Safety, Pharmacokinetics, and Antiviral Activity of the Class II Capsid Assembly Modulator ALG-000184 in Subjects with Chronic Hepatitis B

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INTRODUCTION

- Worldwide, more than 296 million people are affected by Chronic Hepatitis B (CHB) and approximately 820,000 people per year die from cirrhosis and hepatocellular carcinoma (HCC) due to CHB.[1]
- Long-term treatment with current standard of care for CHB, nucleos(t)ide analogues, suppresses HBV replication and reduces liver injury in most patients, but rarely results in functional cure, the goal of CHB treatment.[2] Therefore, there is a significant medical need for novel approaches to enhance functional cure rates.
- ALG-000184 is a prodrug of ALG-001075, a novel, pan-genotypic Class II CAM (empty capsids) with picomolar potency. ALG-000184 is being developed as a chronic suppressive therapy in CHB subjects with high HBV DNA titers and as a potential component of a finite duration combination regimen to achieve higher rates of functional cure.

AIM

To evaluate the safety, PK, and antiviral activity of multiple doses of ALG-000184 in CHB subjects.

METHODS

ALG-000184-201 is a 3-part, double blind, randomized, placebo (PBO)-controlled Phase 1 study (NCT04536337).

- Parts 1 and 2: all subjects have completed dosing, follow up
  - Single oral doses up to 500 mg and multiple doses (7 days) up to 250 mg were evaluated in healthy volunteers (N=48) and were found to be well tolerated with dose dependent, linear PK[3,4]
- Part 3 is ongoing and evaluating multiple cohorts (N=10/cohort; 8 active: 2 placebo [PBO]) of currently not treated/treatment naïve HBeAg negative or positive CHB subjects, who receive daily (QD) oral doses of ALG-000184 for 28 days, after which they are followed up for 8 weeks
  - Key Inclusion Criteria: ALT & AST ≤ 5x ULN; HBV DNA > 2000 IU/mL; not receiving CHB treatment
  - Key Exclusion Criteria: ≥ F3 liver fibrosis
- Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories), PK, and viral markers were collected and analyzed
- A Study Review Committee and ALT Flare Committee (AFC) review safety and PK data on a regular basis for study oversight and to determine dose escalation
- Plasma concentrations of ALG-001075 are quantified using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method
- PK parameters are determined by non-compartmental analysis using Phoenix WinNonlin

Here, we report preliminary safety, PK and antiviral data for CHB subjects enrolled in the following cohorts in Part 3:

- Cohort 1: 100 mg ALG-000184/PBO in HBeAg negative CHB
- Cohort 2: 50 mg ALG-000184/PBO in HBeAg negative CHB
- Cohort 3: 10 mg ALG-000184/PBO in HBeAg negative CHB
- Cohort 4: 100 mg ALG-000184/PBO in HBeAg positive CHB

BASELINE CHARACTERISTICS

Compared to HBeAg negative CHB subjects, HBeAg positive subjects were younger, more often male, all Asian with a lower BMI, a different predominant HBV genotype, and higher mean HBV DNA and RNA levels.

Dose level	100 mg ALG-000184/PBO	50 mg ALG-000184/PBO	10 mg ALG-000184/PBO	100 mg ALG000184/PBO
N	N=10	N=10	N=9*	N=10
Age, years, mean (SEM)	44.7 (2.9)	42.7 (2.8)	45.4 (1.8)	30.2 (2.4)
Male, N (%)	6 (60.0)	4 (40.0)	4 (44.4)	8 (80.0)
White/Asian/Other, N (%)	9(90)/ 1(10)/ 0	2(20)/ 7(70)/ 1(10)	3(33)/ 4(44)/ 2(22)	0/ 10(100)/ 0
BMI, kg/m^2, mean (SEM)	26.7 (1.80)	24.3 (1.7)	26.2 (1.1)	21.8 (0.9)
Weight, kg, mean (SEM)	78.7 (6.8)	66.5 (6.8)	73.0 (5.3)	62.8 (2.8)
HBeAg negative (%)	100	100	100	0
HBV Genotype: A/B/C/D/E/unknown, (%)	A: 1 (10) B: 1 (10) C: 0 (0) D: 8 (80)	A: 1 (10) B: 6 (60) C: 1 (10) D: 2 (20)	A: 1 (11) B: 2 (22) C: 1 (11) D: 4 (44) E: 1 (11)	A: 0 (0) B: 4 (40) C: 6 (60) D: 0 (0)
HBV DNA, $\log_{10}$ IU/mL, mean (SEM)	4.2 (0.3)	4.7 (0.4)	4.1 (0.1)	8.1 (0.3)
HBV RNA, $\log_{10}$ cp/mL, mean (SEM)	1.6 (0.3)	2.1 (0.3)	1.3 (0.3)	7.8 (0.4)

PBO= Placebo. BMI= Body Mass Index. SEM= Standard Error of the Mean
*Cohort 3 (10 mg ALG-000184/placebo) was considered completed with N=9 subjects enrolled.

SAFETY

10 mg, 50 mg, & 100 mg of ALG-000184/PBO for 28 days were well tolerated:

- An unrelated serious adverse event (SAE) was reported in a subject with a history of sciatica, who was hospitalized briefly for pain management
- No treatment emergent adverse events (TEAEs) causing discontinuation
- TEAEs were generally mild (Grade 1) or moderate (Grade 2) in severity without dose response. Three subjects had a Grade 3 TEAE of ALT elevation during follow up that were:
  - Asymptomatic and not associated with change in liver synthetic function
  - Related to HBV DNA rebound after discontinuation of dosing
  - Reviewed by the AFC, which did not consider these due to drug toxicity
  - Resolved or improved after initiation of licensed HBV drugs
- No clinically concerning laboratory, ECG, vital sign or physical examination findings were reported

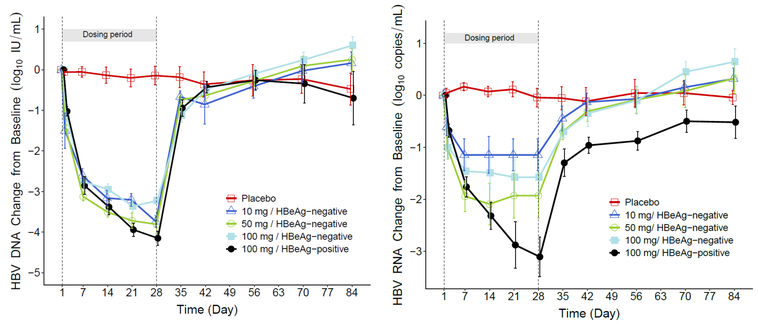
Dose level	100 mg ALG-000184/PBO HBeAg neg	50 mg ALG-000184/PBO HBeAg neg	10 mg ALG-000184/PBO HBeAg neg	100 mg ALG-000184/PBO HBeAg pos
N	N=10	N=10	N=9	N=10
Any TEAE	6 (60)	6 (60)	1 (11)	10 (100)
SAE	1	0	0	0
TEAE leading to study drug discontinuation	0	0	0	0
Worst reported grade TEAE*				
TEAE Grade 1	4 (40)	5 (50)	1 (11)	10 (100)
TEAE Grade 2	2 (20)	3 (30)	0	3 (30)
TEAE Grade 3	1 (10)	0	0	2 (20)
TEAE Grade 4	0	0	0	0

PBO = Placebo
*If a subject experienced two or more different TEAEs of different grading, the subject was counted more than once

ANTIVIRAL ACTIVITY

- Among HBeAg negative subjects, the 10 mg, 50 mg, and 100 mg dose levels were associated with comparable
  - Declines in DNA (3.2-3.8 $\log_{10}$ IU/mL) and RNA (1.1-1.9 $\log_{10}$ copies/mL)
  - % of subjects <LLOQ for DNA (75-100%) and RNA (100%)
  - % of subjects <LLOD for RNA (83-88%)
- 100 mg ALG-000184 in HBeAg positive vs. negative CHB had similar DNA/RNA declines through Day 7 with greater reductions at Day 28 in HBeAg positive CHB.

Figure 1: Mean (SEM) Serum HBV DNA and HBV RNA Levels Change from Baseline Through the End of Study



	HBV DNA					HBV RNA				
Dose level	100 mg HBeAg neg	50 mg HBeAg neg	10 mg HBeAg neg	100 mg HBeAg pos	PBO	100 mg HBeAg neg	50 mg HBeAg neg	10 mg HBeAg neg	100 mg HBeAg pos	PBO
N	N=8	N=8	N=7	N=8	N=8	N=8	N=8	N=7	N=8	N=8
Baseline mean (SEM)	4.2 (0.4)	4.8 (0.4)	4.1 (0.1)	8.3 (0.3)	4.9 (0.6)	1.7 (0.4)	2.1 (0.4)	1.2 (0.4)	7.8 (0.4)	3.1 (1.1)
Change from BL* mean (SEM)	-3.2 (0.1)	-3.8 (0.2)	-3.7 (0.2)	-4.2 (0.2)	-0.14 (0.2)	-1.6 (0.3)	-1.9 (0.4)	-1.1 (0.3)	-3.1 (0.4)	-0.04 (0.20)
Subjects < LLOQ* N (%)	6/8 (75)	5/6[a] (83)	7/7 (100)	0	0	8/8 (100)	6/6[a] (100)	7/7 (100)	0	1/8[b] (13)
Subjects < LLOD* N (%)	2/8 (25)	1/6[a] (17)	3/7 (43)	0	0	7/8 (88)	5/6[a] (83)	6/7 (86)	0	0

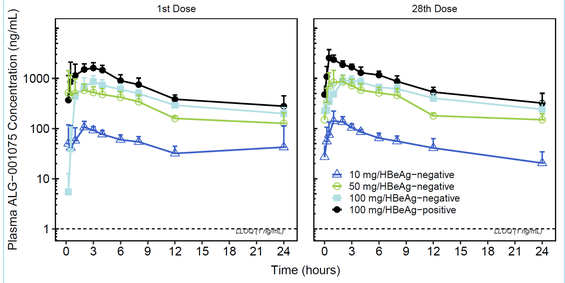
PBO= Placebo. BL= Baseline. SEM - Standard Error of the Mean. * Values at Day 28 (last visit during the dosing period)
a. Two subjects had missing HBV DNA and RNA data due to early discontinuation for personal reasons (not safety related) (N=1) and because the subject did not attend Day 28 visit due to COVID lock down (N=1). b. One subject had HBV RNA <LLOQ at baseline.

Virologic Assays:

- HBV DNA Roche Cobas® assay
  - Sonic central laboratory: Lower Limit of Quantification (LLOQ) = 10 IU/mL. Lower limit of detection (LLOD) = 2.8 IU/mL
  - KingMed central laboratory: LLOQ and LLOD = 10 IU/mL
- HBV RNA Investigational Assay (IA): Roche Cobas® assay. The HBV RNA assay is not approved in any market
  - LLOQ = 10 copies/mL. LLOD = 3.3 copies/mL
- HBV RNA China local assay:
  - LLOQ and LLOD = 200 copies/mL

PHARMACOKINETICS

- Plasma ALG-001075 exposure increased proportionally to ALG-000184 dose with low to moderate PK variability
- Minimal accumulation (~30%) was seen with dosing x 28 days



CONCLUSIONS

- Oral daily dosing for 28 days with 10 mg, 50 mg, and 100 mg of ALG-000184/placebo was generally well tolerated.
- Similar rapid declines in HBV DNA and HBV RNA were observed at all dose levels, regardless of HBeAg status. Among HBeAg negative subjects, high rates of DNA and RNA <LLOQ were observed with 100% of subjects <LLOQ for both DNA and RNA at the 10 mg dose level. The largest DNA (4.2 $\log_{10}$ IU/mL) and RNA (3.1 $\log_{10}$ copies/mL) reductions were observed in HBeAg positive subjects, presumably due to higher baseline levels.
- ALG-001075 plasma exposures increased dose proportionally with low PK variability and minimal accumulation with daily dosing.
- Dosing in additional cohorts is ongoing. A longer-term study evaluating ALG-000184 in combination with nucleos(t)ide analog therapy in HBeAg positive CHB is planned.

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