ALG-000184, A CAPSID ASSEMBLY MODULATOR, DOSED WITH ENTECAVIR FOR UP TO 28 WEEKS IS WELL TOLERATED AND RESULTED IN SUBSTANTIAL DECLINES IN SURFACE ANTIGEN LEVELS IN UNTREATED HEPATITIS B E ANTIGEN POSITIVE SUBJECTS WITH CHRONIC HEPATITIS B

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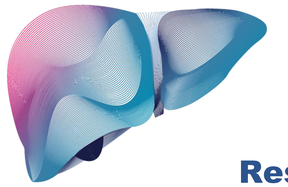

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ALIGOS THERAPEUTICS

Introduction

Functional cure, defined as sustained hepatitis B surface antigen (HBsAg) loss with virologic suppression after a finite treatment course, is the desired outcome for new treatment approaches for the management of chronic hepatitis B (CHB).[1]

Capsid assembly modulators which produce empty viral particles (CAM-E) inhibit hepatitis B virus (HBV) replication via two mechanisms:

- Inhibition of HBV pregenomic RNA (pgRNA) encapsidation leading to reductions in HBV DNA and RNA
- Prevention of de novo cccDNA synthesis leading to HBsAg reductions

ALG-000184 (an oral prodrug of the CAM-E, ALG-001075) is currently being evaluated in a multipart, randomized, double-blind Phase 1 study (ALG-000184-201), which is being conducted in healthy volunteers (HVs) as well as untreated (treatment naïve (TN) and currently not treated (CNT)) CHB subjects. Previously, single and multiple daily doses of ALG-000184 for 7 days have shown acceptable tolerability and pharmacokinetics (PK) in HVs (Parts 1 and 2).[2,3] In addition, favorable safety, PK and antiviral activity, including HBsAg declines, were observed in untreated CHB subjects who received daily doses of ≤300 mg ALG-000184 with or without entecavir (ETV) for 28 days and up to 28 weeks in Part 3 and Part 4 Cohorts 1-2 , respectively.[4,5,6]
Here we report emerging additional data in untreated CHB subjects receiving 300 mg ALG-000184 + ETV in Part 4 Cohort 2.

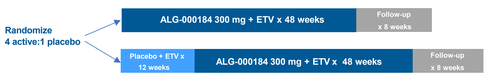
Aim

To evaluate the safety, PK and antiviral activity of ALG-000184 with or without ETV in untreated CHB subjects.

Methods

- ALG-000184-201 (NCT04536337) is a multipart, double blind, randomized placebo-controlled Phase 1 study. Part 4 Cohort 2 is a double blind, randomized (4 active:1 placebo) cohort that is evaluating oral daily doses of 300 mg ALG-000184 or placebo in combination with 0.5 mg ETV for 12 weeks in TN/CNT HBeAg+ CHB subjects. After dosing for 12 weeks, all subjects subsequently are receiving 300 mg ALG-000184 with ETV for a total planned treatment duration of 48 weeks (Figure 1).

Figure 1 Design of Part 4 Cohort 2 in Study ALG-000184-201



- Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories), PK, and viral markers are regularly 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 dosing regimen, including total dosing duration
- Plasma concentrations of ALG-001075 are quantified using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS)
- Virology assays in Part 4 Cohort 2 are:
  - HBV DNA (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 LLOQ = 0.05 IU/mL
- Blinded results are summarized for the overall cohort. Antiviral activity data are summarized as change from baseline (CFB) and include subjects on study drug at the relevant timepoint

Results

Baseline Characteristics

- Fifteen subjects were enrolled in China between September 2022 and February 2023. All subjects were Asian, genotype B or C, and HBeAg+. Consistent with this patient population, subjects were young with high HBV DNA, RNA and HBsAg levels at baseline. Notably, nearly half of subjects (53%) had normal alanine aminotransferase (ALT) levels at baseline.

Table 1 Baseline characteristics and Demographics

	Part 4 Cohort 2 N=15
Age, years, mean (SEM)	31.4 (2.4)
Male, N(%)	8 (53%)
Asian, N(%)	15 (100)
BMI, kg/m^2, mean (SEM)	22.2 (0.8)
HBV Genotype, N(%)	B: 5 (33), C: 10 (67)
HBV DNA $\log_{10}$ IU/mL, mean (SEM)	8.1 (0.2)
HBV RNA $\log_{10}$ copies/mL, mean (SEM)	6.7 (0.3)
HBsAg $\log_{10}$ IU/mL, mean (SEM)	4.4 (0.2)
ALT U/L, mean (SEM)	40.9 (5.3)

Subject Disposition

- Dosing ongoing: N=12 (80%) ; median duration of dosing: 232 days
- Dosing prematurely stopped: N=3 (20%) due to non-safety related personal reasons (N=2) and confirmed non-compliance beginning at Week 12 (N=1)

Safety

- 300 mg ALG-000184 + 0.5 mg ETV for up to 36 weeks was generally well tolerated

Table 2: Summary of Treatment Emergent AEs (TEAEs)

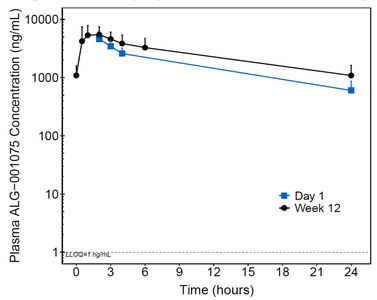
	Part 4 Cohort 2 N=15
Serious Adverse Events (SAEs)	0
TEAEs leading to study drug discontinuation	0
Subjects with Grade ≥ 3 TEAEs	3 (↑ transaminases (N=2)*, neutropenia (N=1)**)
Concerning TEAE, laboratory, ECG, vital sign, or physical examination findings or trends	None

*One subject experienced a Grade 4 ALT elevation with associated Grade 3 AST elevation on Day 41. Another subject experienced a Grade 4 ALT elevation with associated Grade 2 AST elevations on Day 171. Both events resolved despite continued dosing and the AFC assessed these events as not being due to drug toxicity.
**One subject experienced Grade 4 neutropenia probably related to an acute upper respiratory infection, per investigator. This event resolved following the resolution of this infection and despite continued dosing of study drug.

Pharmacokinetics

- Plasma ALG-001075 accumulation at Week 12 was ~60%
- PK was generally similar compared to a prior cohort given 300 mg ALG-000184 alone, suggesting no impact of ETV on ALG-000184 exposure
- ETV exposures were similar with or without ALG-000184 co-administration

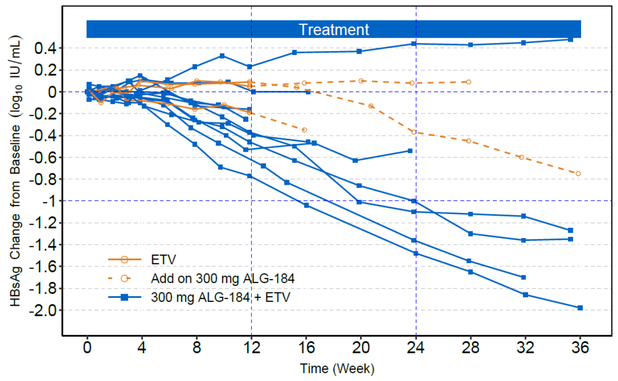
Figure 2: Mean (SD) Plasma ALG-001075 at Day 1 and Week 12



Antiviral Activity: HBsAg

- HBsAg declined steadily on treatment in the majority of subjects (Figure 3). Specifically, after dosing with ALG-000184 + ETV, HBsAg declined by:
  - ≥0.4 $\log_{10}$ IU/mL in 7/12 subjects dosed for 12 weeks
  - ≥1.0 $\log_{10}$ IU/mL in 4/7 subjects dosed for 24 weeks
- Maximum HBsAg decline observed to date: 2 $\log_{10}$ IU/mL (Week 36)
- Two (2) of 3 subjects originally receiving placebo + ETV experienced more substantial HBsAg reductions after adding on ALG-000184 at Week 12.

Figure 3: Individual (N=15) HBsAg Change from Baseline Over Time

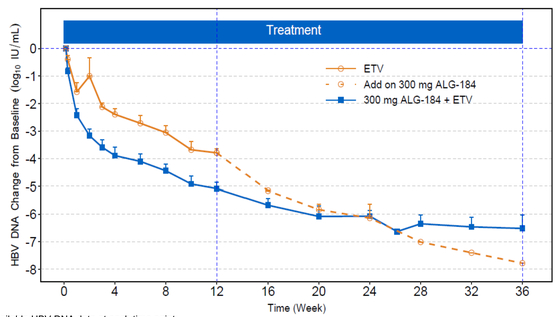


Antiviral Activity: HBV DNA and HBV RNA

300 mg ALG-000184 + ETV resulted in substantial, ongoing declines in HBV DNA (Figure 4) and RNA (Figure 5):

- The addition of 300 mg ALG-000184 at Week 12 in subjects initially receiving ETV resulted in additional rapid declines in HBV DNA and RNA to similar levels as subjects initially randomized to ALG-000184 + ETV
- HBV DNA & RNA levels are <LLOD in N=3 and N=9 subjects, respectively

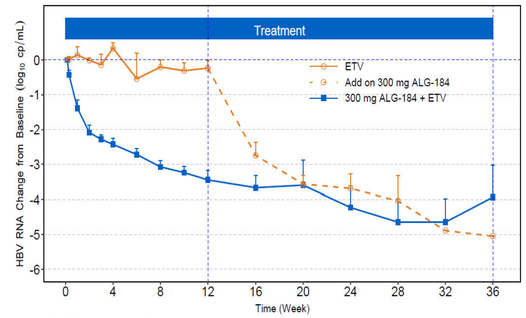
Figure 4: Mean (SEM) HBV DNA Change from Baseline Over Time



Numbers of available HBV DNA data at each time point

300 mg ALG-184 + ETV	12	11	11	10	8	4	6	5	5	4
ETV	3	3	3	3						
Add on 300 mg ALG-184					3	2	2	2	1	1

Figure 5: Mean (SEM) HBV RNA Over Time (Change from Baseline)



Numbers of available HBV RNA data at each time point

300 mg ALG-184 + ETV	12	11	11	10	8	4	6	5	5	3
ETV	3	3	3	3						
Add on 300 mg ALG-184					3	2	2	2	1	1

Conclusions

- Untreated HBeAg positive CHB subjects given 300 mg of ALG-000184 and ETV for up to 36 weeks resulted in:
  - A favorable safety and PK profile
  - Significant reductions in HBV DNA and RNA which are superior to those seen with ETV alone
  - Substantial HBsAg reductions in most subjects:
    - ≥0.4 $\log_{10}$ IU/mL in 7/12 subjects dosed x 12 weeks
    - ≥1.0 $\log_{10}$ IU/mL in 4/7 subjects dosed x 24 weeks
    - Maximum reduction observed to date: 2.0 $\log_{10}$ IU/mL (Week 36)
- Treatment in this cohort is ongoing and will evaluate if further reductions in HBsAg can be achieved with longer duration of dosing
- In addition, 300 mg of ALG-000184 is being evaluated as monotherapy in TN/CNT CHB patients, including HBeAg negative and positive subjects
- These results demonstrate that treatment with ALG-000184, an orally administered CAM-E, can result in multi-log reductions of HBsAg confirming that it may have a direct effect on cccDNA activity. As such, ALG-000184 could be utilized as a key component of combination therapies targeting complete suppression of HBsAg and functional cure.

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Disclosures

Hou J.: Aligos, Assembly Biosciences, Ascletis, Ascentage Pharma, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Janssen, Roche, Huahuihealth, Qilu Pharma. **Niu J.**: nothing to disclose. **Ding Y.**: nothing to disclose. **Liang X.**: nothing to disclose. **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. **Wu M, Le K, Meenakshi V, Westland C, Maderazo M, Chanda S, Beigelman L, Blatt L, Lin T, McClure M, Fry J**: Employees of Aligos Therapeutics, Inc.

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