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Safety, Pharmacokinetics (PK), and Antiviral Activity of the Capsid Assembly Modulator (CAM) ALG-000184 in Subjects with HBeAg Positive Chronic Hepatitis B (CHB)

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INTRODUCTION

- Long-term treatment of CHB with nucleos(t)ide analogues suppresses HBV replication and reduces liver injury, but rarely results in functional cure, the goal of CHB treatment.[1] 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 and is being developed for the treatment of CHB. In addition to inhibiting pg-RNA encapsidation (primary mechanism of action [MoA]), ALG-000184 has been described in vitro to inhibit the production of HBsAg through the regulation of the de-novo establishment and replenishment of cccDNA (2nd MoA). This 2nd MoA was observed at higher concentrations (EC_{50} 70.0 nM) than those associated with the inhibition of HBV DNA and RNA replication (EC_{50} 1.98 nM)[2]. Based on available Phase 1 data, ALG-000184 doses ≥100 mg are projected to achieve exposures required to engage the 2nd MoA.

AIM

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

MATERIALS AND METHODS

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

- Parts 1 and 2 evaluated single and multiple oral doses in healthy volunteers that were 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
- Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories), PK, and viral markers were collected
- 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
- Virology assays:
  - HBV DNA: Roche Cobas® assay. KingMed laboratory: Lower Limit Quantification (LLOQ): 10 IU/mL Lower Limit Detection (LLOD): 10 IU/mL
  - HBV RNA: China local assay: LLOQ and LLOD = 200 copies/mL
  - HBsAg: Roche Elecsys® HBsAg II quant II
- Here we report preliminary safety, PK and antiviral data for 2 cohorts of HBeAg + CHB subjects enrolled in Part 3:
  - 100 mg ALG-000184/placebo for 28 days
  - 300 mg ALG-000184/placebo for 28 days

RESULTS

BASELINE CHARACTERISTICS

HBeAg positive subjects were mostly male, all Asian with a low BMI, HBV genotype B or C, and high mean HBV DNA, RNA and HBsAg levels

Table 1: Baseline characteristics

	ALG-000184/placebo	
Dose level	**100 mg**	**300 mg**
N	**10**	**12***
Age, years, mean (SEM)	30.2 (2.4)	31.9 (1.4)
Male, N (%)	8 (80.0)	6 (50)
Asian, N (%)	10 (100)	12 (100)
BMI, kg/m², mean (SEM)	21.8 (1.0)	22.4 (0.9)
HBV Genotype, N (%)	B: 4 (40) C: 6 (60)	B: 5 (42) C: 7 (58)
HBV DNA, log_{10} IU/mL, mean (SEM)	8.1 (0.3)	8.4 (0.2)
HBV RNA, log_{10} cp/mL, mean (SEM)	7.8 (0.4)	7.3 (0.2)
HBsAg, log_{10} IU/mL, mean (SEM)	4.5 (0.1)	4.5 (0.1)

*Two subjects had to be replaced due to missing laboratory data due to Covid lockdown
BMI= Body Mass Index. SEM= Standard Error of the Mean

SAFETY

100 mg & 300 mg ALG-000184 QD x 28 days were well tolerated:

- Serious AE (SAE): one subject in the 300 mg cohort was hospitalized for a pneumothorax more than 8 weeks after the last dose of study drug, which was considered unlikely related to study drug
- No treatment emergent AEs (TEAE) led to premature discontinuation
- The most commonly (≥3 subjects) reported TEAEs were:
  - ALT elevation: N=8 (100 mg cohort); N=5 (300 mg cohort)
  - AST elevation: N=6 (100 mg cohort); N=5 (300 mg cohort)
  - Hyperuricemia N=6 (100 mg cohort); N=1 (300 mg cohort)
  - Upper Respiratory Tract Infection: N=3 (300 mg cohort)
- TEAEs were generally mild (Grade 1) or moderate (Grade 2) in severity and without dose response. Six subjects had Grade ≥ 3 TEAEs of ALT elevations that were
  - Assessed by the AFC as not due to drug toxicity
  - Not associated with clinically concerning changes in other laboratory parameters (e.g bilirubin, INR)
  - Resolved spontaneously (N=2) or improved/resolved after initiation of licensed HBV drugs (N=4)
  - Often associated with reduction in HBV-DNA and/or HBsAg
- No clinically concerning laboratory, ECG, vital sign or physical examination findings were reported

ANTIVIRAL ACTIVITY: HBsAg

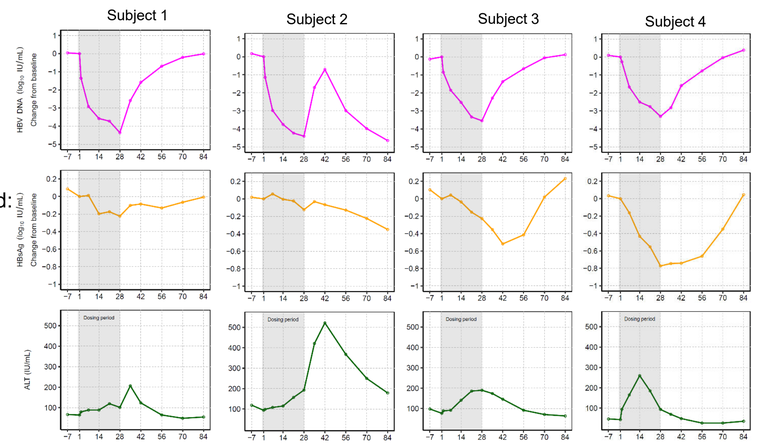
- 3 out of 7 evaluable* subjects dosed with 300 mg ALG-000184 experienced reduction in HBsAg ranging from 0.23 to 0.78 log_{10} IU/mL
- A subject in the 100 mg cohort with high exposures of ALG-001075 equivalent to 300 mg had a 0.5 log_{10} IU/mL decline in HBsAg

Table 2: Subjects with HBsAg decline in the 100 mg and 300 mg Cohorts

Subject*	Dose (mg)	HBsAg baseline (log_{10} IU/mL)	Max HBsAg decline (log_{10} IU/mL)
1	300	3.66	-0.23
2	300	4.82	-0.35
3	100	4.80	-0.52
4	300	4.27	-0.78

*Among the 12 subjects enrolled in the 300 mg dose cohort, only 7 were evaluable: 2 subjects had missing laboratory data due to prolonged COVID lockdown in China, 2 subjects were randomized to placebo and 1 subject had HBsAg levels above the upper limit of assay sensitivity throughout the study

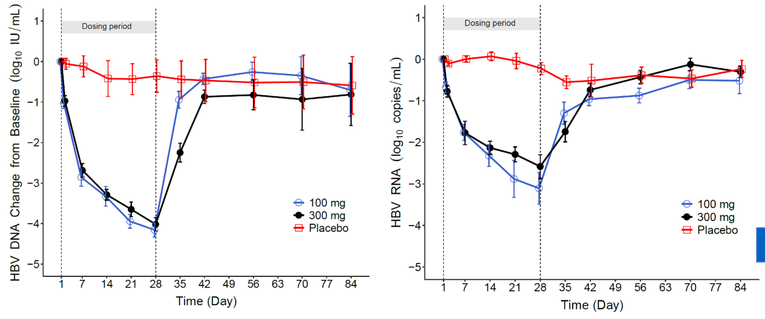
Figure 1: Individual HBV DNA, HBsAg and ALT profiles of 4 subjects with HBsAg declines



ANTIVIRAL ACTIVITY: HBV DNA and HBV RNA

- HBeAg positive CHB subjects dosed with 100 mg and 300 mg ALG-000184 had similar rapid & profound declines in HBV DNA/RNA at Day 28:
  - HBV DNA mean decline: 4.2 (100 mg), 4.02 log_{10} IU/mL (300 mg)
  - HBV RNA mean decline: 3.1 (100 mg), 2.6 log_{10} copies/mL (300 mg)

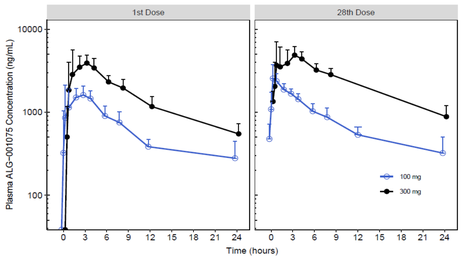
Figure 2: Mean (SEM) Change from Baseline in HBV DNA and RNA



PHARMACOKINETICS

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

Figure 3: Mean (+SD) Plasma ALG-001075 at Day 1 and 28



CONCLUSIONS

- Oral daily dosing for 28 days with 100 mg and 300 mg of ALG-000184 in HBeAg positive CHB subjects was generally well tolerated with a favorable PK profile
- Similar rapid and profound declines in HBV DNA and RNA were observed at both dose levels
- The observation of HBsAg declines as high as 0.78 log_{10} IU/mL in subjects achieving drug exposures corresponding to 300 mg for 28 days suggests that this dose/exposure level may be engaging the CAM 2nd MoA
- This finding supports the further evaluation of ALG-000184 over longer durations to further characterize its ability to lower HBsAg levels

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1. Lok A.S., J of Hepatology 2017. 2. Q Zhang EASL 2020. 3. Gane E, APASL 2021. 4. Gane E, HBV-TAG 2021.

DISCLOSURES

Hou J.: AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson, Roche. **Niu J**: Assembly Biosciences, Shanghai Zhimeng Biopharma. **Ding Y.**: nothing to disclose. **Liang X.**: nothing to disclose. **Yuen MF**: AbbVie, Aligos, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Bristol-Myers Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Merck Sharp and Dohme, Roche, Springbank Pharmaceuticals, Silverback Therapeutics, Sysmex Corporation and Vir Bio. **Gane E**: AbbVie, Abbott Diagnostics, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, Enanta, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche and Vir Bio. **Agarwal K**: Abbott, Aligos, Arbutus, Assembly, BMI, BI, Gilead, Janssen, Immunocore, Roche, Sobi, Vir Bio. **Massetto B**, **Le K, Westland K, Maderazo M, Zhang Q, Blatt L, Beigelman L, Chanda S, Lin T, McClure M, Fry J**: Employees of Aligos Therapeutics Inc.

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