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

ALIGOS THERAPEUTICS

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Abstract #843

INTRODUCTION

CHB affects >250 million people worldwide and complications of CHB are associated with an annual mortality rate of ~900,000.[1] Despite its significant impact on global health, the current standard of care for CHB, nucleos(t)ide analogs, rarely results in functional cure, the goal of CHB treatment. As such, there is a significant unmet 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 CHB subjects.

MATERIALS AND METHODS

ALG-000184-201 is a three-part, multicenter, double blind, randomized, placebo-controlled study (NCT04536337).

- In Parts 1 and 2, single oral doses up to 500 mg and multiple doses up to 250 mg were evaluated in healthy volunteers (N=48) and found to be well tolerated with dose dependent, linear PK[2,3]
- Part 3 is ongoing and evaluating multiple cohorts (N=10/cohort; 8 active: 2 placebo) of currently not treated/treatment naïve (CNT/TN) hepatitis B e antigen (HBeAg) negative or positive CHB subjects, who are receiving daily (QD) oral doses of ALG-000184 or placebo for 28 days
- 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 review safety and PK data on a regular basis to review safety data and determine dose escalation
- Plasma concentrations of ALG-001075 (active moiety) were quantified using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method
- PK parameters were determined by non-compartmental analysis using Phoenix WinNonLin

Here, we report preliminary safety, PK, and antiviral activity data from Part 3 Cohorts 1 (100 mg) and 2 (50 mg), in HBeAg-negative CHB subjects.

RESULTS

BASELINE CHARACTERISTICS

- Baseline characteristics were similar across Cohorts 1 and 2, except for ethnicity and genotype

Characteristics	Cohort 1, 100 mg ALG00184/placebo N=10	Cohort 2, 50 mg ALG00184/placebo N=10
Age (years), mean (SEM)	44.7 (2.9)	42.7 (2.8)
Male, N (%)	6 (60)	4 (40.0)
White/Asian/Other, N (%)	9 (90)/1 (10)/0	2 (20)/ 7 (70)/1 (10)
BMI (kg/m^2), mean (SEM)	26.7 (1.8)	24.3 (1.7)
HBV Genotype: A/B/C/D, N (%)	1 (10)/1 (10)/ 0 /8 (80)	1 (10)/6 (60)/1 (10)/2 (20)
HBV DNA (log_{10} IU/mL), mean (SEM)	4.2 (0.3)	4.7 (0.4)
HBV RNA (log_{10} copies/mL), mean (SEM)	1.6 (0.3)	2.1 (0.3)
HBsAg (log_{10} IU/mL), mean (SEM)	3.4 (0.2)	3.0 (0.3)
HBcrAg (log_{10} pg/mL), mean (SEM)	36.4 (33.7)	80.8 (51.1)

BMI = Body Mass Index; SEM - Standard Error of the Mean

SAFETY

Administration of 100 mg and 50 mg of ALG-00184 or placebo QD for 28 days was well tolerated:

- A 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 generally mild or moderate in intensity
  - Four subjects (2 in each cohort) had a TEAE of ALT elevation:
    - Three were Grade 1 and one was Grade 3. None were symptomatic or associated with changes in liver synthetic function
    - Three occurred after the completion of treatment. One (Grade 1) occurred at Day 2 after the first dose and resolved spontaneously despite continued dosing; the event was considered a spontaneous flare by the ALT Flare Committee
- No clinically concerning laboratory, ECG, vital sign or physical examination findings

Subjects, N* (%)	Cohort 1, 100 mg ALG00184/placebo N=10	Cohort 2, 50 mg ALG00184/placebo N=10
SAE	1 (10)	0
TEAE Any	6 (60)	6 (60)
TEAE leading to study drug discontinuation	0	0
TEAE Grade 1	5 (50)	5 (50)
TEAE Grade 2	3 (30)	3 (30)
TEAE Grade 3	1 (10)	0
TEAE Grade 4	0	0
TEAE in ≥ 2 subjects	• Back pain (n=3) • ALT elevation (n=2)	• Headache (n=3) • ALT elevation (n=2) • Diarrhoea (n=2)

*If a subject experienced two or more 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 (Fig. 1 and 2)
- No clinically significant declines in HBsAg were observed

Figure 1: Mean (SEM) HBV DNA Over Time

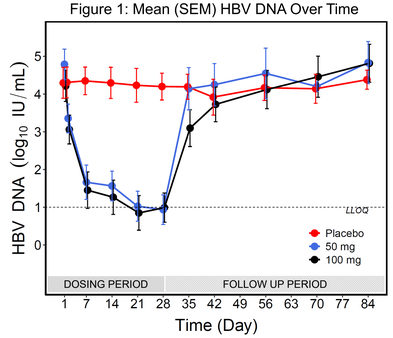
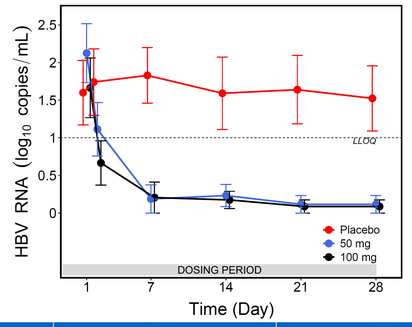


Figure 2: Mean (SEM) HBV RNA Over Time



	HBV DNA			HBV RNA		
ALG-000184 Dose	100 mg N=8	50 mg N=8	Placebo N=4	100 mg N=8	50 mg N=8	Placebo N=4
Baseline, mean (SEM)	4.2 (0.4)	4.8 (0.4)	4.3 (0.4)	1.7 (0.4)	2.1 (0.4)	1.6 (0.4)
Change from Baseline at Day 28, mean (SEM)	-3.2 (0.1)	-3.8 (0.2)	-0.1 (0.1)	-1.6 (0.3)	-1.9 (0.4)	-0.08 (0.1)
Subjects <LLOQ at Day 28, N (%)	6 (75.0)	5 (83.0)*	0 (0)	8 (100.0)	6 (100.0)*	1 (25.0)

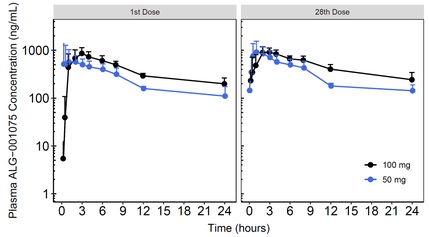
SEM - Standard Error of the Mean. HBV DNA values: log_{10} IU/mL; HBV RNA values: log_{10} copies/mL
* Two subjects had missing HBV DNA and RNA data due to early discontinuation for personal reasons (not safety related) (N=1) and because the subject did not attend Day 28 visit due to COVID level 4 lock down (N=1)

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.

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

Figure 3 : Mean (+SD) Plasma Concentration-Time Profiles



ALG-000184 Dose (mg)	Dose No.	N	BW (kg)	ALG-001075 C_{max} (ng/mL)	t_{max} (hr)	ALG-001075 AUC_{024h} (ng.hr/mL)
50	1st dose	8	69.4 (32.8)	773 (61.5)	1.5 (0.25,6)	6330 (31.5)
	28th dose	6	59.9 (27)	982 (46.1)	1 (0.5,2)	8500 (35.4)
100	1st dose	8	78.7 (29.5)	959 (19.9)	2.5 (1,4)	9180 (21)
	28th dose	8	78.7 (29.5)	1070 (21)	2.5 (0.5,3)	11300 (19.9)

Values represent geometric mean (CV) except for BW [average (SD)] and t_{max} [median (minimum, maximum)]

CONCLUSIONS

Oral daily dosing for 28 days with 100 mg and 50 mg of ALG-000184 was well tolerated and resulted in rapid declines in HBV DNA and RNA levels to below LLOQ in ≥75% of subjects. Exposures increased in a dose proportional manner with low inter-subject variability. 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

1. WHO HBV fact sheet 2020. 2. Gane E, APASL 2021. 3. Gane E, HBV-TAG 2021

DISCLOSURES

Gane E: AbbVie, Abbott Diagnostics, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, Enanta, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche and Vir Bio. **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. **Jucov A**. nothing to disclose. **Schwabe C**: nothing to disclose. **Agarwal K**: Abbott, Aligos, Arbutus, Assembly, BMI, BI, Gilead, Janssen, Immunocore, Roche, Sobi, Vir Bio. **Le K, Westland K, Zhang Q, Blatt L, Chanda S, McClure M, Fry J**: Employees of Aligos Therapeutics Inc.

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