AASLD The Liver Meeting® Nov. 10-14, 2023

LONG-TERM DOSING WITH THE CAPSID ASSEMBLY MODULATOR ALG-000184 RESULTS IN MULTI-LOG REDUCTIONS OF DNA, RNA, HBsAg, HBeAg AND HBcrAg IN UNTREATED HBeAg POSITIVE CHRONIC HEPATITIS B SUBJECTS

YUEN Man-Fung [1]; GANE Edward J [2]; AGARWAL Kosh [3]; DING Hua Yan [4]; JUCOV Alina [5]; WU Min [6]; LE Kha [6]; MADERAZO Maida [6]; WESTLAND Christopher [6]; BLATT Lawrence M [6]; BEIGELMAN Leonid N [6]; CHANDA Sushmita [6]; LIN Tse-I [6]; McCLURE Matthew [6]; HOU Jinlin [7]

1. Department of Medicine, School of Clinical Medicine, The University of Hong Kong. 2. Auckland Clinical Studies Limited. 3. Institute of Liver Studies, King's College Hospital. 4. First Hospital of Jilin University. 5. Arensia Exploratory Medicine Gmbh. 6. Aligos Therapeutics, Inc. 7. Nanfang Hospital, Southern Medical University

ALIGOS THERAPEUTICS

Abstract #48366
Poster #5028-C

INTRODUCTION

- Chronic hepatitis B (CHB) treatment is challenging due to persistence of intrahepatic cccDNA, which acts as a reservoir for infection in hepatocytes [1]
- In vitro, the capsid assembly modulator producing empty (CAM-E) viral particles, ALG-000184, inhibits both viral assembly in infected hepatocytes by modulating pg-RNA encapsidation (1st mechanism of action (MOA)) and viral disassembly (2nd MOA), which prevents de novo cccDNA establishment in uninfected hepatocytes [2]
- Previously, we have reported that, in ongoing Study ALG-000184-201, HBeAg+ CHB subjects that received ALG-000184 + Entecavir (ETV) x ≤36 weeks experienced multi-log_{10} reductions in viral DNA, RNA and HBsAg with no safety concerns [3,4]
- Here we report emerging data from the same study, including subjects dosed for ≤48 weeks

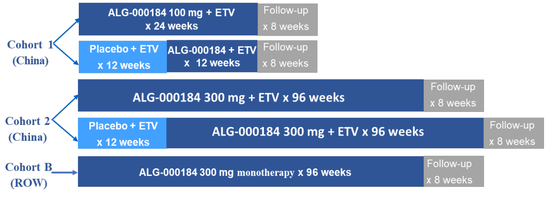
AIM

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

MATERIALS AND METHODS

ALG-000184-201 (NCT04536337) is a multipart Phase 1 study. Parts 1-3 are complete. Part 4 consists of three cohorts, the designs of which are shown in Figure 1. Briefly, each cohort assesses the safety, PK, & antiviral activity of an oral daily 100 mg (Cohort 1) or 300 mg (Cohorts 2 & B) dose of ALG-000184 with (Cohorts 1-2) or without (Cohort B) ETV in HBeAg+ (Cohorts 1, 2 & B) or HBeAg- (Cohort B) CHB subjects. The planned dosing duration was 24 weeks (Cohort 1) or 96 weeks (Cohorts 2 & B) and there was an active comparator (ETV monotherapy x 12 weeks) in Cohorts 1-2.

Figure 1 ALG-000184-201 Part 4 Study Design



Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories), PK, and viral markers are regularly collected. The Study Review Committee (SRC) and ALT Flare Committee (AFC) review safety and PK data on a regular basis for study oversight and to determine the dosing regimen. Parts 1-3 and Part 4 Cohort 1 (P4C1) data have been reported previously. [3,4] This data summary focuses primarily on untreated HBeAg+ CHB subjects in Part 4 Cohorts 2 (P4C2) and B (P4CB).

Virology assays were performed in KingMED (China) and Sonic Laboratories (Rest-of-World, ROW). Lower Limit of Quantitation (LLOQ) of HBV DNA, HBsAg, HBeAg and HBcrAg assays are 10 IU/mL, 0.05 IU/mL, 1COI or 0.01 PEI U/mL and 3 log U/mL, respectively. P4C2 & P4CB virology summaries generally only include data at time points where subjects were compliantly receiving 300 mg ALG-000184 ± ETV (confirmed by PK).

RESULTS

BASELINE CHARACTERISTICS

- Baseline characteristics were comparable (Table 1) among HBeAg+ subjects enrolled in P4C2 (n=15), and P4CB (n=10) as well as P4C1 (N=11; data not shown)
- As expected for an HBeAg+ population, subjects were young with high titers of all CHB viral markers. Nearly all subjects were Asian and HBV genotype B/C
- 53% of subjects had normal baseline ALT levels in P4C2 compared to 10% in P4CB

Table 1: Baseline characteristics of HBeAg+ CHB Subjects

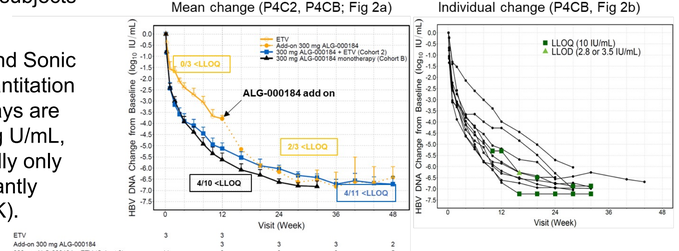
Characteristic	P4C2 (n=15*)	P4CB (n=10)
Age, years, mean (SEM)	31.4 (3.3)	36.8 (2.9)
Male, n(%)	8 (53)	7 (70)
Asian, n(%)	3 (100)	9 (90)
BMI, kg/m², mean (SEM)	22.2 (0.8)	22.4 (0.8)
HBV Genotype, n(%)	B: 5 (33); C: 10 (67)	B: 5 (50); C: 4 (40) D: 1 (10)
HBV DNA, log_{10} IU/mL, mean (SEM)	8.1 (0.2)	8.0 (0.2)
HBV RNA, log_{10} copies/mL, mean (SEM)	6.7 (0.3)	5.3 (0.4)
HBsAg, log_{10} IU/mL, mean (SEM)	4.4 (0.2)	4.3 (0.1)
HBeAg, log_{10} PEI U/mL, mean (SEM)	2.4 (0.1)	2.6 (0.3)
HBcrAg, log_{10} U/mL, mean (SEM)	8.3 (0.3)	8.3 (0.2)
ALT, U/L, mean (SEM)	38.7 (5.2)	60.7 (11.7)

SEM: standard error of mean.
*Three subjects prematurely discontinued due to non-safety related personal reasons (n=2) and non-compliance of dosing (n=1)

ANTIVIRAL ACTIVITY: HBV DNA and HBV RNA

- 300 mg ALG-000184 given with or without ETV (± ETV) resulted in DNA reductions that were greater than those seen with ETV monotherapy (Fig 2a) and similar to 100 mg ALG-000184 + ETV (data not shown)
- Prolonged treatment with 300 mg ALG-000184 ± ETV resulted in a mean maximum DNA reduction of ~6.8 log_{10} IU/mL with ~40% of patients being <LLOQ (Fig 2a)
- Switching to a combination of ALG-000184 + ETV following 12 weeks of ETV monotherapy resulted in additional HBV DNA declines to levels similar to those in subjects initially receiving 300 mg ALG-000184 ± ETV (Fig 2a)
- No viral breakthrough has been observed in any subject receiving ALG-000184 monotherapy for ≤44 weeks (Fig 2b)
- Mean maximum reduction of HBV RNA was ~4.5 log_{10} copies/mL with 64% of subjects being <LLOQ while receiving 300 mg ALG-000184 ± ETV for ≤48 weeks (data not shown). ETV monotherapy did not change HBV RNA levels (Fig 3b)

Figure 2: DNA changes in subjects receiving 300mg ALG-000184±ETV



ANTIVIRAL ACTIVITY: HBsAg, HBeAg, HBcrAg

- Mean declines of 1.2 log_{10} IU/mL, 1.7 log_{10} PEI U/L and 2.0 log_{10} U/mL for HBsAg, HBeAg, and HBcrAg, respectively, were observed among HBeAg+ subjects receiving 300 mg ALG-000184 ± ETV (Fig 3a). Maximum declines were 2.0 log_{10} IU/mL, 2.1 log_{10} PEI U/L and 2.5 log_{10} U/mL, respectively.
- ETV alone x 12 weeks had no impact on HBV antigens (Fig 3b), suggesting the HBV antigen declines are mediated by ALG-000184
- HBV antigen levels were reduced in a dose-dependent manner (Fig 4), further indicating the effects seen are mediated by ALG-000184
- Among subjects dosed for at least 12 weeks, HBcrAg declines were observed in 22/22 subjects, HBeAg declines were observed in 21/22 subjects, and HBsAg declines were observed 16/22 subjects (Fig 5-6)

Figure 3: Mean changes in HBV viral markers over time

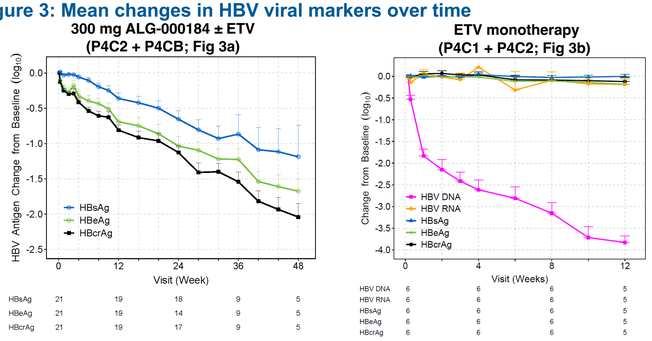


Figure 4: Mean changes in HBsAg, HBeAg & HBcrAg over time in subjects receiving 100mg ALG-000184+ETV (P4C1) vs. 300mg ALG-000184+ETV (P4C2)

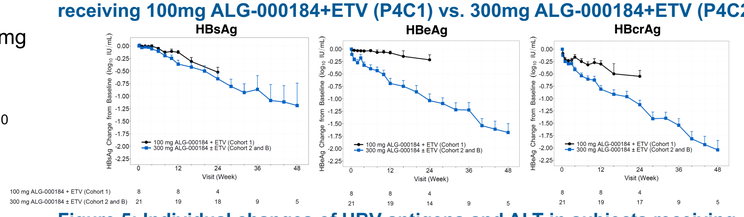


Figure 5: Individual changes of HBV antigens and ALT in subjects receiving 300 mg ALG-000184 + ETV (P4C2) for ≥12 weeks

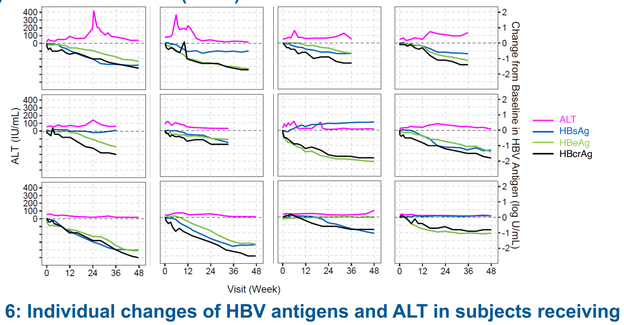
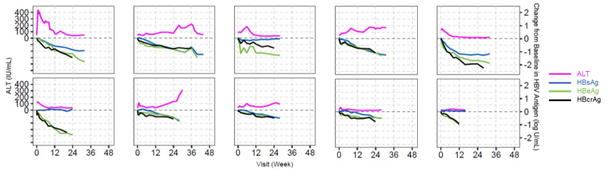


Figure 6: Individual changes of HBV antigens and ALT in subjects receiving 300 mg ALG-000184 monotherapy (P4CB) for ≥12 weeks



SAFETY

- 300 mg ALG-000184 ± ETV x ≤48 weeks was well tolerated with no SAEs, TEAEs leading to discontinuation, or concerning trends in TEAEs, laboratories, ECGs, or vital signs
- Five Grade ≥3 TEAEs of liver transaminase elevations were reported, all of which have recovered, returned to baseline, or are improving while continued dosing. None of these events was associated with concerning symptoms or laboratory evidence of hepatic synthetic dysfunction and none were considered clinically concerning by the AFC. All ALT flares occurred in the setting of significant declines in HBV DNA, RNA, and antigens (Figures 2,5, and 6)

300 mg ALG-000184 +/- ETV	P4C2 (n=15)	P4CB (n=10)
Serious Adverse Events (SAEs)	None	
Treatment emergent AEs (TEAEs) leading to study drug discontinuation	None	
Subjects with Grade ≥3 TEAEs	2 ALT/AST↑ (n=2) neutropenia↑ (n=1)*	3 ALT/AST↑
Concerning TEAE, laboratory, ECG, vital sign, or physical examination findings or trends	None	

* One subject experienced Grade 4 neutropenia, which was considered probably related to an acute upper respiratory infection. This event resolved following the resolution of this infection and despite continued dosing with study drug.

CONCLUSIONS

- Daily oral dosing with 300 mg ALG-000184 ± ETV x ≤48 weeks in untreated HBeAg+ CHB subjects demonstrates:
  - A favorable safety profile
  - Greater suppression of HBV DNA & RNA vs. ETV alone (1st MOA)
  - No viral breakthrough when ALG-000184 is given as monotherapy for ≤44 weeks
  - Multi-log reductions in HBsAg, HBeAg, and HBcrAg, which appear to be ALG-000184-mediated (2nd MOA)
- ALG-000184 appears to lower cccDNA levels via CAM 1st and 2nd MOAs
- When given alone, ALG-000184 may provide an alternative to nucleoside analogs in achieving chronic DNA suppression. When combined with complementary MOAs, ALG-000184 may play a central role in efforts to achieve functional cure
- Phase 2 enabling activities for ALG-000184 are underway

REFERENCES

1. Norah A. Terrault, Hepatology 2015; 2. Q Zhang EASL 2020.
3. Ed Gane, APASL 2023; 4. Jinlin Hou, EASL 2023

DISCLOSURES

Yuen MF: AbbVie, Aligos Therapeutics, AiCuris, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology and Visirna Therapeutics. **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. **Ding Y:** nothing to disclose. **Jucov A:** nothing to disclose. **Wu M, Le K, Maderazo M, Westland C, Blatt L, Beigelman L, Chanda S, Lin T, McClure M**: Employees of Aligos Therapeutics Inc. **Hou J.:** Aligos, Assembly Biosciences, Ascletis, Ascentage Pharma, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Janssen, Roche, Huahuihealth, Qilu Pharma.

CONTACT

Min Wu mwu@aligos.com