Dosing with the Capsid Assembly Modulator ALG-000184 in Untreated HBeAg Negative CHB Subjects Results in Potent Antiviral Effects Including Suppression of HBV DNA/RNA and Declines in HBcrAg Levels

Kosh Agarwal[1], Edward Gane[2], Man-Fung Yuen[3], Christian Schwabe[4], Alina Jucov[5], Alexei Haceatraian[5], Min Wu[6], Kha Le[6], Maida Maderazo[6], Lawrence M. Blatt[6], Sushmita Chanda[6], Tse-I Lin[6], Matthew McClure[6]

[1]King's College Hospital, Institute of Liver Studies, [2]Faculty of Medicine, University of Auckland, [3]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, [4]New Zealand Clinical Research Limited, Auckland, New Zealand, [5] ARENSIA Exploratory Medicine, Republican Clinical Hospital and Nicolae Testemitanu State University of Medicine and Pharmacy, Moldova, [6]Aligos Therapeutics, Inc.

EASL CONGRESS Milan, Italy 5–8 June 2024

ALIGOS THERAPEUTICS

WED-361

Contact information
Min Wu mwu@aligos.com

Introduction

- The sustained HBV DNA suppression (< lower limit of Quantitation [LLOQ]) in chronic hepatitis B (CHB) patients with antiviral treatment has been associated with favorable disease outcomes [1].
- ALG-000184 is a prodrug of ALG-001075 which is a novel, pan-genotypic CAM-E (empty capsids) with high in vitro potency.
- The dual mechanism of action (MOA) of ALG-001075 has been demonstrated in vitro: 1) inhibition of pg-RNA encapsidation (1st MOA); 2) inhibition of HBV antigen production through blocking cccDNA establishment/replenishment at higher concentrations (2nd MOA) [2].
- ALG-000184-201 (NCT04536337) is a multipart Phase 1 study. Parts 1-2 in healthy volunteers are complete. HBeAg-positive (HBeAg+) or HBeAg-negative (HBeAg-) subjects with chronic hepatitis B (CHB) or chronic HBV infection were evaluated in Parts 3 to 5. Part 3 and Part 4 Cohort 1 are complete, Part 4 Cohort 2/B and Part 5 Cohort B are on going.
- The potent antiviral effects and favorable safety profile in HBeAg+ CHB subjects receiving 300 mg ALG-000184 ± entecavir (ETV) ≤ 72 weeks from an ongoing Phase 1 study – ALG-000184-201 are reported in poster WED-365, EASL 2024 [3].

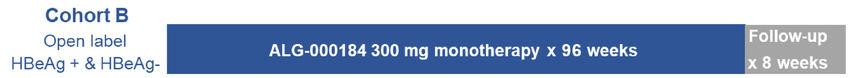
Aim

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

Method

- HBeAg- CHB subjects were enrolled in Part 3 which evaluated 10-100 mg ALG-000184 monotherapy for 28 days versus the matching Placebo, and Part 4 Cohort B which is evaluating 300 mg ALG-000184 monotherapy for up to 96 weeks (Figure 1).
- Part 3 data, reported previously, demonstrated potent antiviral effects and comparable safety profile in HBeAg- CHB subjects received daily oral doses of 10-100 mg ALG-000184 for 28 days compared with placebo [4].
- Here, for the first time, we report the data in HBeAg- CHB subjects who received 300 mg ALG-000184 monotherapy for up to 60 weeks from Part 4 Cohort B.

Figure 1 ALG-000184-201 Part 4 Cohort B Design



Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories), PK, and viral markers were collected at regular intervals. The Study Review Committee (SRC) and ALT Flare Committee (AFC) have study oversight where they review safety and PK data on a regular basis.

Virology markers were analyzed at Sonic Laboratory. Lower Limit of Quantitative (LLOQ) and Detection (LLOD) of HBV DNA are 10 IU/mL and ≤ 4.92 IU/mL, respectively. LLOQs of RNA, HBsAg and HBcrAg (iTACT-HBcrAg) are 10 copies/mL, 0.05 IU/mL, and 1.8 log_{10} U/mL, respectively.

Results

Baseline Characteristics

- A total of 11 enrolled HBeAg- CHB subjects had a mean BMI of 26 kg/m^2, 55.5% were males and 72.7% were non-Asians.
- Age and all HBV baseline markers were in line with disease characteristics of HBeAg- CHB population.
- The mean values at baseline were age 48.5 years, HBV DNA 4.3 log_{10} IU/mL, HBV RNA 2.0 log_{10} copies/mL, HBsAg 3.5 log_{10} IU/mL and HBcrAg 3.1 log_{10} U/mL.

Safety

300 mg ALG-000184 monotherapy in HBeAg- CHB subjects for up to 60 weeks of treatment was well tolerated:

- No serious adverse event (SAE) was reported.
- No treatment emergent adverse event (TEAE) led to study discontinuation.
- Grade 3 TEAEs were reported in two subjects:
  - One subject experienced a Grade 3 TEAE of asymptomatic ALT elevation due to diet change and alcohol use during holiday and recovered in the setting of dosing continuation. AFC reviewed this event as not being related to drug toxicity.
  - One subject with Grade 1 cholesterol and Grade 2 triglycerides abnormalities at baseline experienced Grade 3 TEAEs of cholesterol and triglycerides increase and returned to baseline level in setting of dosing continuation.
- No clinically concerning changes or trends were observed in any other laboratory tests, electrocardiograms, vital signs or physical examinations.

Antiviral Activity: HBV DNA and HBV RNA

- HBeAg- CHB subjects (n=11) receiving 300 mg ALG-000184 monotherapy x ≤ 60 weeks experienced rapid and profound reductions in HBV DNA (Figure 2a).
  - 100% subjects achieved HBV DNA < LLOQ (10 IU/mL) by Week 20.
  - 91% subjects (n=10) achieved HBV DNA < LLOD (≤ 4.92 IU/mL) by Week 48.
  - The mean maximum reduction of HBV DNA was 4.13 log_{10} IU/mL.
  - Time to HBV DNA < LLOQ was dependent on baseline level of HBV DNA (Figure 2b).
  - No viral breakthrough was observed in any subject.
  - 100% subjects achieved HBV RNA < LLOQ (10 copies/mL) by Day 42.

Figure 2a: Individual HBV DNA Level Over Time

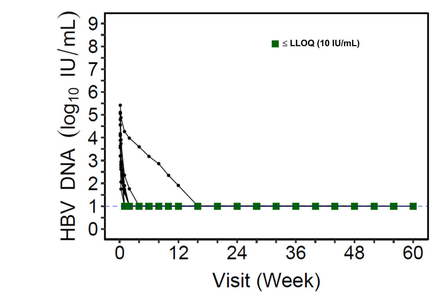
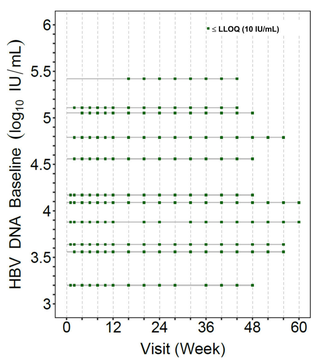


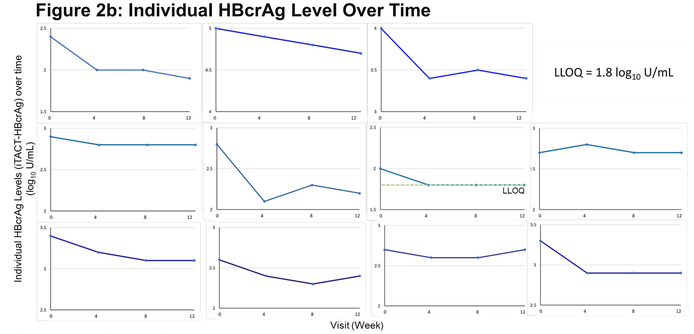
Figure 2b: Individual time to HBV DNA < LLOQ



Antiviral Activity: HBsAg, HBcrAg

- Declines in HBcrAg were observed in 9 of 11 HBeAg- CHB subjects.
- At Week 12, the mean decline in HBcrAg was 0.27 log_{10} U/mL with a maximum reduction of 0.7 log_{10} U/mL.
- One subject with low baseline of HBcrAg (2 log_{10} U/mL) achieved < LLOQ (< 1.8 log_{10} U/mL) .
- No apparent changes in HBsAg were observed.

Figure 2b: Individual HBcrAg Level Over Time



Conclusions

- Daily oral dose of 300 mg ALG-000184 monotherapy ≤ 60 weeks in untreated HBeAg- CHB subjects demonstrated:
  - A favorable safety profile
  - Rapid HBV DNA and HBV RNA suppression (<LLOQ) in all HBeAg-negative subjects (1st MOA)
  - 100% of subjects achieved HBV DNA < LLOQ, 91% of subjects < LLOD and 100% of subjects achieved HBV RNA < LLOQ by Week 48
  - There was no viral breakthrough in any subject
  - HBcrAg decline following ALG-000184 monotherapy may suggest hepatocyte cccDNA formation was inhibited by ALG-000184 (2nd MOA)
- ALG-000184 monotherapy achieves sustained HBV DNA suppression levels by Week 48 which appear to exceed those reported by nucleo(t)sides [5], suggesting the possibility for superior chronic suppression treatment for CHB patients.
- Based on its reduction of antigen levels, ALG-000184 may also play a pivotal role in combination with complementary MOAs for functional cure.
- Further studies are warranted and Phase 2 enabling activities for ALG-000184 are underway.

References

1. AASLD, EASL, APASL guideline; 2. Ling EASL 2020; 3. MF Yuen EASL 2024; 4.Ed Gane APASL Oral 2023; 5. Buti M. et. al, Lancet 2016

Acknowledgements

The authors wish to thank the subjects for participating in this clinical study. The Sponsor is grateful to the staff of the clinical sites and to NOVOTECH for assisting in the conduct of the study. The authors also wish to thank Aligos team members Jen Rito and Chris Burnett for their aid in the conduct of the study.