# ALG-000184, an Orally Administered Capsid Assembly Modulator (CAM) Reduces HBsAg in Subjects with HBeAg Positive Chronic Hepatitis B (CHB)

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## Background

Long-term CHB treatment with nucleos(t)ide analogues suppresses HBV replication and reduces liver injury, but rarely results in functional cure, the goal of CHB treatment. Therefore, there is a significant medical need for novel approaches to enhance functional cure rates. ALG-000184, a prodrug of ALG-001075, a novel, pan-genotypic Class II CAM (empty capsids) with picomolar potency and is being developed for the treatment of CHB. In addition to inhibiting pg-RNA encapsidation (primary mechanism of action [MoA]), ALG-000184 has inhibited the production of HBsAg in vitro through the regulation of the de-novo establishment and replenishment of cccDNA (2nd MoA). The 2nd MoA was observed at higher concentrations ($EC_{50}$ 70.0 nM) than those associated with the inhibition of HBV DNA and RNA replication ($EC_{50}$ 1.98 nM).
Plasma exposures required to engage the secondary MoA are expected to be achieved at the 300 mg dose level.

## Methods

ALG-000184-201 is a multi-part, double blind, randomized, placebo-controlled Phase 1 study (NCT04536337):

- Parts 1 and 2 evaluated single and multiple oral doses in healthy volunteers that were well tolerated with dose dependent, linear PK
- Part 3 evaluated multiple cohorts (N=10/cohort; 8 active: 2 placebo [PBO]) 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
- Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratories), PK, and viral markers were 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 dose escalation
- Plasma concentrations of ALG-001075 are quantified using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS)
- Virology assays:
  - HBV DNA: Roche Cobas® assay. 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

Previously, in treatment naïve (TN) subjects with CHB, daily oral doses of 10-100 mg ALG-000184 for 28 days were well tolerated with linear PK and were associated with profound reductions of HBV DNA and RNA regardless of HBeAg status or dose

Here we report safety, PK and antiviral data for 2 cohorts of HBeAg positive CHB subjects:

- 100 mg ALG-000184/placebo for 28 days
- 300 mg ALG-000184/placebo for 28 days

## Results

### BASELINE CHARACTERISTICS

HBeAg positive subjects were mostly male, all Asian with a low BMI, HBV genotype B or C, and high mean HBV DNA, RNA and HBsAg levels

**Table 1: Baseline characteristics**

| | ALG-000184/placebo | |
|---|---|---|
| **Dose level** | **100 mg** | **300 mg** |
| **N** | **10** | **12*** |
| Age, years, mean (SEM) | 30.2 (2.4) | 31.9 (1.4) |
| Male, N (%) | 8 (80.0) | 6 (50) |
| Asian, N (%) | 10 (100) | 12 (100) |
| BMI, kg/m$^2$, mean (SEM) | 21.8 (1.0) | 22.4 (0.9) |
| HBV Genotype, N (%) | B: 4 (40)<br>C: 6 (60) | B: 5 (42)<br>C: 7 (58) |
| HBV DNA, $log_{10}$ IU/mL, mean (SEM) | 8.1 (0.3) | 8.4 (0.2) |
| HBV RNA, $log_{10}$ cp/mL, mean (SEM) | 7.8 (0.4) | 7.3 (0.2) |
| HBsAg, $log_{10}$ IU/mL, mean (SEM) | 4.5 (0.1) | 4.5 (0.1) |

*Two subjects had to be replaced due to missing laboratory data due to Covid lockdown

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

### SAFETY

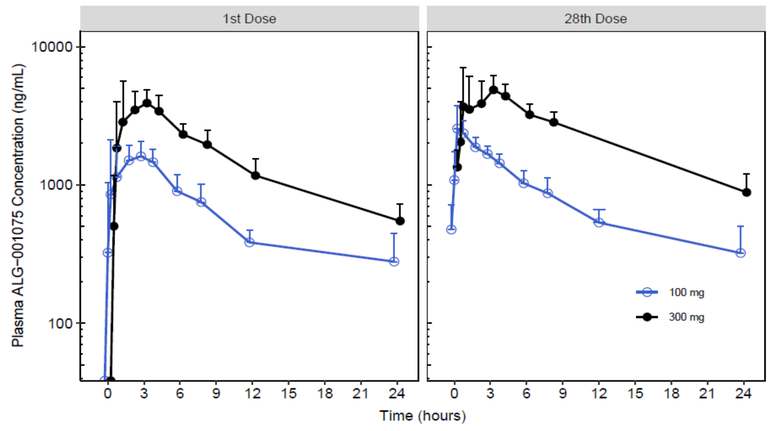
100 mg and 300 mg ALG-000184 QD x 28 days were well tolerated:

- Serious AE (SAE): one subject in the 300 mg cohort was hospitalized for a pneumothorax more than 8 weeks after the last dose of study drug, which was considered unlikely related to study drug
- No treatment emergent AEs (TEAE) led to premature discontinuation
- The most commonly (≥3 subjects) reported TEAEs were:
  - ALT elevation: N=8 (100 mg cohort); N=5 (300 mg cohort)
  - AST elevation: N=6 (100 mg cohort); N=5 (300 mg cohort)
  - Hyperuricemia N=6 (100 mg cohort); N=1 (300 mg cohort)
  - Upper Respiratory Tract Infection: N=3 (300 mg cohort)
- TEAEs were generally mild (Grade 1) or moderate (Grade 2) in severity and without dose response. Six subjects had Grade ≥ 3 TEAEs of ALT elevations that were:
  - Assessed by the AFC as not being due to drug toxicity
  - Not associated with clinically concerning changes in other laboratory parameters (e.g., bilirubin, INR)
  - Resolved spontaneously (N=2) or improved/resolved after initiation of licensed HBV drugs (N=4)
  - Often associated with reduction in HBV-DNA and/or HBsAg
- No clinically concerning laboratory, ECG, vital sign or physical examination findings were reported

## Results

### PHARMACOKINETICS

**Figure 1: Mean (+SD) Plasma ALG-001075 on Day 1 and 28**



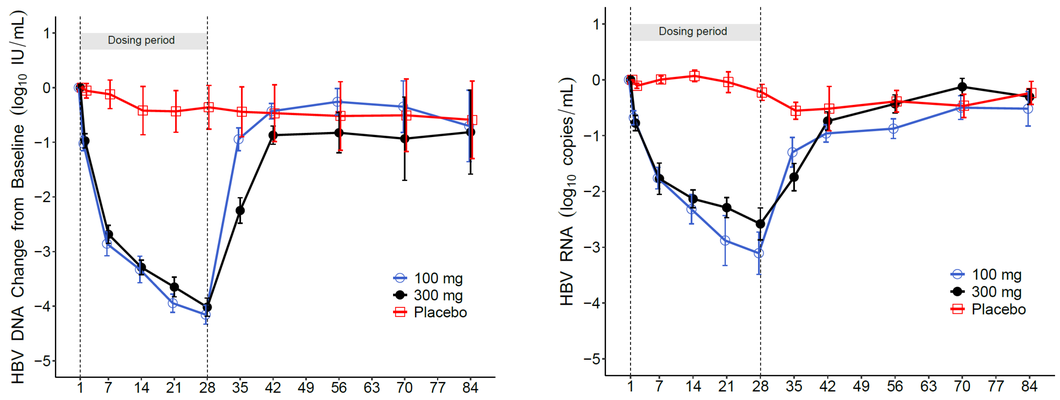

Plasma ALG-001075 exposure increased proportionally to ALG-000184 dose with low to moderate PK variability
Minimal accumulation (~30%) was seen over 28 days.

### ANTIVIRAL ACTIVITY: HBV DNA and HBV RNA

HBeAg positive CHB subjects dosed with 100 mg and 300 mg ALG-000184 had similar rapid and profound declines in HBV DNA/RNA at Day 28:

- HBV DNA mean decline: 4.2 (100 mg), 4.02 $log_{10}$ IU/mL (300 mg)
- HBV RNA mean decline: 3.1 (100 mg), 2.6 $log_{10}$ copies/mL (300 mg)

**Figure 2: Mean (SEM) Change from Baseline in HBV DNA and RNA**




### ANTIVIRAL ACTIVITY: HBsAg

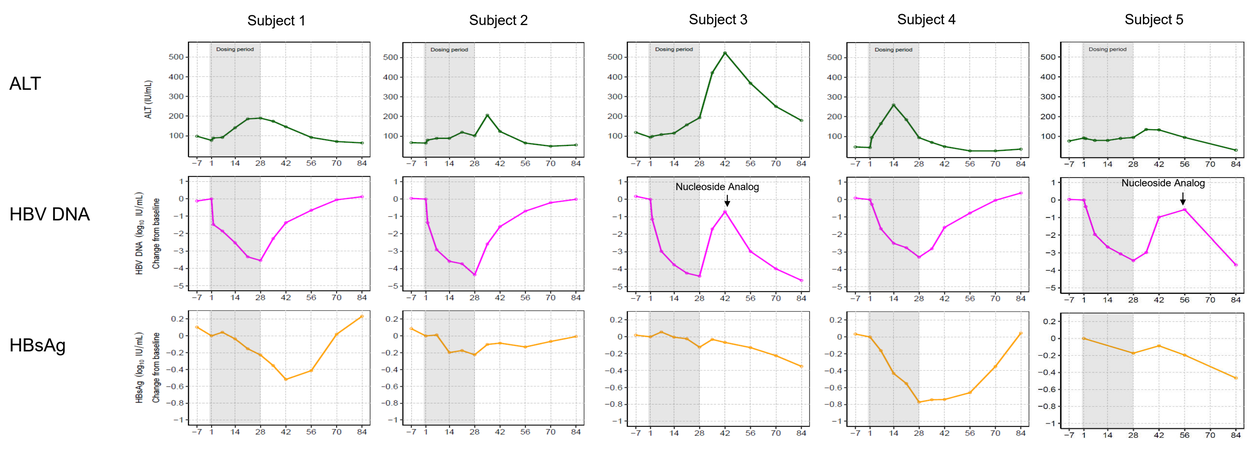
Four out of 8 evaluable* subjects dosed with 300 mg of ALG-000184 experienced reduction in HBsAg ranging from 0.23 to 0.78 $log_{10}$ IU/mL. A subject in the 100 mg cohort with high exposures of ALG-001075 equivalent to 300 mg had a 0.5 $log_{10}$ IU/mL decline in HBsAg. Subjects 1, 2 and 4 had responses that were clearly temporally related to the administration of ALG-000184 i.e., HBsAg declined during the treatment phase and reversed after completion of dosing. Subjects 3 and 5 had minor reductions during the treatment phase which continued to decline following completion of dosing. All subjects who responded had elevated ALT levels at baseline.

**Table 2: Subjects with HBsAg decline in the 100 mg and 300 mg Cohorts**

| Subject* | Dose (mg) | HBsAg baseline ($log_{10}$ IU/mL) | Baseline ALT (U/L) | Max HBsAg decline ($log_{10}$ IU/mL) |
|---|---|---|---|---|
| 1 | 100 | 4.80 | 77 | -0.52 |
| 2 | 300 | 3.66 | 65 | -0.23 |
| 3 | 300 | 4.82 | 94 | -0.35 |
| 4 | 300 | 4.27 | 44 | -0.78 |
| 5 | 300 | 5.34 | 92 | -0.50 |

*Among the 12 subjects enrolled in the 300 mg dose cohort, only 8 were evaluable: 2 subjects had missing laboratory data due to prolonged COVID lockdown in China, 2 subjects were randomized to placebo.

**Figure 3: Individual HBV DNA, HBsAg and ALT profiles of 5 subjects with HBsAg declines**




## Conclusions

- Oral daily dosing for 28 days with 100 mg and 300 mg of ALG-000184 in HBeAg positive CHB subjects was generally well tolerated with a favorable PK profile
- Similar rapid and profound declines in HBV DNA and RNA were observed at both dose levels
- The observation of HBsAg declines as high as 0.78 $log_{10}$ IU/mL in subjects achieving drug exposures corresponding to 300 mg for 28 days suggests that this dose/exposure level may be engaging the CAM 2nd MoA
- Of note, the subjects who responded had elevated serum ALT levels. In comparison, subjects with normal ALT levels had no meaningful reduction in HBsAg over this timeframe
- This finding supports the further evaluation of ALG-000184 over longer durations to further characterize its ability to lower HBsAg levels

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