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ALG-000184 (300 mg) ± Entecavir Results in Substantial HBV Antigen Declines in Untreated HBeAg-Positive Subjects with CHB

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Disclosure

- Member of Scientific Advisory Board for AbbVie, Abbott Diagnotics, Aligos Therapeutics, AiCuris, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Precision BioSciences, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology and Visirna Therapeutics.

- Speaker for Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corporation

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Background

- Chronic hepatitis B (CHB) treatment is challenging due to persistence of intrahepatic cccDNA, which acts as a reservoir for HBV infection in hepatocytes[1]
- Capsid assembly modulators which produce empty viral particles (CAM-E) have two antiviral mechanisms of action:
  - Inhibition of capsid assembly, leading to reductions in HBV DNA and RNA levels
  - Prevention of establishment/replenishment of cccDNA, leading to reductions in antigen levels (e.g., HBsAg)
- ALG-000184 is a prodrug of the potent capsid assembly modulator, ALG-001075
- Study ALG-000184-201[2] is an ongoing multipart, randomized, double-blind Phase 1 study which is currently evaluating the risk-benefit profile of multiple doses of ALG-000184 in treatment naïve or currently not treated CHB subjects
  - Part 4 Cohorts 2 and B are evaluating 300mg ALG-000184 with ETV or without ETV, respectively, x ≤96 weeks in untreated CHB subjects
  - This regimen has previously been reported to be well tolerated and resulted in multi-log reductions in HBV DNA, RNA, HBsAg, HBcrAg, and HBeAg in HBeAg+ subjects after dosing x ≤48 weeks[3]
  - Here we report additional safety & pharmacodynamic data from HBeAg+ subjects who have now dosed for ≤64 weeks

[1]Ed Gane et al., APASL 2023. [2]NCT04536337. [3]Yuen et al., AASLD 2023.

ALG-000184-201 Part 4 Study Design

Cohort 1
N=11
HBeAg+

Randomize 3 active:1 placebo

- ALG-000184 100 mg + ETV x 24 weeks → Follow-up (ETV) x 8 weeks
- PBO* + ETV x 12 weeks → ALG-000184 + ETV x 12 weeks → Follow-up (ETV) x 8 weeks

Cohort 2
N=15
HBeAg+

Randomize 3 active:1 placebo

- ALG-000184 300 mg + ETV x 96 weeks → Follow-up (± ETV) x 8 weeks
- PBO + ETV x 12 weeks → ALG-000184 300 mg + ETV x 96 weeks → Follow-up (± ETV) x 8 weeks

Cohort B
N=21
HBeAg+ (n=10)
HBeAg- (n=11)

- ALG-000184 300 mg monotherapy x 96 weeks → Follow-up (± ETV) x 8 weeks

*PBO=Placebo

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HBeAg-positive data in Cohort 1 are presented in Oral 101813

Cohort 2
N=15
HBeAg+

Randomize 3 active:1 placebo

- ALG-000184 300 mg + ETV x 96 weeks → Follow-up (± ETV) x 8 weeks
- PBO + ETV x 12 weeks → ALG-000184 300 mg + ETV x 96 weeks → Follow-up (± ETV) x 8 weeks

Cohort B
N=21
HBeAg+ (n=10)
HBeAg- (n=11)

ALG-000184 300 mg monotherapy x 96 weeks → Follow-up (± ETV) x 8 weeks

*PBO=Placebo

ALG-000184-201 Part 4 C2/CB
Key Study Entry Criteria

Adult subjects with chronic hepatitis B or chronic HBV infection

- Treatment naïve or currently not treated
- HBeAg positive
- ALT and AST ≤ 5 × ULN
- HBV DNA ≥ 2000 IU/mL
- HBsAg ≥ 100 IU/mL
- Metavir score < F3 or liver stiffness measurement < 8.5 kPa

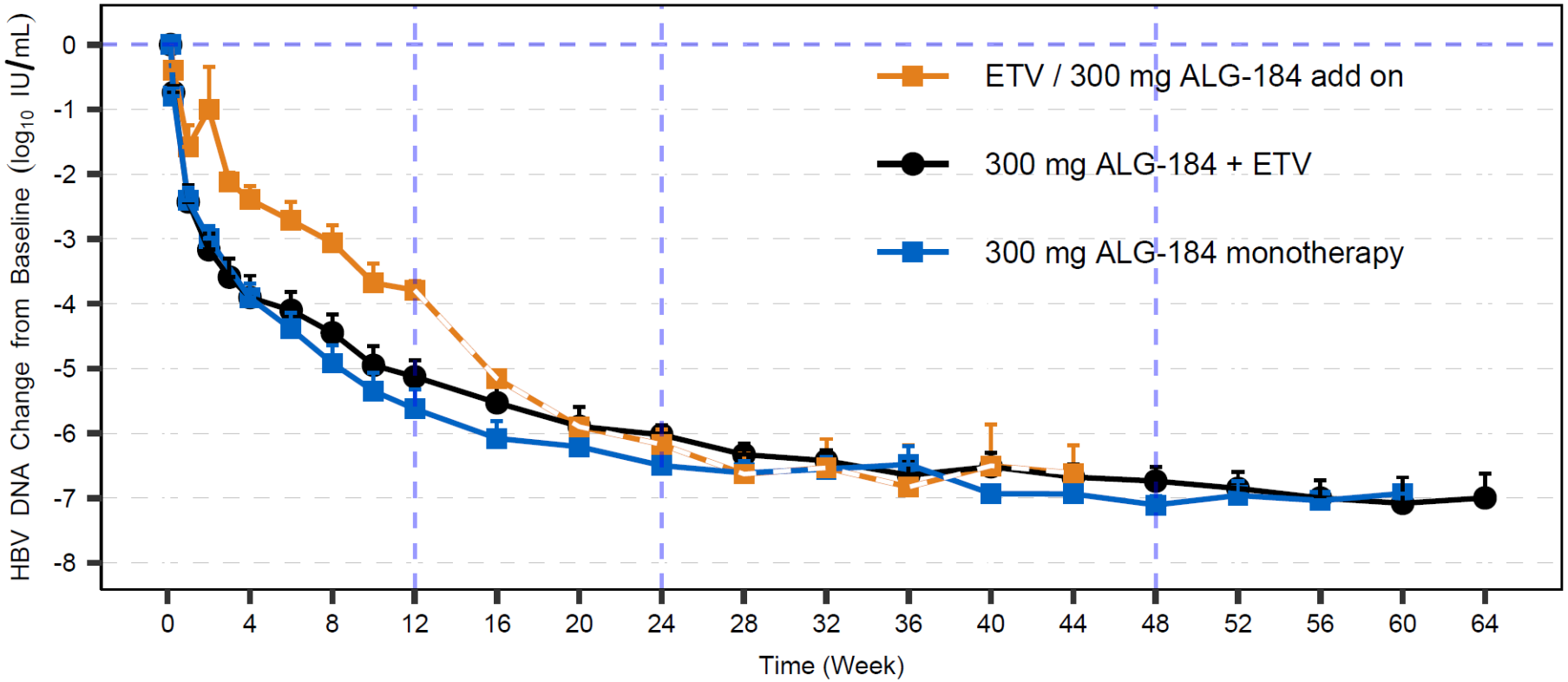
ALG-000184-201 Part 4 C2/CB Baseline Characteristics

N	300mg ALG-000184 + ETV	ETV	300mg ALG-000184
	N=11*	N=3	N=10
Age, years, mean (SEM)	31.0 (2.9)	28 (2.6)	36.8 (2.9)
Male, N (%)	5 (45))	2 (66.7)	7 (70)
Asian, N (%)	11 (100)	3 (100)	9 (90)
BMI, kg/m^2, mean (SEM)	21.7 (0.8)	22.3 (1.6)	22.4 (0.8)
HBV Genotype B/C, N (%)	B: 4 (33); C: 7 (64)	B: 1 (33); C: 2 (67)	B: 5 (50); C: 4 (40); D: 1 (10)
HBV DNA, $\log_{10}$ IU/mL, mean (SEM)	8.1 (0.3)	7.8 (0.6)	8.0 (0.2)
HBV RNA, $\log_{10}$ copies/mL, mean (SEM)	6.7 (0.4)	6.5 (0.5)	5.3 (0.4)
HBsAg, $\log_{10}$ IU/mL, mean (SEM)	4.4 (0.2)	4.1 (0.2)	4.3 (0.1)
HBeAg, $\log_{10}$ PEI U/mL, mean (SEM)	2.4 (0.1)	2.0 (0.2)	2.6 (0.3)
HBcrAg, $\log_{10}$ U/mL, mean (SEM)	8.4 (0.2)	8.0 (0.7)	8.3 (0.2)

Typical profile for HBeAg+ CHB population

* Excludes one subject who was non-compliant with dosing

ALG-000184-201 Part 4 C2/CB
Mean HBV DNA Change Over Time

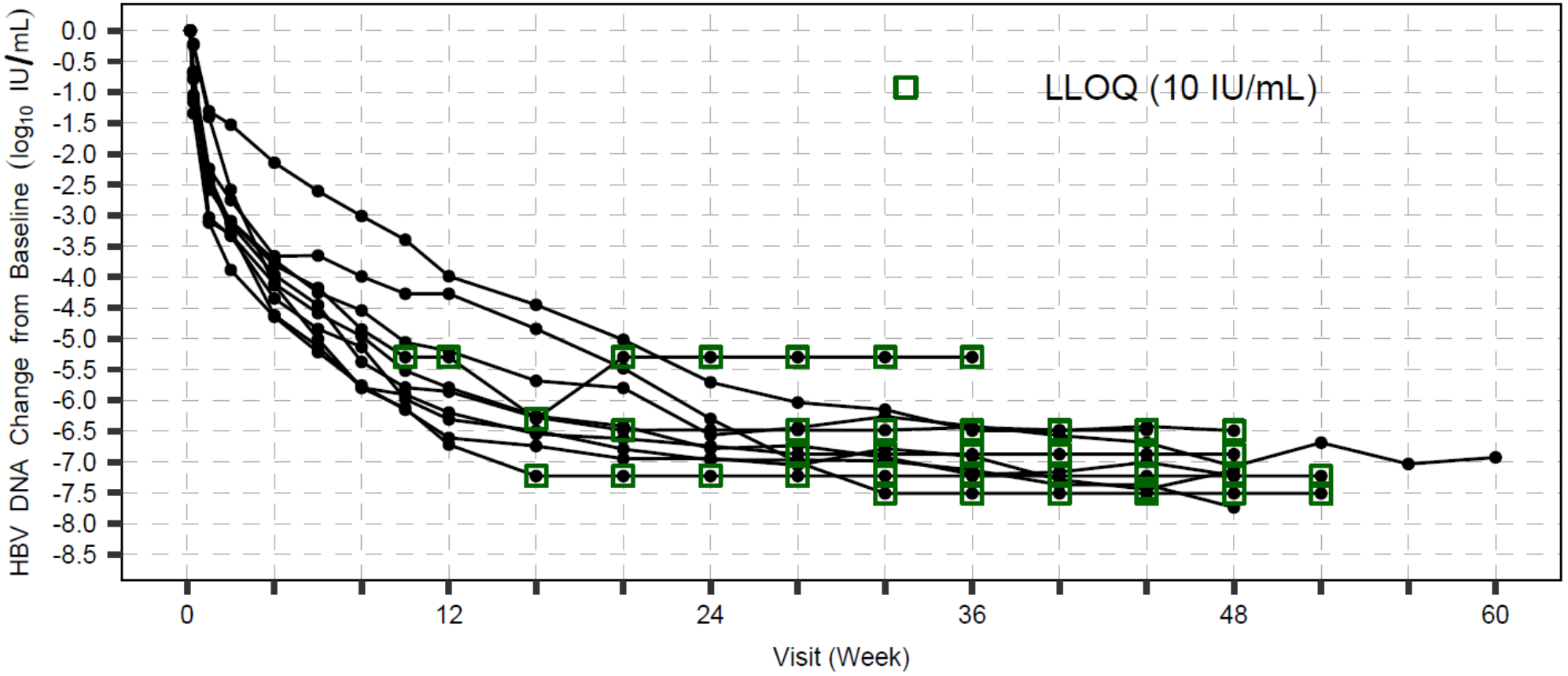


ETV / 300 mg ALG-184 add on	3	3	3	3		
300 mg ALG-184 + ETV	11	9	9	9	8	6
300 mg ALG-184 monotherapy	10	10	10	10	8	1

At Week 12, 300mg ALG-000184 ± ETV had similar declines that were 1.3-1.8 log_{10} greater than ETV
Subjects receiving ETV alone experienced similar DNA declines after adding ALG-000184 at Week 12
Maximum DNA reduction: 7.8 log_{10} IU/mL

* Excludes one subject who was non-compliant with dosing.

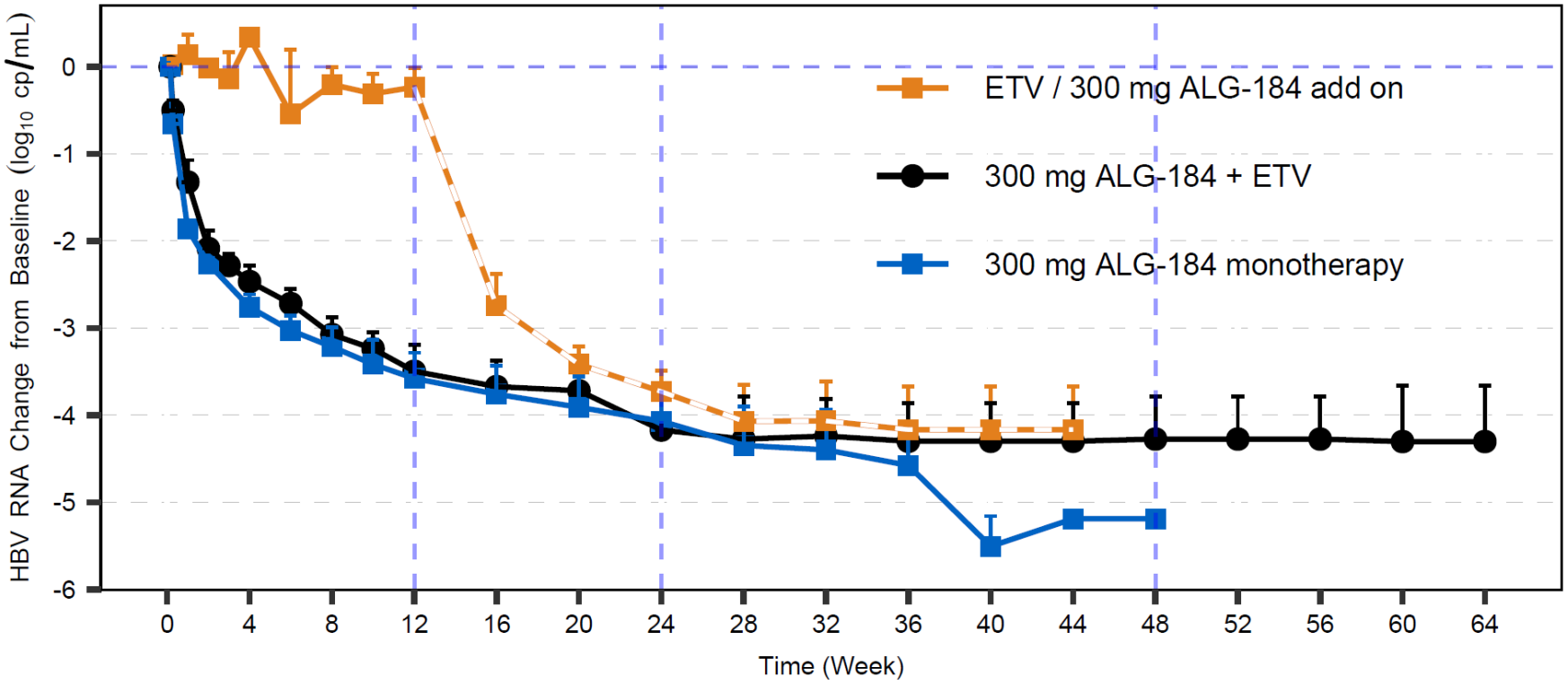
300 mg ALG-000184 Monotherapy Individual HBV DNA Over Time



Total n	10	10	10	10	10	10	10	10	10	9	9	9	8	3	1	1

No viral breakthrough during ALG-000184 monotherapy x ≤60 weeks
100% (10/10) of subjects achieved HBV DNA < 29 IU/mL
70% (7/10) of subjects achieved HBV <10 IU/mL

ALG-000184-201 Part 4 C2/CB
Mean HBV RNA Over Time

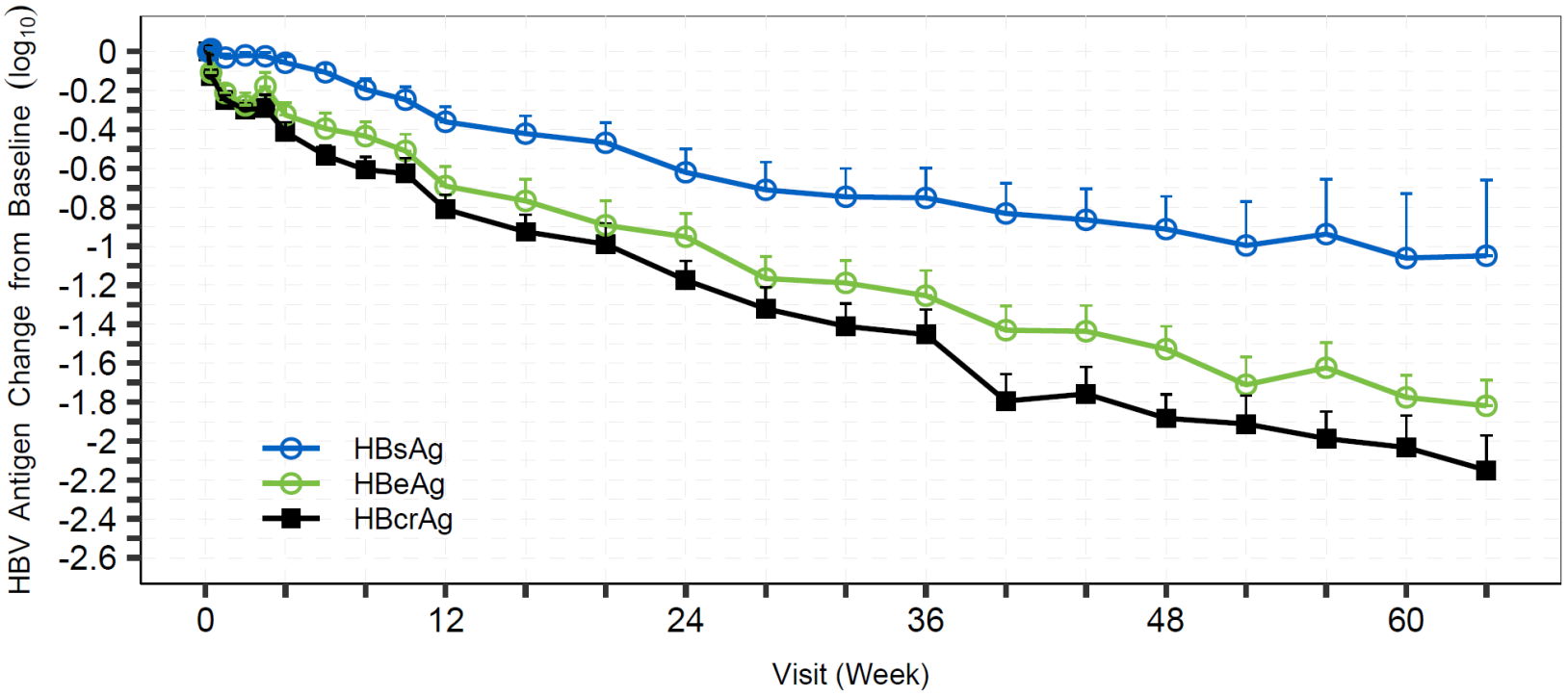


ETV / 300 mg ALG-184 add on	3	3	3	3		
300 mg ALG-184 + ETV	11	9	9	9	8	6
300 mg ALG-184 monotherapy	10	10	9	8	1	

At Week 12, there was a >3 log_{10} copies/mL RNA decline with ALG-000184 ± ETV vs. no change with ETV
After adding ALG-000184 on top of ETV at Week 12, the RNA decline was similar to the combo regimen
Up to Week 64, 100% of subjects experienced HBV RNA < LLOQ
Maximum reduction: 6.2 log_{10} copies/mL

* Excludes one subject who was non-compliant with dosing.

ALG-000184-201 Part 4 C2/CB
Mean Antigen Levels Over Time*



HBsAg	21	19	19	19	16	7
HBeAg	21	19	19	18	16	7
HBcrAg	21	19	18	17	9	6

Continued multi-log reductions of HBsAg, HBeAg and HBcrAg seen with 300mg ALG-000184 ± ETV
Up to 60 weeks, mean log_{10} reductions of HBsAg, HBeAg and HBcrAg were -1.1, -1.8, -2.0, respectively
Maximum log_{10} reductions: -1.9, -2.2, -2.6 for HBsAg, HBeAg and HBcrAg, respectively
≥0.5 log_{10} reduction of HBsAg, HBeAg and HBcrAg in 67% (14/21), 90% (19/21) and 90%(19/21) subjects

* Excludes one non-compliant subject and 3 subjects that initially received ETV alone.

ALG-000184-201 Part 4 C2/CB
Safety

	300mg ALG-000184 + ETV	300mg ALG-000184
	N=15	N=10
Serious Adverse Event (SAE)	0	0
Treatment Emergent Adverse Event (TEAE) leading to study drug discontinuation	0	0
Grade ≥3 TEAE	4*,#	3#
Concerning laboratory, ECG, vital sign, or physical examination findings	0	0

* 3 subjects experienced Grade ≥ 3 TEAEs of asymptomatic laboratory abnormalities including eGRF decrease, uric acid increase and neutrophil count decrease. All had normalized or returned to baseline in setting of continued study dosing.

2 subjects in Part 4 Cohort 2 and 3 subjects in Part 4 Cohort B experienced Grade ≥ 3 ALT ↑ with or without associated AST ↑. All were asymptomatic and none were associated with hepatic synthetic dysfunction or considered concerning to the study's ALT Flare Monitoring Committee.

300 mg ALG-000184 ± ETV well tolerated x ≤64 weeks

Conclusion

300 mg ALG-000184 ± ETV x ≤64 weeks in untreated HBeAg+ CHB subjects resulted in:

- A favorable safety profile
- Greater suppression of HBV DNA & RNA vs. ETV alone (1st MOA)
- No viral breakthrough when ALG-000184 is given as monotherapy (x ≤60 weeks)
- Multi-log reductions in HBsAg, HBeAg, & HBcrAg, which appear to be ALG-000184-mediated (2nd MOA)
- ALG-000184 may lower cccDNA levels via CAM 1st and 2nd MOAs
- When given alone, ALG-000184 may provide 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
- Phase 2 enabling activities for ALG-000184 are underway

Additional data in this study are presented in:
- Oral 101813: 100mg ALG-000184 + ETV in HBeAg-positive subjects with chronic HBV infection; AND
- Oral 101816: Analysis of ethnicity on safety/efficacy among HBeAg-negative CHB subjects dosed with ALG-000184 x 28 days