (0.04036)	0.727194
HBV Genotype	C 0.28792 (0.19766) D 0.08646 (0.45718)	0.16244 0.85212
Baseline HBV DNA	-0.2348(0.1969)	0.2477
Baseline HBV RNA	-0.08017(0.08454)	0.35488
Baseline HBeAg	0.2431(0.1616)	0.14891
Baseline HBcrAg	0.01825(0.06314)	0.775699
Baseline ALT	-0.002193 (0.003034)	0.478710
AUC ₀₋₂₄	-9.735e-06 (2.943e-06)	0.00416
C _{trough} (24hr)	-0.0002120 (0.0001157)	0.0844

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