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The Safety and Antiviral Effect of Oral Daily 300 mg ALG-000184 in Combination with Entecavir for up to 96 Weeks in Untreated HBeAg-Positive Subjects with Chronic Hepatitis B Virus Infection

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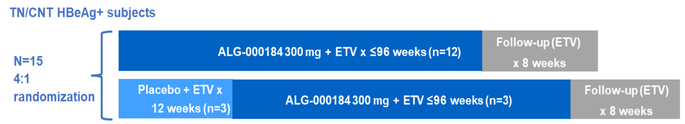
BACKGROUND AND AIMS

- The maximum reduction in HBV DNA with sustained suppression in chronic HBV infection patients undergoing antiviral treatment has been associated with favorable disease outcomes.
- ALG-000184 is a prodrug of the Class E capsid assembly modulator (empty), ALG-001075, which has demonstrated potent, pan-genotypic antiviral activity in vitro through a dual mechanism of action (MOA)[1]:
  - inhibition of pg-RNA encapsidation (1st MOA);
  - inhibition of HBV antigen production by blocking cccDNA establishment (2nd MOA).
- The ongoing phase 1 study ALG-000184-201 (NCT04536337) evaluates the safety, tolerability, and antiviral activity of ALG-000184 in healthy volunteers (HVs), and treatment-naïve (TN) or currently-not-treated (CNT) subjects with chronic HBV infection. Previously published data demonstrated a favorable safety profile of ALG-000184 in HVs and the patient population. Furthermore, in TN/CNT HBeAg-positive patients with chronic HBV infection receiving 300 mg ALG-000184 ± entecavir (ETV) ≤ 96 weeks, multiple-log reductions of HBV DNA ,HBV RNA, and HBV antigens were observed[2,3].

METHODS

In study ALG-000184-201, a total of 15 TN/CNT HBeAg-positive subjects were enrolled (Table 1) and randomized 4:1 to 300 mg ALG-000184 + ETV or placebo + ETV for 12 weeks, followed by 300 mg ALG-000184 + ETV for ≤ 96 weeks. Subsequently, subjects entered up to 8 weeks of follow-up, during which only ETV was dosed (Figure 1).

Figure 1. Study Design



Throughout the study, safety assessments and viral markers were regularly collected. The Study Review Committee and ALT Flare Committee reviewed clinical safety data on a regular basis.
Lower Limit of Quantitation (LLOQ) were as follows: HBV DNA10 IU/mL, HBV RNA 200 copies/mL, HBsAg 0.05 IU/mL, HBeAg 1COI and HBcrAg 3 $\log_{10}$ U/mL.

Table 1. Baseline Characteristics and Demographics

	300mg ALG-000184 + ETV N=11*	Placebo + ETV N=3
Age, years, mean (SEM)	31.0 (2.9)	28 (2.6)
Male, N (%)	5 (45))	2 (66.7)
Asian, N (%)	11 (100)	3 (100)
BMI, kg/m^2, mean (SEM)	21.7 (0.8)	22.3 (1.6)
HBV Genotype B/C, N (%)	B: 4 (33); C: 7 (64)	B: 1 (33); C: 2 (67)
HBV DNA, $\log_{10}$ IU/mL, mean (SEM)	8.1 (0.3)	7.8 (0.6)
HBV RNA, $\log_{10}$ copies/mL, mean (SEM)	6.7 (0.4)	6.5 (0.5)
HBsAg, $\log_{10}$ IU/mL, mean (SEM)	4.4 (0.2)	4.1 (0.2)
HBeAg, $\log_{10}$ PEI U/mL, mean (SEM)	2.4 (0.1)	2.0 (0.2)
HBcrAg, $\log_{10}$ U/mL, mean (SEM)	8.4 (0.2)	8.0 (0.7)
ALT, U/L, mean (SEM)	41.2 (6.6)	38.7 (9.2)

* Excludes one subject with dosing non-compliance confirmed by PK

REFERENCES

[1] Sandrine Vendeville et. al, Journal of Medicinal Chemistry 67:23; [2] Hou JL oral 101813 APASL 2024; [3] MF Yuen OP0394 APASL 2025

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RESULTS - SAFETY
300 mg ALG-000184 +ETV for ≤ 96 had a favorable safety profile

Table 2. Safety Summary

	TN/CNT HBeAg-positive subjects
Numbers of subjects with	N=15
• at least one TEAE, n (%)	14 (93)
• SAE	0
• TEAE leading to study drug discontinuation	1*
• TEAE Grade ≥3	4#,^

* One subject was discontinued due to an unlikely-related Grade 1 TEAE of cirrhosis (progression of underlying liver disease).
\# Three Grade ≥3 TEAEs of ALT/AST elevation, with preserved synthetic and excretory function, were not considered clinically concerning by the ALT Flare Committee.
^ The other ≥3 TEAEs were neutrophil count decrease (n=1), uric acid increase (n=1) and eGFR decrease (n=1). All resolved in setting of continued ALG-000184 dosing.

ANTIVIRAL EFFECT

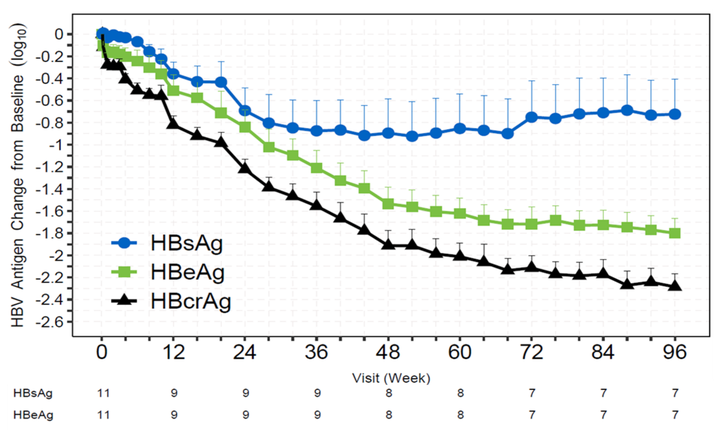
Table 3: Maximum Mean Change and Individual Maximum Change in HBV Markers from Baseline During Dosing with 300 mg ALG-000184 + ETV

Subjects initially receiving 300 mg ALG-000184 + ETV N=11	Maximum mean reduction	Individual maximum reduction
HBV DNA ($\log_{10}$ IU/mL)	-6.9	-8.3
HBV RNA ($\log_{10}$ copies/mL)	-4.3	-5.8
HBsAg ($\log_{10}$ IU/mL)	-0.9	-2.1
HBeAg ($\log_{10}$ PEI U/mL)	-1.8	-2.2
HBcrAg ($\log_{10}$ U/mL)	-2.3	-2.9

HBV ANTIGEN LEVELS

- ETV alone showed no meaningful reduction in HBV antigens at Week 12 compared to ALG-000184 + ETV. After adding ALG-000184, subjects in the ETV arm experienced significant declines in HBV antigens for up to 96 weeks.
- Eleven subjects initially assigned to 300 mg ALG-000184 + ETV had multiple-log reductions in HBsAg, HBeAg, and HBcrAg from baseline over 96 weeks (Figure 2, Table 3):
  - Of them, 7 subjects who completed the dosing with 300 mg ALG-000184 + ETV for 96 weeks:
    57% (4/7) had ≥1 $\log_{10}$ IU/mL decline in HBsAg with a maximum reduction of 2.1 $\log_{10}$ IU/mL;
    100% (7/7) had HBeAg decline ≥1 $\log_{10}$ PEI U/mL with a maximum reduction of 2.2 $\log_{10}$ PEI U/mL;
    100% (7/7) had HBcrAg decline ≥1 $\log_{10}$ U/mL with a maximum reduction of 2.9 $\log_{10}$ U/mL.

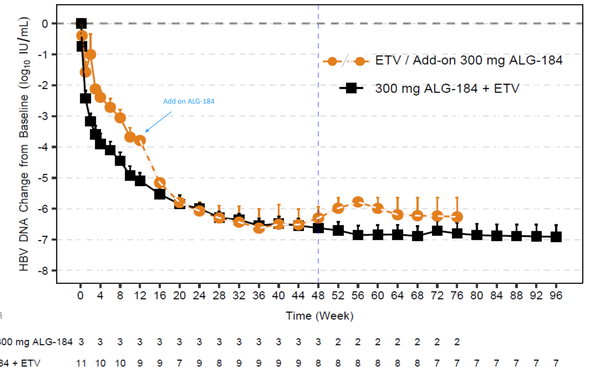
Figure 2. Mean (SEM) serum HBV antigen change from baseline



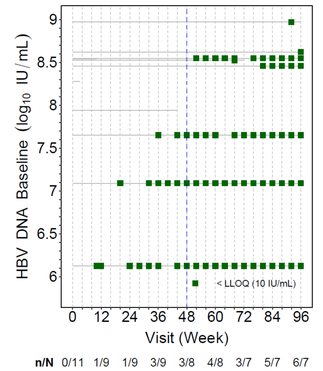
HBV DNA AND HBV RNA LEVELS

- HBV DNA levels in subjects receiving 300 mg ALG-000184 + ETV demonstrated a 1.3 $\log_{10}$ IU/mL greater decrease at Week 12 compared to ETV alone. Following the addition of ALG-000184, HBV DNA in the ETV group further declined by Week 24, reaching comparable levels to ALG-000184 + ETV (-6.1 vs. -6.0 $\log_{10}$ IU/mL). The time to achieve HBV DNA < LLOQ depended on baseline levels, with 3/8 subjects reaching this level at Weeks 48, increased to 6/7 subjects at Week 96 (Figure 3).
- And HBV RNA in subjects receiving 300 mg ALG-000184 + ETV decreased by -3.5 $\log_{10}$ copies/mL at Week 12, with no change in those on ETV alone, but by Week 24, the addition of ALG-000184 resulted in similar decreases in both groups (-3.7 vs. -4.0 $\log_{10}$ copies/mL), and all subjects achieved HBV RNA < LLOQ by Week 28.

Figure 3. Mean (SEM) Serum HBV DNA Change From Baseline



Time to HBV DNA < LLOQ



HBV DNA AND ANTIGEN LEVELS DURING ETV ALONE IN POST-ALG-000184 FOLLOW-UP PERIOD

Figure 4. HBV DNA Level

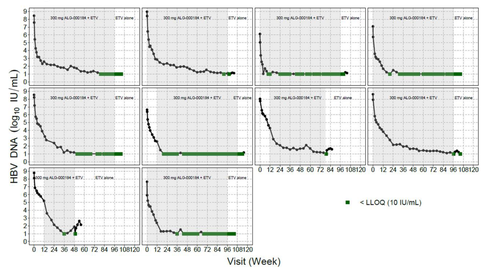
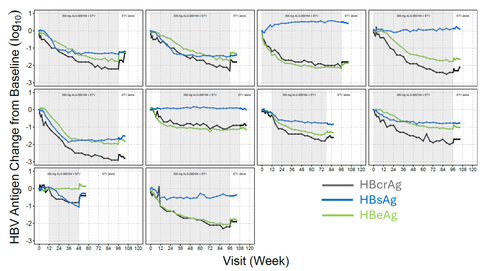


Figure 5. HBV Antigen Changes from Baseline



During the ETV-only follow-up, six subjects rebounded in HBV DNA from < LLOQ (Figure 4), and all experienced HBeAg and HBcrAg rebound (Figure 5) among the 10 HBeAg-positive subjects who completed up to 96 weeks of 300 mg ALG-000184 + ETV and 8 weeks of follow-up. HBsAg levels seem to have sustainable response in subjects who completed 96 weeks of 300 mg ALG-00018 4 + ETV treatment (Figure 5).

CONCLUSION

- **300 mg ALG-000184 in combination with ETV in TN/CNT HBeAg-positive subjects for ≤ 96 weeks demonstrated:**
  - **a favorable safety profile**
  - **more potent antiviral effect in HBV DNA reduction compared to ETV alone**
  - **additional antiviral in HBV antigen decline suggestive of cccDNA reduction**
- **ALG-000184 provides an alternative MOA compared 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**
- **A Phase 2 clinical study to evaluate the superiority of ALG-000184 monotherapy in HBV DNA suppression compared to a nucleoside analogs (NA) is expected to begin in mid-2025.**