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MONOTHERAPY WITH THE CAPSID ASSEMPLY MODULATOR, ALG-000184, RESULTS IN HIGH VIRAL SUPPRESSION RATES IN UNTREATED HBEAG+ AND HBEAG- SUBJECTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

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ALIGOS THERAPEUTICS

INTRODUCTION

- Sustained suppression of HBV DNA in chronic hepatitis B (CHB) patients undergoing antiviral treatment has been associated with favorable disease outcomes[1].
- ALG-000184 is a prodrug of the Capsid Assembly Modulator (CAM) E, ALG-001075, which has demonstrated potent, pan-genotypic antiviral activity in vitro through the dual mechanism of action (MOA) [2]:
  - inhibition of pg-RNA encapsidation (1st MOA);
  - blocking cccDNA establishment/replenishment at higher concentrations (2nd MOA).
- ALG-000184-201 (NCT04536337) is a multipart Phase 1 study. Preliminary data demonstrated potent antiviral effect, with significant suppression of HBV DNA, RNA and decline in HBV antigens [3,4].
- Here, we present emerging data from the 300 mg ALG-000184 monotherapy cohort in HBeAg positive (HBeAg+) and HBeAg negative (HBeAg-) CHB subjects dosed for up to 96 weeks (Figure 1).

AIM

To evaluate the safety, pharmacokinetics (PK), and antiviral activity following once daily dosing of ALG-000184 in treatment naïve/currently not treated (TN/CNT) HBeAg+ and HBeAg- CHB subjects.

METHOD

- A total of 10 HBeAg+ subjects and 11 HBeAg- subjects were enrolled in open-label Part 4 Cohort B to receive 300 mg ALG-000184 monotherapy for 96 weeks (Figure 1).

Figure 1: ALG-000184 Part 4 Cohort B Design (Open Label)

- Here we present preliminary data from the 300 mg ALG-000184 monotherapy cohort with up to 92 weeks in HBeAg+ and up to 84 weeks in HBeAg- subjects.
- Safety assessments (adverse events [AEs], vital signs, electrocardiogram and laboratories), PK, and viral markers were collected at regular intervals.
- Safety aspects of the study were reviewed by the Study Review Committee (SRC) and ALT Flare Committee (AFC).
- Lower Limit of Quantitative (LLOQ) and Detection (LLOD) of virology assays are listed in Table 1.

Table 1: LLOQ and LLOD of HBV Markers

	HBV DNA (IU/mL)	HBV RNA (copies/mL)	HBsAg (IU/mL)	HBeAg (PEI U/mL)	HBcrAg (log_{10} U/mL)
LLOQ	10	10	0.05	0.01	3 (HBeAg+) 1.8 (HBeAg-)
LLOD	< 4.92	-	-	-	-

RESULTS

Table 2. Baseline Characteristics

Part 4 Cohort B 300 mg ALG-000184 Monotherapy Baseline Characteristics	HBeAg+ n=10	HBeAg- n=11
Age, years, mean (SEM)	34.8 (2.9)	48.5 (3.1)
Male, n(%)	7 (70.0)	6 (54.5)
Asian, n(%)	9 (90.0)	3 (27.3)
BMI, kg/m², mean (SEM)	22.4 (0.8)	26.0 (1.1)
HBV Genotype, n(%)	B: 5 (50); C: 4 (40); D: 1 (10)	B: 2 (18); C: 1 (9); D: 7 (64); A 1 (9)
HBV DNA, log_{10} IU/mL, mean (SEM)	8.0 (0.2)	4.3 (0.2)
HBV RNA, log_{10} copies/mL, mean (SEM)	5.3 (0.4)	2.0 (0.3)
HBsAg, log_{10} IU/mL, mean (SEM)	4.3 (0.1)	3.5 (0.2)
HBeAg, log_{10} PEI U/mL, mean (SEM)	2.3 (0.2)	NA
HBcrAg, log_{10} U/mL, mean (SEM)	8.3 (0.2)	3.2 (0.3)
ALT, U/L, mean (SEM)	60.7 (11.7)	35.0 (4.4)

SEM: standard error of mean; NA: not applicable
*One HBeAg- subjects withdrew at Week 61 due to personal reason (non-safety related).

SAFETY

In general, 300 mg ALG-000184 monotherapy was well tolerated for up to 92 weeks in HBeAg+ subjects and for up to 84 weeks in HBeAg- subjects.

Table 3: Safety Summary

Part 4 Cohort B 300 mg ALG-000184 Monotherapy	HBeAg + n=10	HBeAg- n=11
Total number of subjects with at least one TEAE	9	8
Subjects with Grade 3-4 TEAE		
Liver transaminase elevation	3*	1*
Other	0	1#
SAE	0	0
Total number of subjects withdrawn from study due to a TEAE	0	0
Concerning laboratory, ECG, vital sign, or physical examination findings	0	0

TEAE: treatment Emergent Adverse Event; SAE: serious adverse event; ECG: electrocardiogram

* 3 HBeAg+ subjects and 1 HBeAg- subject experienced Grade ≥ 3 ALT↑ with or without associated AST↑. All subjects were asymptomatic and none of the ALT increases were associated with hepatic synthetic dysfunction. The ALT Flare Monitoring Committee assessed the events were associated with potent antiviral effects; There was no concern of liver toxicity. All ALT↑ resolved in setting of continued ALG-000184 dosing.
# 1 HBeAg- subjects with abnormal lipid measurements at baseline experienced asymptomatic increase in cholesterol and LDL levels, that fluctuated between Grade 2 and Grade 4 during the dosing period.

ANTIVIRAL ACTIVITY

- A potent sustained antiviral effect was observed in all HBeAg+ subjects and HBeAg- subjects received 300 mg ALG-000184 monotherapy.
- The maximum mean reduction and individual maximum decline from baseline in HBV markers are listed in Table 4.

HBV DNA AND HBV RNA SUPPRESSION

- At Weeks 48, 72 and 84, 6/10 (60%), 8/9 (89%), and 7/7 (100%) HBeAg+ subjects achieved sustained HBV DNA <LLOQ (Figure 2B), respectively; and
- All HBeAg- subjects achieved sustained HBV DNA suppression by Week 24. At Week 48, 11/11 (100%) subjects achieved sustained HBV DNA <LLOQ and 10/11 (91%) subjects achieved HBV DNA <LLOD (Figure 3B).
- All subjects achieved sustained HBV RNA < LLOQ by Week 44 in HBeAg+ subjects and Week 8 in HBeAg- subjects.
- No viral breakthrough, as assessed by HBVDNA levels, was observed in any subject. No known major ALG-000184 resistant mutations were identified during monotherapy (Figure 2A and 3A).

Figure 2: Individual Change in HBV DNA Level from Baseline in HBeAg+ Subjects Following 300 mg ALG-000184 Monotherapy

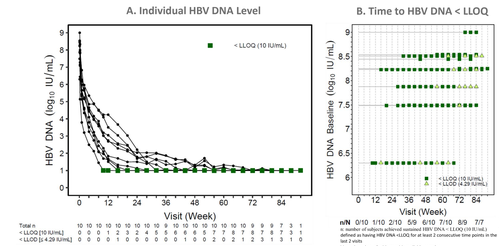


Figure 3: Individual Change in HBV DNA Level from Baseline in HBeAg- Subjects Following 300 mg ALG-000184 Monotherapy

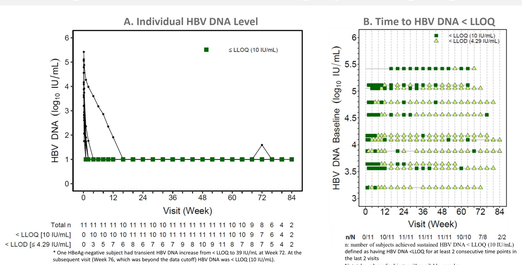


Table 4: Maximum Mean Change and Individual Maximum Change in HBV Markers from Baseline

	Maximum mean reduction		Individual maximum reduction	
	HBeAg +	HBeAg -	HBeAg +	HBeAg -
HBV DNA (log_{10} IU/mL)	-7.3	-3.4	-8.0	-4.4
HBV RNA (log_{10} copies/mL)	-5.5	-1.0	-6.2	-2.5
HBsAg (log_{10} IU/mL)	-1.2	-0.03	-1.5	-0.2
HBeAg (log_{10} PEI U/mL)	-1.7	--	-2.6	--
HBcrAg (log_{10} U/mL)	-2.6	-0.4	-3.2	-0.7

HBSAG, HBEAG, HBCRAG DECLINE

- Multi-log_{10} reductions in HBsAg, HBeAg and HBcrAg were observed in HBeAg+ subjects receiving 300 mg ALG-000184 monotherapy for up to 92 weeks (Figure 4A).
- While HBcrAg declined in HBeAg- subjects, no apparent HBsAg decrease was observed (Figure 5A).
- There was no clear correlation between ALT elevations and the magnitude of antigen decline (Figure 4B and 5B).

Figure 4: Changes in HBV Antigen Levels from Baseline in HBeAg+ Subjects Following 300 mg ALG-000184 Monotherapy

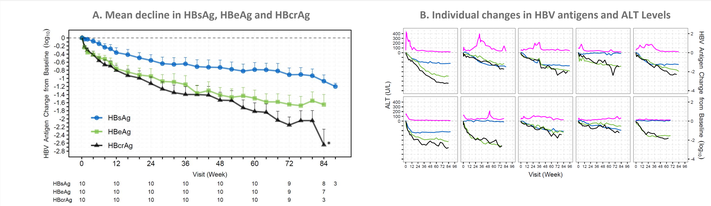
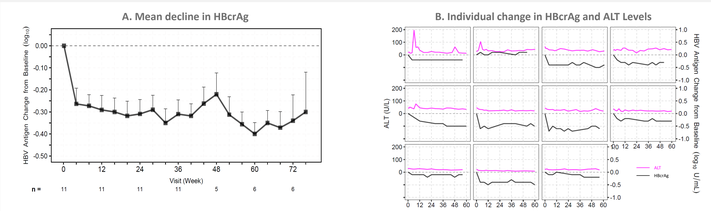


Figure 5: Changes in HBV Antigen Levels from Baseline in HBeAg- Subjects Following 300 mg ALG-000184 Monotherapy



Treatment with 300 mg ALG-000184 monotherapy in HBeAg+ CHB subjects for up to 92 weeks and in HBeAg- CHB subjects for up to 84 weeks resulted in:

- **A favorable safety profile.**
- **High rates of HBV DNA and HBV RNA suppression:**
  - **At Week 48, 60% HBeAg+ and 100% HBeAg- subjects achieved HBV DNA levels < LLOQ (10 IU/mL);**
  - **All HBeAg+ and HBeAg- subjects achieved HBV RNA level < LLOQ (10 copies/mL);**
  - **No viral breakthrough was observed in any subject, and no known major ALG-000184 resistant mutations were identified.**
- **Multi-log_{10} reduction in HBsAg, HBeAg and HBcrAg were observed in HBeAg+ subjects, and HBcrAg decline was observed in HBeAg- subjects.**
- **The proportion of subject achieved HBV DNA < 10 IU/mL at Week 48 surpassed those reported by nucleo(t)ides analogs[5,6]. This suggests the potential for superior chronic suppression treatment for CHB patients.**
- **Phase 2 enabling activities are underway.**

REFERENCES 1. AASLD, EASL, APASL guidelines; 2. Ling EASL 2020; 3. MF Yuen 2024; 4. Kosh EASL 2024; 5. Buti Lancet 2016; 6. Chan Lance 2016;

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