ALG-000184, a Capsid Assembly Modulator, Demonstrates Superior Antiviral Activity in Combination with Entecavir Compared to Entecavir in HBeAg Positive Subjects with Chronic Hepatitis B infection

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ALG-000184
Background

- Capsid assembly modulators which produce empty viral particles (CAM-E) have been extensively studied for treating Chronic Hepatitis B (CHB)
- CAM-E drugs have 2 antiviral mechanisms of action:
  - Inhibition of capsid assembly leading to reductions in HBV DNA and RNA levels
  - Prevention of de novo cccDNA synthesis leading to reductions in HBsAg levels
- ALG-000184 (oral prodrug of CAM-E, ALG-001075) is currently being evaluated in a multipart, randomized, double-blind Phase 1 study (ALG-000184-201*), including in treatment naïve (TN) or currently not treated (CNT) CHB subjects
- Previously demonstrated favorable safety, pharmacokinetics (PK), and potent antiviral activity when dosed x 28 days**
- Dosing for longer durations being evaluated in China (2 cohorts in Part 4)

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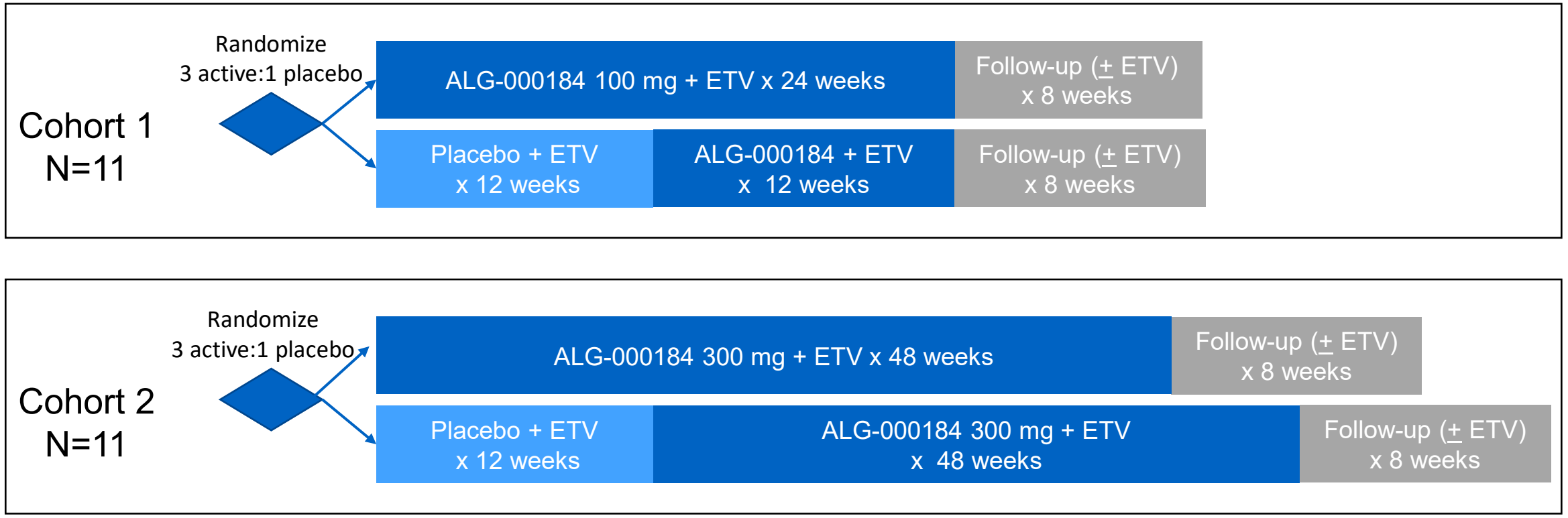
**Hou et al., AASLD 2022, Abstract #33693; Yuen et al., EASL 2022, SAT-145

ALG-000184-201
Part 4 Study Design



Available preliminary safety, PK, and antiviral activity data as of 23 Dec 2022 are presented
ETV = entecavir

ALG-000184-201
Part 4 Key Study Entry Criteria

Cohort 1 (Chronic HBV infection)

- Treatment naïve
- ALT and AST ≤1.2 × ULN
- HBV DNA >10^7 IU/mL

Cohort 2 (Chronic hepatitis B)

- Treatment naïve or currently not treated
- ALT and AST ≤5 × ULN
- HBV DNA >2000 IU/mL

Both Cohorts

- HBeAg positive
- HBsAg >100 IU/mL

ALT/AST = alanine or aspartate aminotransferase; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; ULN = upper limit of normal

ALG-000184-201
Baseline Characteristics

	Cohort 1 (100 mg ALG-000184 + ETV and Placebo + ETV)	**Cohort 2** (300 mg ALG-000184 + ETV and Placebo + ETV)
N	N=11	N=11
Age, years, mean (SEM)	35.1 (2.1)	31.4 (3.3)
Female, N (%)	7 (64)	6 (55)
Asian, N (%)	11 (100)	11 (100)
BMI, kg/m^2, mean (SEM)	22.1 (0.8)	21.7 (0.8)
HBeAg positive, N (%)	11 (100)	11 (100)
HBV Genotype B/C, N (%)	B: 2 (18) C: 9 (82)	B: 3 (27) C: 8 (73)
HBV DNA, log_{10} IU/mL, mean (SEM)	8.6 (0.1)	8.1 (0.3)
HBV RNA, log_{10} copies/mL, mean (SEM)	7.2 (0.1)	6.8 (0.3)
HBsAg, log_{10} IU/mL, mean (SEM)	4.6 (0.1)	4.4 (0.2)
ALT, U/L, mean (SEM) - Male (normal range 0-41 U/L) - Female (normal range 0-31 U/L)	 25 (5.9) 15.6 (1.8)	 29.0 (4.0) 38.7 (9.5)
ALT<1.2 x ULN, N (%)	11 (100)	9 (82)

BMI = body mass index; SEM= standard error of the mean

ALG-000184-201
Safety

		Cohort 1 100 mg ALG-000184 + ETV Placebo + ETV	Cohort 2 300 mg ALG-000184 + ETV Placebo + ETV
N		N=11	N=11
Serious Adverse Event (SAE)		0	0
Treatment Emergent Adverse Event (TEAE) leading to study drug discontinuation		0	0
Grade ≥3 TEAE		0	0
ALT elevation	Grade 1	5	4
	Grade 2	1	1
Concerning laboratory, electrocardiogram, vital sign, or physical examination findings		None	

100 mg and 300 mg ALG-000184 + ETV well tolerated
Most common TEAEs (≥4 subjects) included transaminase elevations & upper respiratory tract infection

Pharmacokinetics
Plasma ALG-001075 Levels

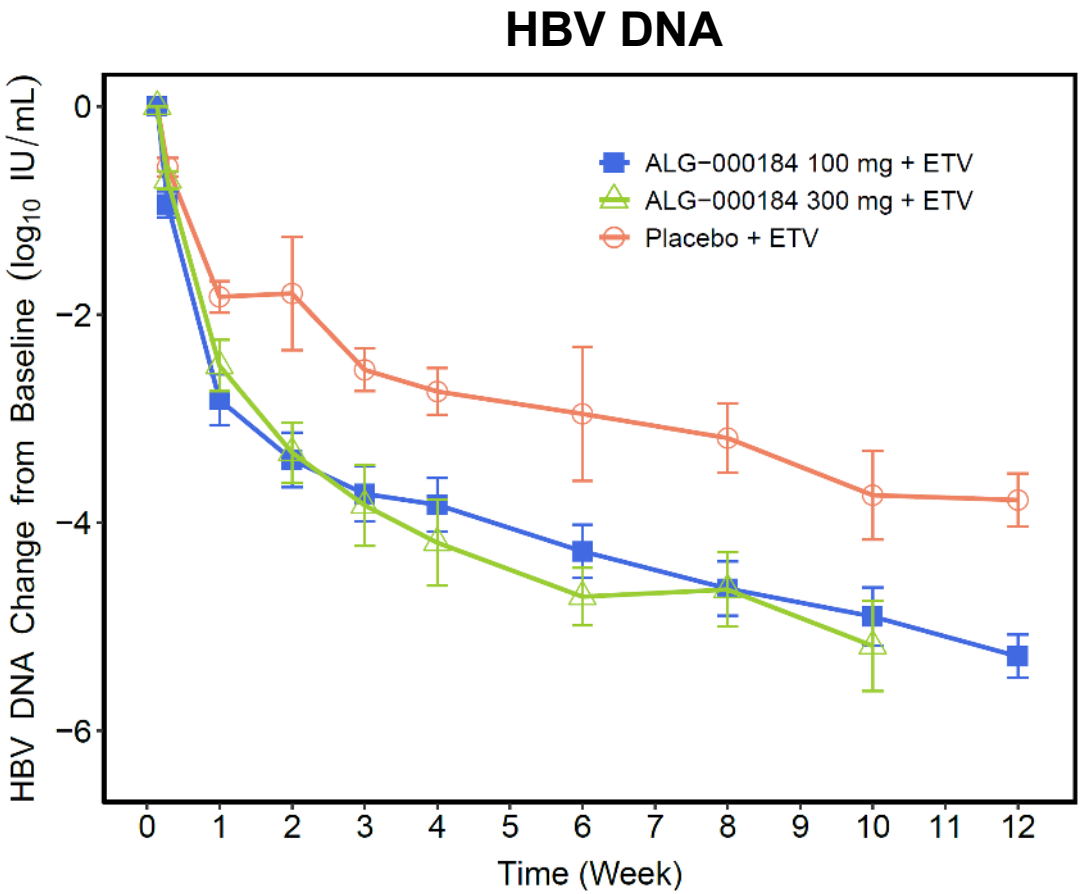
Cohort	N	AUC_{0-24} (ng.hr/mL)	C_{max} (ng/mL)
100 mg ALG-000184 + ETV	8	12,400 (15.5)	1,590 (21.4)
300 mg ALG-000184 + ETV	6	37,700 (25.7)	4,320 (31.5)

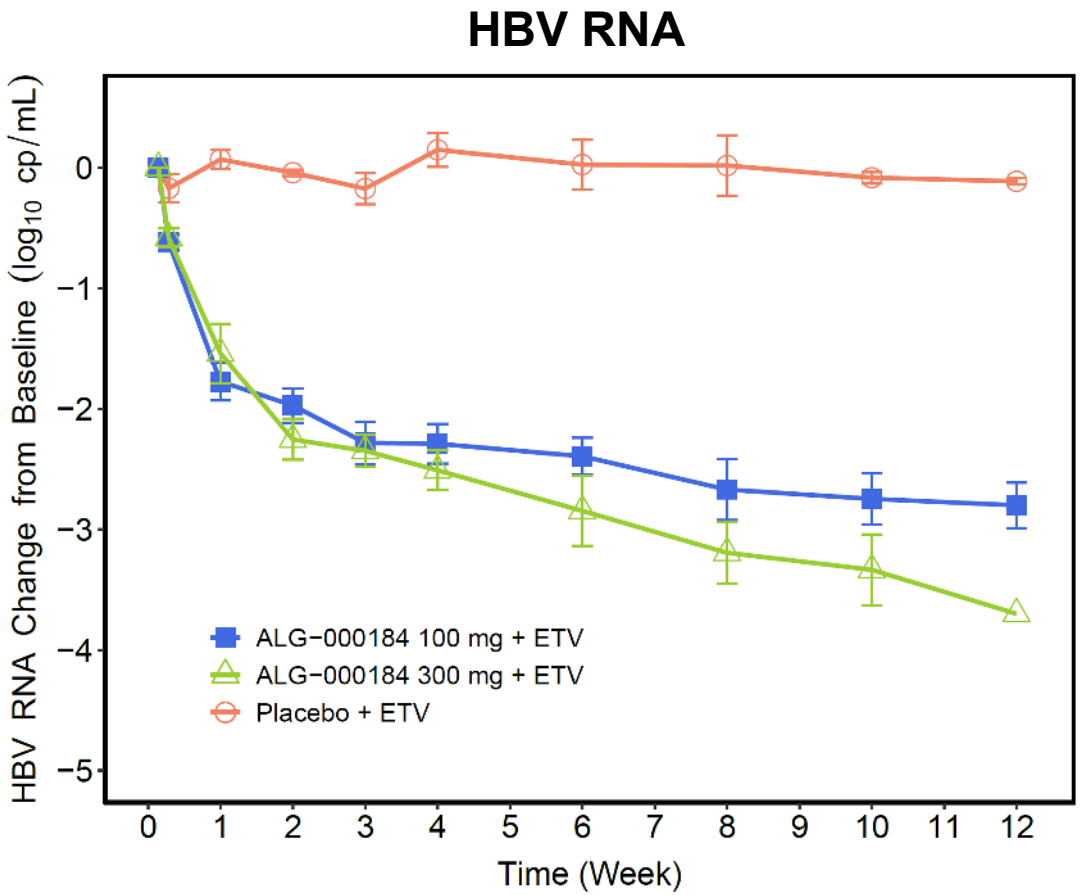
Geometric mean (Geometric CV)

- Plasma exposures at Day 1 increased dose proportionally with a low coefficient of variation (CV <32%)
- No evidence of PK interaction between ALG-000184 and ETV

AUC = area under the curve; C_{max} = maximum concentration; CV = coefficient of variation

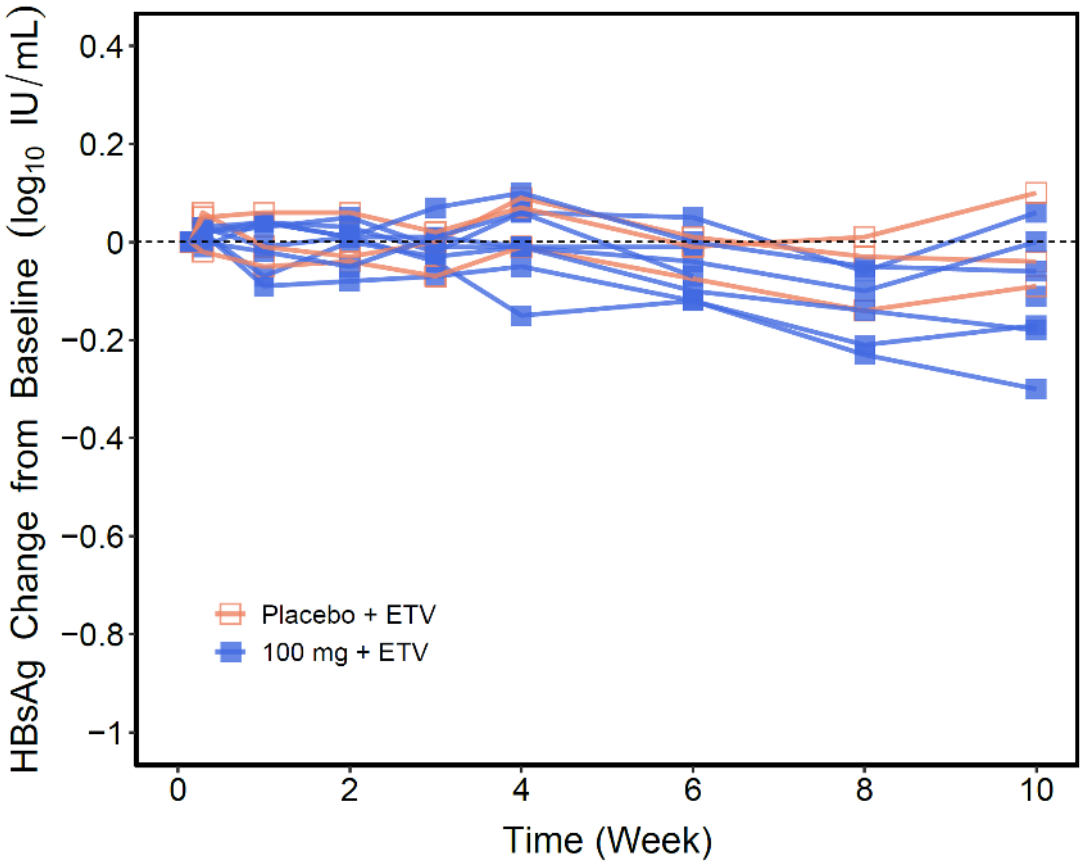
Antiviral Activity
Change in HBV DNA and RNA Over Time

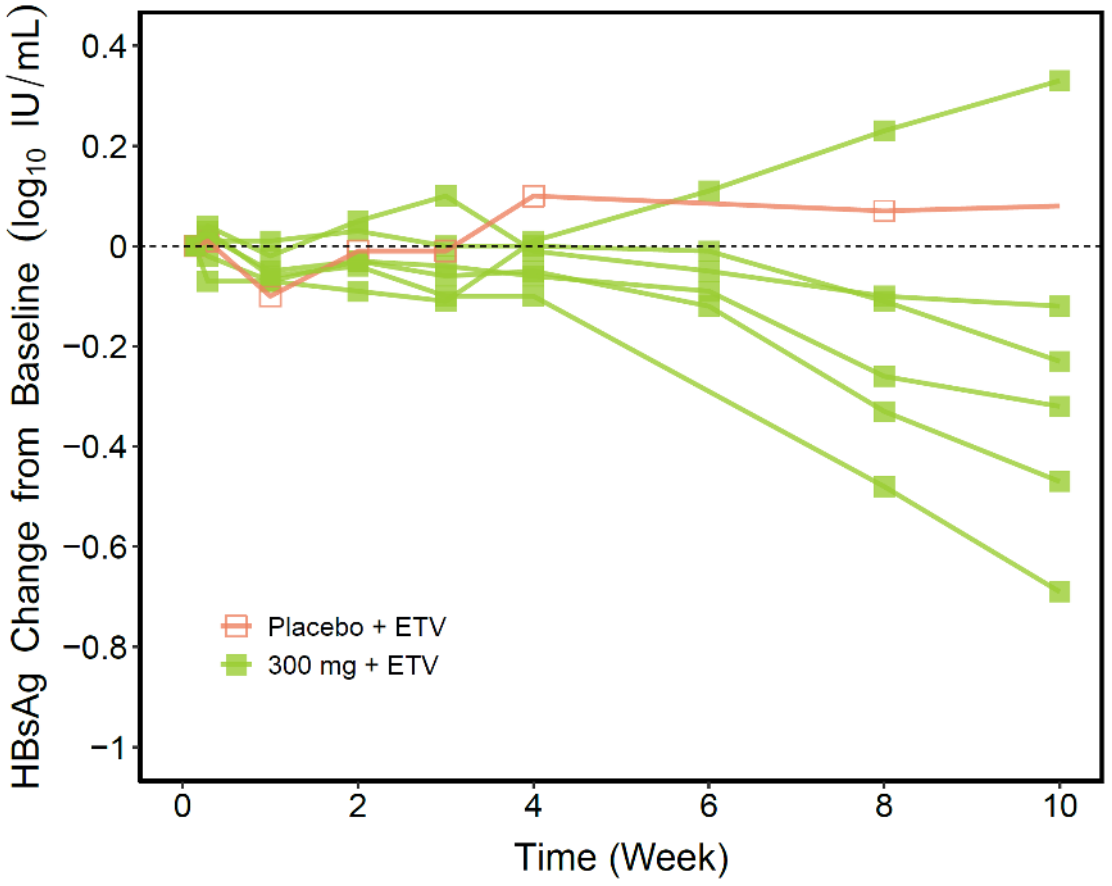




Reduction at Week 10	Placebo + ETV N=3	ALG-000184 100 mg + ETV N=7	ALG-000184 300 mg + ETV N=6
HBV DNA, mean (SEM) $\log_{10}$ IU/mL	-3.7 (0.43)	-4.9 (0.28)	-5.2 (0.3)
HBV RNA, mean (SEM) $\log_{10}$ copies/mL	0.08 (0.05)	-2.7 (0.21)	-3.3 (0.29)

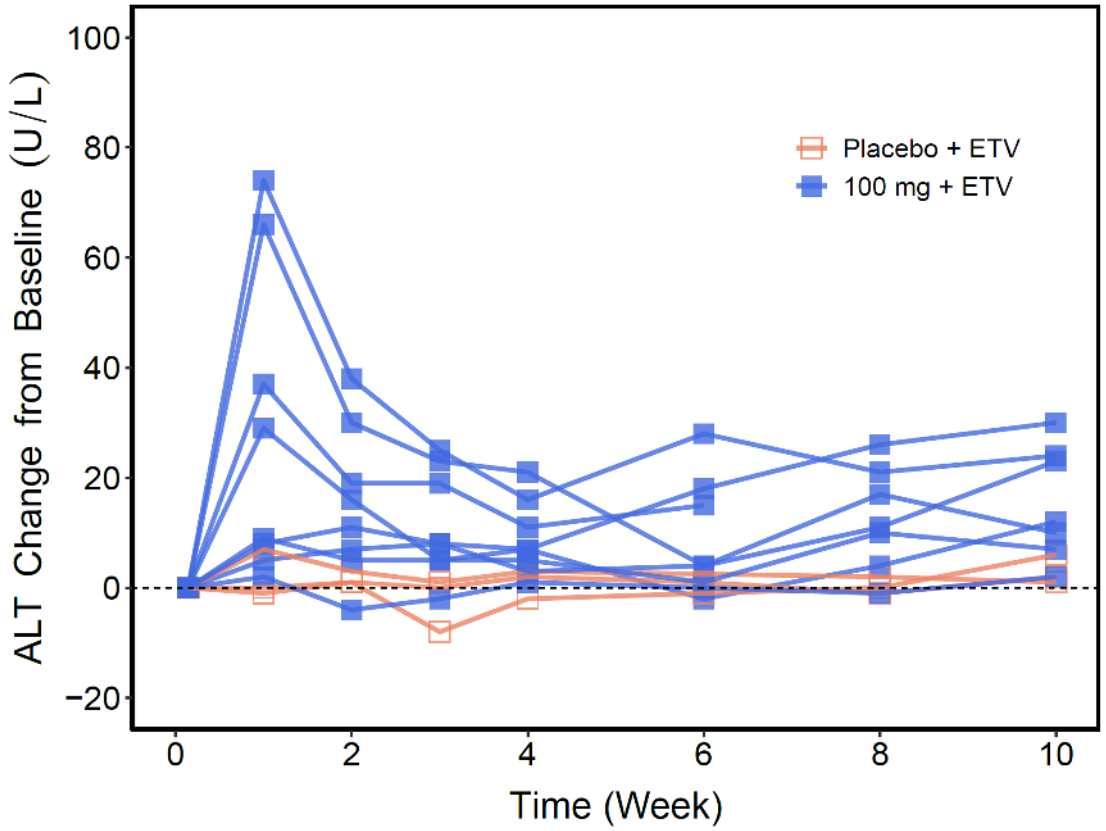
Cohorts 1 and 2 (100 and 300 mg ALG-000184 + ETV)
Change in HBsAg For Subjects Dosed At Least 10 Weeks

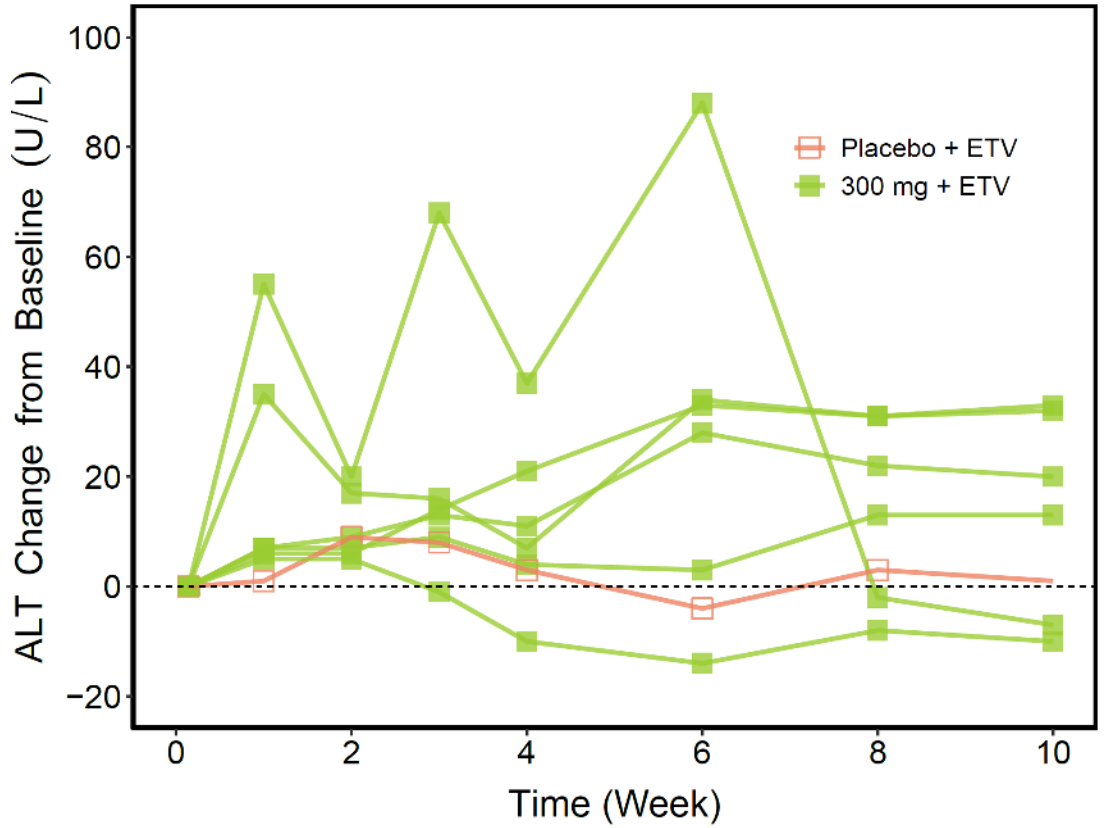




Clear downward trend for HBsAg among majority of 300 mg ALG-000184 treated subjects
Effect more apparent with dosing beyond 4 weeks

Cohorts 1 and 2 (100 and 300 mg ALG-000184 + ETV)
Change in ALT For Subjects Dosed At Least 10 Weeks





Subjects with normal baseline ALT levels who had a $\geq$0.2 $\log_{10}$ reduction in HBsAg experienced mild and persistent elevations in ALT while receiving ALG-000184 and ETV, regardless of dose.

Conversely, subjects with normal baseline ALT who had no change in HBsAg had no notable change in ALT.

ALT changes were not associated with symptoms, change in bilirubin/INR and didn't worsen with continued dosing.

ALG-000184-201
Conclusions

ALG-000184 combined with ETV in untreated HBeAg+ subjects with chronic HBV infection or CHB

- Demonstrated a favorable safety and PK profile
- Resulted in superior antiviral activity (HBV DNA and RNA) compared to ETV alone
- Resulted in superior reductions in HBsAg (especially 300 mg cohort), which suggest that ALG-000184 has best in class properties and a potential role in combination regimens for functional cure

Longer dosing in these and other cohorts is planned to further define the safety, PK, and antiviral activity of ALG-000184 with or without ETV

Additional information on HBsAg reductions seen with ALG-000184 over 28 days can be seen in Poster PC-019

ALG-000184-201
Acknowledgments

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