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Monotherapy with the Novel Capsid Assembly Modulator ALG-000184 for up to 96 Weeks Results in Profound and Sustained HBV DNA Suppression in Untreated Subjects with Chronic HBV Infection

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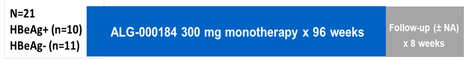
BACKGROUND AND AIMS

- The maximum reduction in HBV DNA with sustained suppression in chronic HBV infection patients undergoing antiviral treatment has been associated with favorable disease outcomes[1].
- 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)[2]:
  - 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[3,4].

METHODS

In study ALG-000184-201, a total of 10 TN/CNT HBeAg-positive and 11 HBeAg-negative subjects were enrolled (Table 1) and received open-label monotherapy with 300 mg ALG-000184 for ≤ 96 weeks. Subsequently, subjects entered up to 8 weeks of follow-up, during which only nucleos(t)ide analogue (NA) was dosed (Fig.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) of HBV DNA, HBV RNA, HBsAg and HBeAg assays were 10 IU/mL, 10 copies/mL, 0.05 IU/mL, 0.01 PEI U/mL, respectively. LLOQs of HBcrAg were 3 log_{10} U/mL for HBeAg-positive and 1.8 log_{10} U/mL for HBeAg-negative, respectively.

REFERENCES

1. AASLD, EASL, APASL guidelines; 2. Sandrine Vendeville et. al, Journal of Medicinal Chemistry 67:23; 3. Hou JL oral 101813 APASL 2024; 4. MF Yuen OP0394 APASL 2025

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RESULTS

Table 1. Baseline Characteristics and Demographics

	HBeAg-positive	HBeAg-negative
	N=10	N=11
Age, years, mean (SEM)	36.8 (2.9)	48.5 (3.1)
Male, N (%)	7 (70)	6 (55)
Asian, N (%)	9 (90)	3 (27)
BMI, kg/m², mean (SEM)	22.4 (0.8)	26.0 (1.1)
HBV Genotype B/C, N (%)	B: 5 (50); C: 4 (40); D: 1 (10)	B:2(18), C:1(9), D:7(64), A:1(9)
HBV DNA, log_{10} IU/mL, mean (SEM)	8.0 (0.2)	4.3 (0.2)
HBV RNA, log_{10} copies/mL, mean (SEM)	5.3 (0.4)	2.0 (0.3)
HBsAg, log_{10} IU/mL, mean (SEM)	4.3 (0.1)	3.5 (0.2)
HBeAg, log_{10} PEI U/mL, mean (SEM)	2.6 (0.3)	Not applicable
HBcrAg, log_{10} U/mL, mean (SEM)	8.3 (0.2)	3.1 (0.3)
ALT, U/L, mean (SEM)	60.7 (36.9)	35 (14.5)

SAFETY

300 mg ALG-000184 ≤ 96 had a favorable safety profile (Table 2).

Table 2. Safety Summary

	HBeAg-positive	HBeAg-negative
Numbers of subjects with	N=10	N=11
• at least one TEAE, n (%)	9 (90)	6 (55)
• SAE	0	0
• TEAE leading to study drug discontinuation	0	0
• TEAE Grade ≥3	3*	2*,#

* Grade ≥3 TEAEs of ALT/AST elevation were observed in 3 HBeAg-positive and 1 HBeAg-negative subjects with preserved synthetic and excretory functions. All events resolved in the setting of continued ALG-000184 dosing and were not considered clinically concerning by the ALT Flare Committee

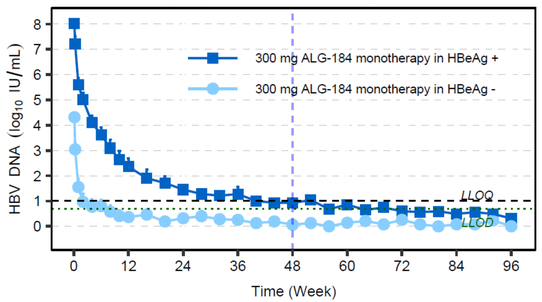
Grade 3 cholesterol/triglycerides increase in HBeAg-negative subject resolved in the setting of continued ALG-000184 dosing.

ANTIVIRAL EFFECT

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

	HBeAg-positive	HBeAg-negative
HBV DNA (log_{10} IU/mL)	-7.2	-3.4
HBV RNA (log_{10} copies/mL)	-4.4	-1.0
HBsAg (log_{10} IU/mL)	-1.0	-0.0
HBeAg (log_{10} PEI U/mL)	-2.1	Not applicable
HBcrAg (log_{10} U/mL)	-2.2	-0.4

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

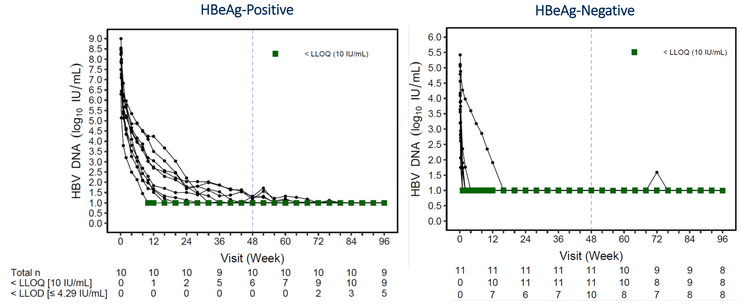


300 mg ALG-184 monotherapy in HBeAg +	10	10	10	10	10	10	10	10	9
300 mg ALG-184 monotherapy in HBeAg -	11	11	11	11	11	10	9	9	8

HBV DNA and RNA LEVEL

- 300 mg ALG-000184 monotherapy demonstrated a profound reduction in HBV DNA in TN/CNT subjects with chronic HBV infection (Table 3, Fig.2). The time to achieve HBV DNA < LLOQ (10 IU/mL) was dependent on the HBV DNA level at baseline (Fig.4).
  - In HBeAg-positive subjects, 60% (6/10) and 100% (9/9) achieved HBV DNA < LLOQ (10 IU/mL) at Week 48 and 96, respectively. Furthermore, 56% (5/9) of subjects achieved HBV DNA < LLOD (at least <4.29 IU/mL) at Week 96 (Fig.4).
  - In HBeAg-negative subjects, 100% (11/11) achieved HBV DNA < LLOQ and < LLOD by Week 20 and Week 96, respectively (Fig.4).
- HBV RNA < LLOQ (10 copies/mL) was achieved in all HBeAg-positive subjects by Week 52 and all HBeAg-negative subjects by Week 6.
- No virologic breakthrough was observed in any subjects receiving ALG-000184 monotherapy (Fig.3).

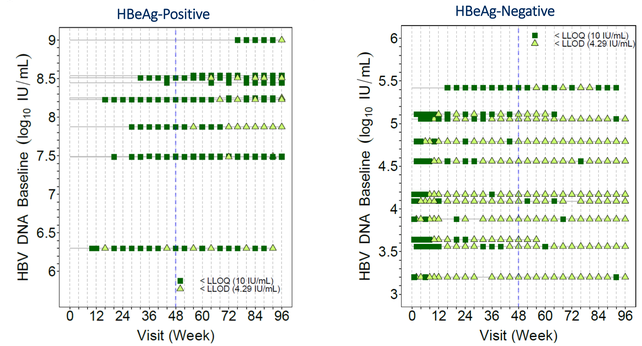
Figure 3. Individual HBV DNA Levels Over Time



Total n	10	10	10	9	10	10	10	10	9	
< LLOQ [10 IU/mL]	0	1	2	5	6	7	9	10	9	
< LLOD [≤ 4.29 IU/mL]	0	0	0	0	0	0	2	3	5	
	11	11	11	11	11	10	9	9	8	
	0	10	11	11	11	10	8	9	8	
	0	7	6	7	10	8	7	8	8	

Note: one HBeAg-negative subject had transient HBV DNA increase from < LLOQ to 39 IU/mL at Week 72. At the subsequent visit (Week 76) HBV DNA was < LLOQ (10 IU/mL).

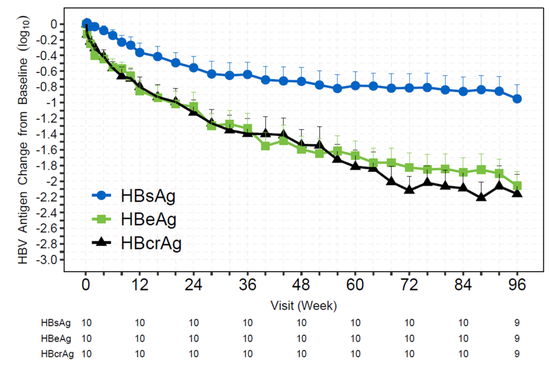
Figure 4. Individual Time to HBV DNA < LLOQ and <LLOD



HBV ANTIGEN LEVEL

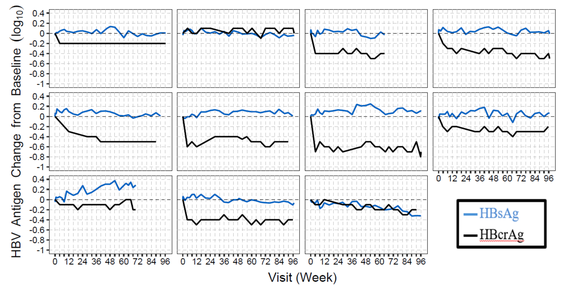
- Multiple-log reductions in HBsAg, HBeAg and HBcrAg were observed in TN/CNT HBeAg-positive subjects who received 300 mg ALG-000184 for ≤ 96 weeks (Table 3, Fig.5):
  - 70% of subjects (7/10) experienced an HBsAg decline ≥1 log_{10} IU/mL, with a maximum reduction of 1.5 log_{10} IU/mL.
  - 100% of subjects (10/10) experienced an HBeAg decline ≥1 log_{10} PEI U/mL, with a maximum reduction of 2.9 log_{10} PEI U/mL.
  - 100% (10/10) subjects experienced an HBcrAg decline ≥1 log_{10} U/mL, with a maximum reduction of 3.5 log_{10} U/mL.
- In TN/CNT HBeAg-negative subjects, 55% (6/11) experienced an HBcrAg reduction ≥0.5 log_{10} U/mL with a maximum decline of 0.7 log_{10} U/mL, while no significant decline in HBsAg level was observed (Table 3, Fig.6).

Figure 5. Mean (SEM) HBV Antigen Change in HBeAg-Positive Subjects



HBsAg	10	10	10	10	10	10	10	10	9
HBeAg	10	10	10	10	10	10	10	10	9
HBcrAg	10	10	10	10	10	10	10	10	9

Figure 6. Mean (SEM) HBV Antigen Change in HBeAg-Negative Subjects



CONCLUSION

- 300 mg ALG-000184 monotherapy in TN/CNT HBeAg-positive and HBeAg-negative subjects for ≤ 96 weeks demonstrated:
  - a favorable safety profile
  - profound HBV DNA suppression
  - concomitant HBV antigen declines suggest cccDNA levels may be lowered as a result of CAM's 1st and 2nd MOAs
- ALG-000184 monotherapy has demonstrated promising potential to become the mainstay of a long-term suppression regimen for the regimen for chronic HBV infection.
- 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.