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

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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 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 Asian and non-Asian CHB subjects.

MATERIALS AND METHODS

ALG-000184-201 is a three-part, multicenter, double blind, randomized, placebo-controlled Phase 1 study conducted in China, Hong-Kong, New Zealand, Moldova, and United Kingdom (NCT04536337).

- Parts 1 and 2: all subjects have completed dosing and follow up
  - Single oral doses up to 500 mg and multiple oral 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 in both Asian and non-Asian subjects [3,4]
- Part 3 is ongoing and evaluating multiple cohorts (N=10/cohort; 8 active: 2 placebo) 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 and AST ≤ 5 x ULN; HBV DNA > 2000 IU/mL
  - Key Exclusion Criteria: liver fibrosis classified as Metavir Score ≥F3 liver disease
- Throughout the study, safety assessments (adverse events (AEs), vital signs, electrocardiogram (ECG) and laboratory abnormalities), 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 determine dose escalation
- Plasma concentrations of ALG-001075 (active moiety) are quantified using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS)
- PK parameters are determined by non-compartmental analysis using Phoenix WinNonlin

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

- Cohort 1: 100 mg ALG-000184 or placebo in HBeAg negative subjects
- Cohort 2: 50 mg ALG-000184 or placebo in HBeAg negative subjects
- Cohort 4: 100 mg ALG-000184 or placebo in HBeAg positive subjects

RESULTS

BASELINE CHARACTERISTICS

- Across the cohorts, Asian CHB subjects had a lower BMI, a higher prevalence of HBeAg positivity, a different predominant HBV genotype, and a higher mean HBV DNA and HBV RNA compared to non-Asian subjects.

	Cohort 1, 100 mg ALG000184/PBO N=10		Cohort 2, 50 mg ALG-000184/PBO N=10		Cohort 4, 100 mg ALG000184/PBO N=10	Total N=30	
	Asian N=1	Non-Asian N=9	Asian N=7	Non-Asian N=3	Asian N=10	Asian N=18	Non-Asian N=12
Age (years), mean (SEM)	56.0	43.4 (2.9)	46.4 (2.8)	34.0 (3.1)	30.2 (2.6)	37.9 (2.7)	41.1 (2.6)
Male, N (%)	0	6 (66.7)	3 (42.9)	1 (33.3)	8 (80.0)	11 (61.1)	7 (58.3)
BMI (Kg/m2), mean (SEM)	20.2	27.4 (1.8)	22.8 (1.5)	27.9 (4.4)	21.8 (0.95)	22.1 (0.8)	27.6 (1.7)
Weight (Kg), mean (SEM)	57.0	81.1 (7.1)	59.0 (6.3)	83.8 (14.1)	62.8 (2.8)	61.0 (2.8)	81. 8 (6)
HBeAg negative (%)	1 (100)	9 (100)	7 (100)	3 (100)	0	8 (44.4)	12 (100)
HBV Genotype: A/B/C/D/unknown, (%)	B (100)	D (89); A (11)	B (86); C (14)	A (33); D (67)	B (30); C (60); Unknown (10)	B (56); C (39); Unknown (5)	D (83); A (17)
HBV DNA (log_{10} IU/mL), mean (SEM)	4.2	4.2 (0.4)	4.7 (0.5)	4.8 (0.5)	8.1 (0.3)	6.6 (0.5)	4.4 (0.3)
HBV RNA (log_{10} copies/mL), mean (SEM)	1.8	1.5 (0.4)	2.1 (0.4)	2.1 (0.5)	7.8 (0.4)	5.2 (0.7)	1.7 (0.3)
HBsAg (log_{10} IU/mL), mean (SEM)	2.7	3.5 (0.2)	2.7 (0.3)	3.8 (0.5)	4.5 (0.1)	3.7 (0.3)	3.5 (0.2)

PBO= Placebo. BMI= Body Mass Index. SEM= Standard Error of the Mean

SAFETY

Administration of 100 mg and 50 mg of ALG-000184 or placebo QD for 28 days was generally well tolerated among both Asian and non-Asian subjects:

- An Asian subject with a history of sciatica experienced mild spinal lumbar pain considered unrelated to study drug, which was reported as a serious AE (SAE) due to brief hospitalization for pain management
- Treatment emergent adverse events (TEAEs):
  - There were no TEAEs leading to study drug discontinuation
  - TEAEs were slightly more frequently reported among Asian (N=14/18 subjects, 77.8%) compared with non-Asian subjects (N=8/12 subjects, 66.7%). However, this was due to the relatively large number of TEAEs, mostly mild in severity, reported in HBeAg-positive subjects enrolled in Cohort 4 (10/10 subjects, 100%), all of whom were Asian.
    - Among HBeAg negative subjects, the rate of TEAEs was higher in non-Asian (8/12=66.7%) than in Asian subjects (N=4/8, 50%). A similar comparison was not feasible among HBeAg positive subjects (all Asian).
  - TEAEs were mostly mild (Grade 1) or moderate (Grade 2) in severity with no evidence of a dose response. Three subjects (two Asian and one non-Asian) had a Grade 3 TEAE of ALT elevations during the follow up period. All three Grade 3 TEAEs of ALT elevation were:
    - Asymptomatic, 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 abnormalities, ECGs, vital signs or physical examination findings were reported

Dose	Cohort 1, 100 mg ALG-000184/PBO N=10 HBeAg negative		Cohort 2, 50 mg ALG-000184/PBO N=10 HBeAg negative		Cohort 4, 100 mg ALG-000184/PBO N=10 HBeAg positive	Total N=30	
Subject, N (%)	Asian N=1	Non-Asian N=9	Asian N=7	Non-Asian N=3	Asian N=10	Asian N=18	Non-Asian N=12
Any TEAE	1 (100)	5 (55.6)	3 (42.9)	3 (100)	10 (100)	14 (77.8)	8 (66.7)
SAE	1	0	0	0	0	0	0
TEAE leading to study drug discontinuation	0	0	0	0	0	0	0
Worst reported grade TEAE*							
TEAE Grade 1	1 (100)	3 (33.3)	3 (42.9)	2 (66.7)	10 (100)	14 (77.8)	5 (41.7)
TEAE Grade 2	0	2 (22.2)	0	3 (100)	3 (30)	3 (16.7)	5 (41.7)
TEAE Grade 3	0	1 (11.1)	0	0	2 (20)	2 (11.1)	1 (8.3)
TEAE Grade 4	0	0	0	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

- Similar rapid and substantial declines in HBV DNA and HBV RNA were observed at the 100 mg and 50 mg dose levels, regardless of HBeAg status (Fig. 1)
- The Asian vs non-Asian analysis was feasible for Cohort 2 only, as in Cohort 1 only one subject was Asian and all subjects in Cohort 4 were Asian.
  - A similar rapid and significant HBV DNA and HBV RNA decline was observed in Asian and non-Asian subjects dosed with 50 mg dose level (Fig.2)

Fig 1: Mean (SEM) Serum HBV DNA and HBV RNA Levels Change from Baseline Through the End of Study (HBV DNA) and through the End of the Dosing Period (HBV RNA), by Cohort.

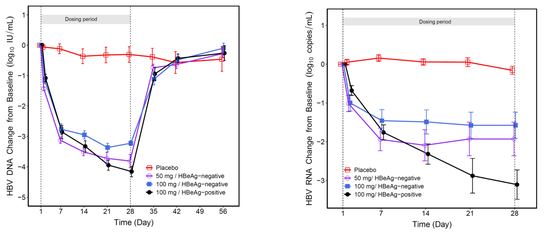
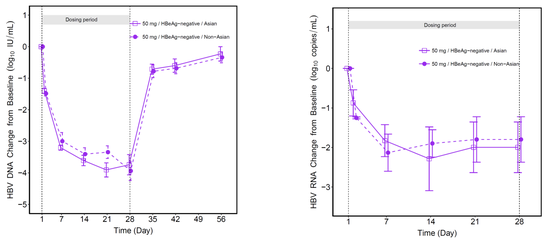


Fig 2: Mean (SEM) Serum HBV DNA and HBV RNA Levels Change from Baseline Through the End of Study (HBV DNA) and through the End of the Dosing Period (HBV RNA), in Cohort 2 (50 mg ALG-000184/placebo) in Asian and non-Asian subjects



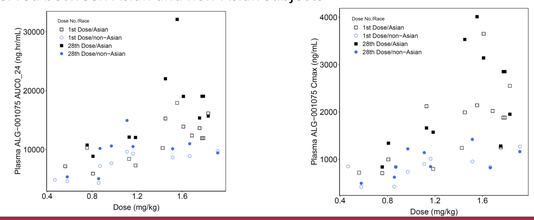
HBV DNA: Roche Cobas® assay, Lower Limit of Quantification (LLOQ): 10 IU/mL
HBV RNA: Roche Cobas® investigational assay (IA), LLOQ: 10 copies/mL. The HBV RNA IA is not approved in any market.

	HBV DNA					HBV RNA				
Cohort, ALG-000184 dose	Cohort 1 100 mg N=8 HBeAg neg	Cohort 2 50 mg N=8 HBeAg neg		Cohort 4 100 mg N=8 HBeAg pos	PBO N=6	Cohort 1 100 mg N=8 HBeAg neg	Cohort 2 50 mg N=8 HBeAg neg		Cohort 4 100 mg N=8 HBeAg pos	PBO N=6
	Overall N=8	Asian N=5	Non-Asian N=3	Asian N=8	Overall N=6	Overall N=8	Asian N=5	Non-Asian N=3	Asian N=8	Overall N=6
Baseline, mean (SEM)	4.2 (0.4)	4.8 (0.6)	4.8 (0.5)	8.3 (0.3)	5.3 (0.7)	1.7 (0.4)	2.1 (0.6)	2.1 (0.5)	7.8 (0.4)	3.6 (1.3)
Change from BL at Day 28, mean (SEM)	-3.2 (0.1)	-3.7 (0.3)	-3.9 (0.3)	-4.2 (0.2)	-0.3 (0.2)	-1.6 (0.3)	-2.0 (0.6)	-1.8 (0.6)	-3.1 (0.4)	-0.2 (0.1)
Subjects < LLOQ at Day 28, N (%)	6 (75)	3 (75)[a]	2 (100)[b]	0	0	8 (100)	4 (100)[a]	2 (100)[b]	0	1 (17)

PBO= Placebo. BL= Baseline. SEM= Standard Error of the Mean. HBV DNA values: log_{10} IU/mL; HBV RNA values: log_{10} copies/mL
a. One Asian subject had missing HBV DNA and RNA data due to early discontinuation for personal reasons (not safety related).
b. One non- Asian subject had missing HBV DNA and RNA data because they did not attend the Day 28 visit due to COVID level 4 lock down

PHARMACOKINETICS

- No significant difference in exposures by body weight adjusted doses was observed between Asian and non-Asian subjects



CONCLUSIONS

- Oral daily dosing for 28 days with 100 mg and 50 mg of ALG-000184/placebo was generally well tolerated among both Asian and non-Asian subjects.
- Similar rapid declines in HBV DNA and HBV RNA were observed at both 50 mg and 100 mg dose levels, regardless of HBeAg status. No differences in antiviral activity were noted between Asian and non-Asian subjects receiving 50 mg ALG-000184. Among HBeAg negative subjects, ≥ 75% of subjects achieved HBV DNA and 100% of subjects had HBV RNA < LLOQ.
- No significant difference in exposures by body weight adjusted doses was observed between Asian and non-Asian subjects
- Dosing in additional cohorts is ongoing. A Phase 2 study to evaluate combinations of ALG-000184 with other novel therapies is planned.

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REFERENCES

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DISCLOSURES

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. **Agarwal K**: Abbott, Aligos, Arbutus, Assembly, BMI, BI, Gilead, Janssen, Immunocore, Roche, Sobi, 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. **Jucov A**. nothing to disclose. **Schwabe C**: nothing to disclose. **Le K, Westland C, Zhang Q, Blatt L, Chanda S, McClure M, Fry J**: Employees of Aligos Therapeutics Inc.

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