Treatment for >12 Weeks with the Capsid Assembly Modulator (CAM) ALG-000184 and Entecavir (ETV) Dose Dependently Reduces HBsAg in HBeAg+ Subjects with Chronic Hepatitis B (CHB)

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Disclosures for Ed Gane

- I have been an advisor and/or speaker for: AbbVie, Abbott Diagnostics, Aligos, Arbutus, Arrowhead, Assembly, Dicerna, Gilead Sciences, Glaxo Smith Kline, Intellia, Janssen, Merck, Novartis, Precision Biosciences, Genentech-Roche, Tune, Vaccitech, Vir Bio and Virion Therapeutics
- I will present investigational use of many drugs in development and also off-label use of approved drugs
- The opinions expressed are entirely my own

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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 hepatitis B virus pregenomic RNA (HBV pgRNA) encapsidation leading to reductions in HBV DNA and RNA
  - Prevention of de novo cccDNA synthesis leading to reductions in HBV surface antigen (HBsAg)
- 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 or currently not treated CHB subjects
- Previously demonstrated favorable safety, pharmacokinetics (PK), and potent antiviral activity when dosed x 28 days**
- Longer dosing durations being evaluated, including in China (2 cohorts in Part 4)
  - Presented are available data in subjects dosed ≥12 weeks with ALG-000184 + entecavir (ETV)

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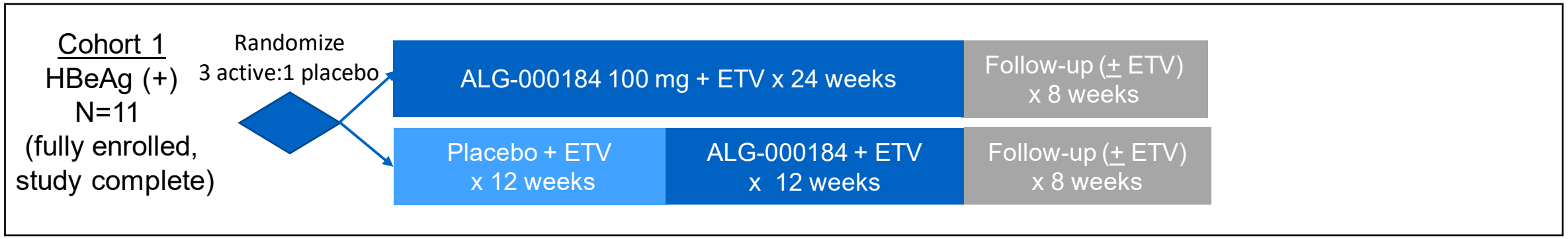
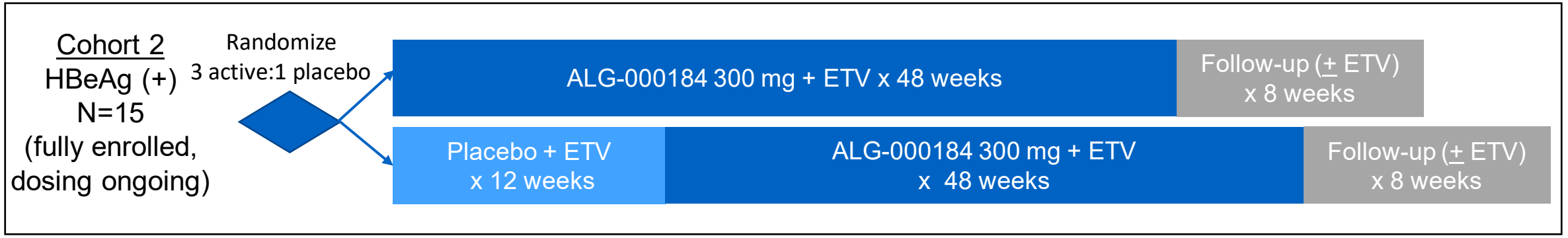
***Hou et al., AASLD 2022, Abstract #33693; Yuen et al., EASL 2022, SAT-145*

ALG-000184-201
Part 4 Cohorts





HBeAg – HBV envelope antigen

ALG-000184-201
Part 4 Key Study Entry Criteria

Entry Criterion	Cohort 1	Cohort 2
Treatment status	Treatment naive	Not on treatment (treatment naïve or treated in past)
ALT/AST	≤1.2 x ULN	≤5 x ULN
HBV DNA	$>10^7$ IU/mL	>2000 IU/mL
HBsAg	>100 IU/mL	

ALT/AST = alanine or aspartate aminotransferase; ULN = upper limit of normal

ALG-000184-201
Part 4 Baseline Characteristics – Typical for HBeAg+ Population

	Cohort 1 (100 mg ALG-000184 + ETV and Placebo + ETV)	Cohort 2 (300 mg ALG-000184 + ETV and Placebo + ETV)
N	N=11	N=15
Age, years, mean (SEM)	35.1 (2.1)	31.4 (3.3)
Female, N (%)	7 (64)	7 (46.7)
Asian, N (%)	11 (100)	15(100)
BMI, kg/m^2, mean (SEM)	22.1 (0.8)	22.2 (0.8)
HBeAg positive, N (%)	11 (100)	15 (100)
HBV Genotype B/C, N (%)	B: 2 (18), C: 9 (82)	B: 5 (33), C: 10 (67)
HBV DNA, log_{10} IU/mL, mean (SEM)*	8.6 (0.1)	8.1 (0.2)
HBV RNA, log_{10} copies/mL, mean (SEM)	7.2 (0.1)	6.7 (0.3)
HBsAg, log_{10} IU/mL, mean (SEM)	4.6 (0.1)	4.4 (0.2)
ALT≥1.2xULN at screening or baseline, N (%)	1 (10)	8 (53)

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

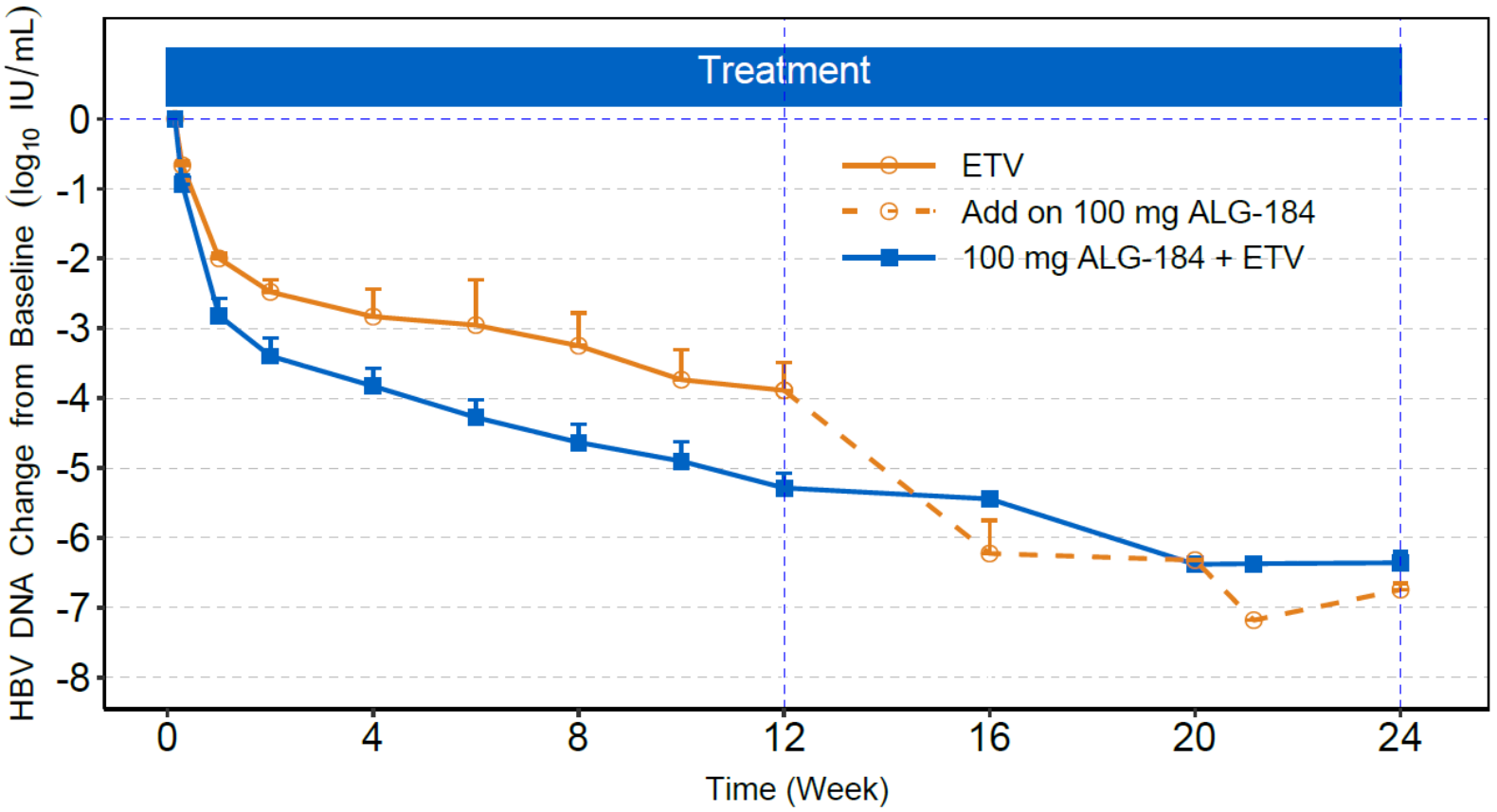
ALG-000184-201
Part 4 Safety

	Cohort 1 100 mg ALG-000184 + ETV or Placebo + ETV	Cohort 2 300 mg ALG-000184 + ETV or Placebo + ETV
N	11	15
Serious Adverse Event (SAE)	0	0
Treatment Emergent Adverse Event (TEAE) leading to study drug discontinuation	0	0
Most common (≥4 subjects) TEAEs	Transaminase elevations, oropharyngeal pain, upper respiratory tract infection	
Subjects with Grade ≥3 TEAE	1 (G3 LDL)	3 (2 G4 ALTs, 1 G4 neutropenia*)
Concerning laboratory, electrocardiogram, vital sign, or physical examination findings	None	

100 mg or 300 mg ALG-000184 + ETV well tolerated
ALT Flare Committee had no concerns regarding ALT flares throughout the study

*Occurred in setting of respiratory infection and resolved while continuing study drug

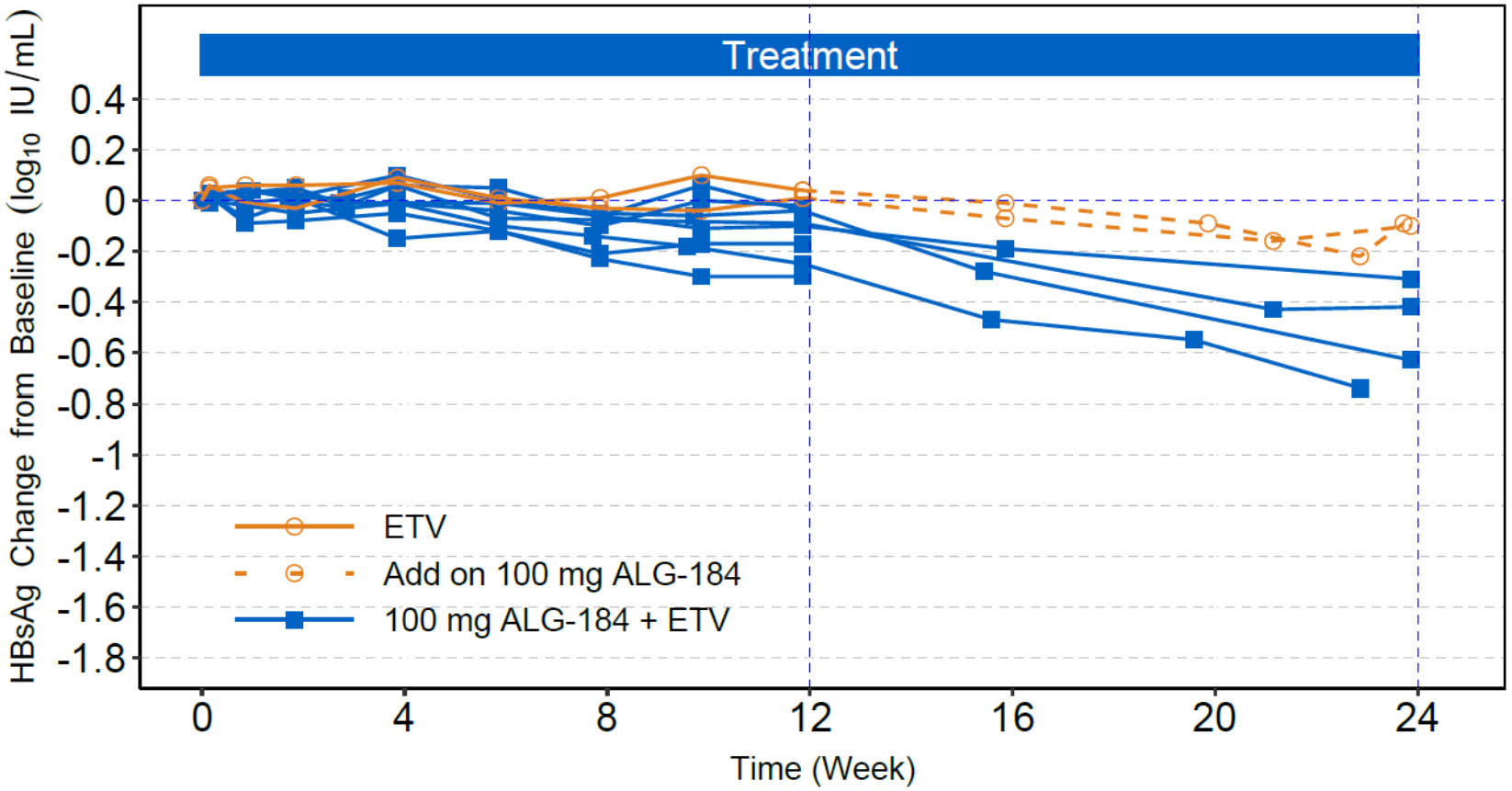
Part 4 Cohort 1 (100 mg ALG-00184 + ETV x 24 weeks)
HBV DNA Declines In Subjects Receiving ALG-000184 x ≥12 Weeks



N=4 dosed with 100 mg ALG-000184 + ETV x 24 weeks
At Week 24, all subjects had HBV DNA of >6 log_{10} IU/mL
Add on ALG-000184 : additional ~2 log_{10} IU/mL HBV DNA decline vs. ETV

Mean ± SEM

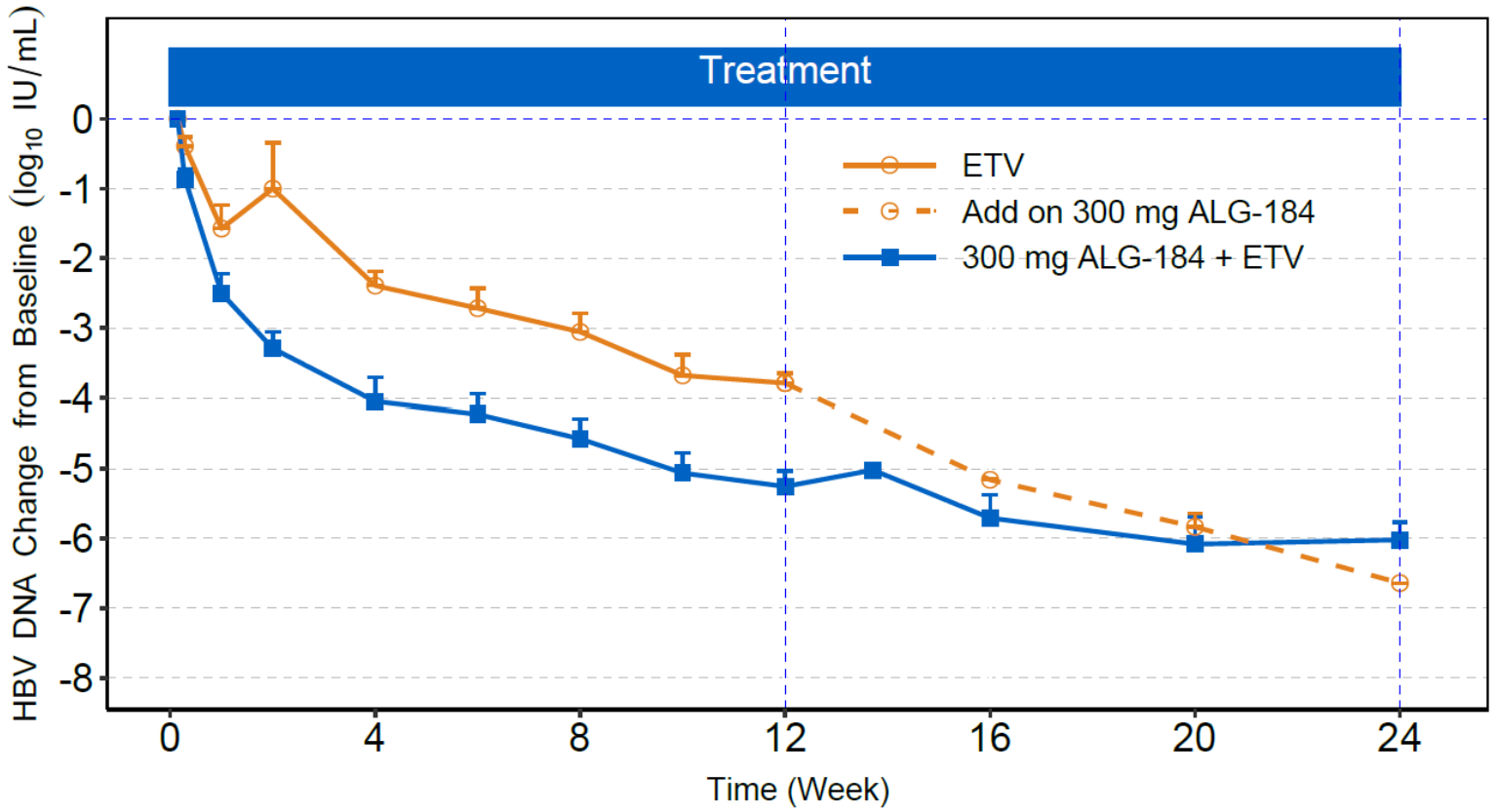
Part 4 Cohort 1 (100 mg ALG-00184 + ETV x 24 weeks)
HBsAg Declines In Subjects Receiving ALG-000184 x ≥12 Weeks



At week 24, 3 of 4 subjects had HBsAg decline of >0.4 log_{10} IU/mL
Maximum HBsAg decline of ~0.7 log_{10} IU/mL

Add on ALG-000184: downward HBsAg trend seen after switch

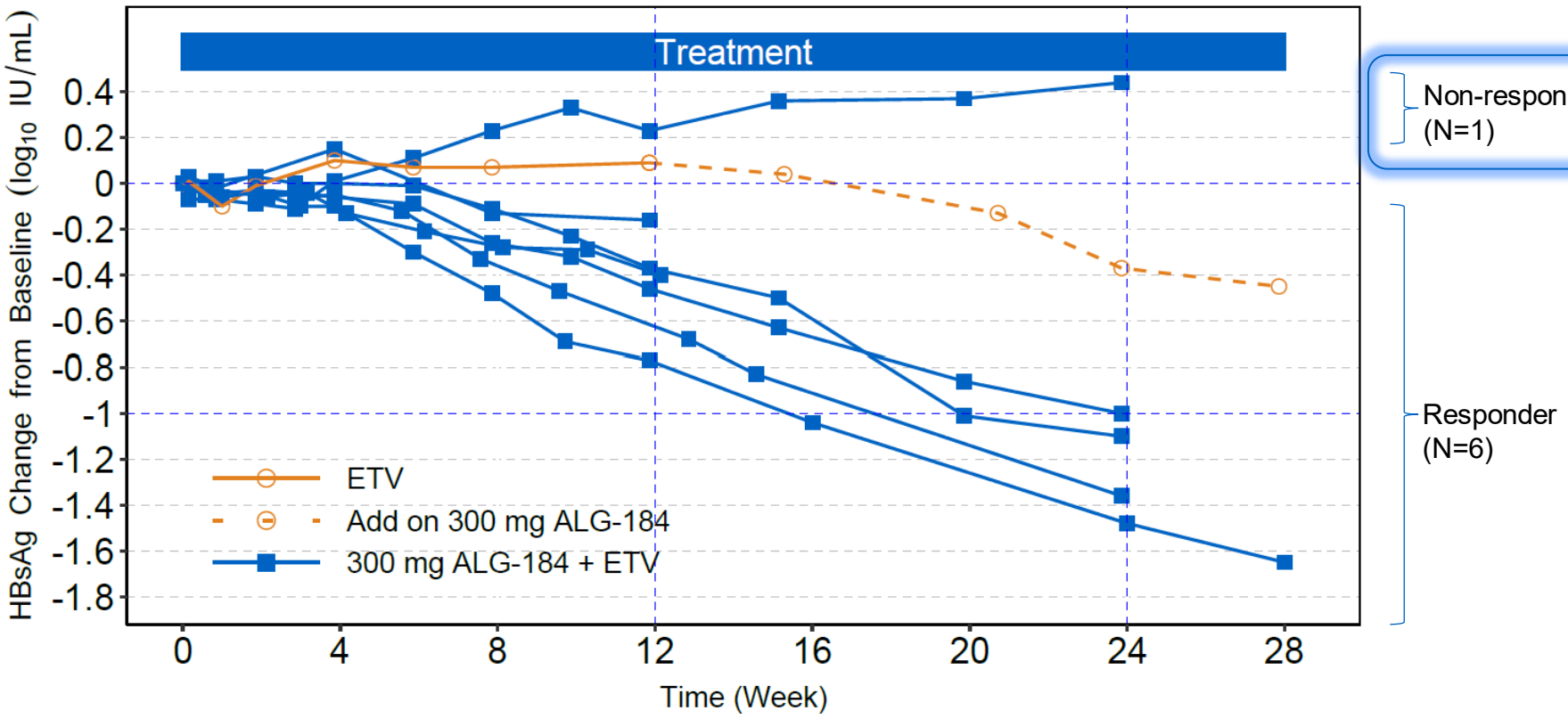
Part 4 Cohort 2 (300 mg ALG-00184 + ETV x 48 weeks)
HBV DNA Declines In Subjects Receiving ALG-000184 x ≥12 Weeks



N=7 and N=5 dosed with 300 mg ALG-000184 + ETV x ≥12 weeks and ≥24 weeks, respectively
At Week 24, all subjects had HBV DNA decline of ≥6 log_{10} IU/mL, 1 subject was undetectable

Mean ± SEM

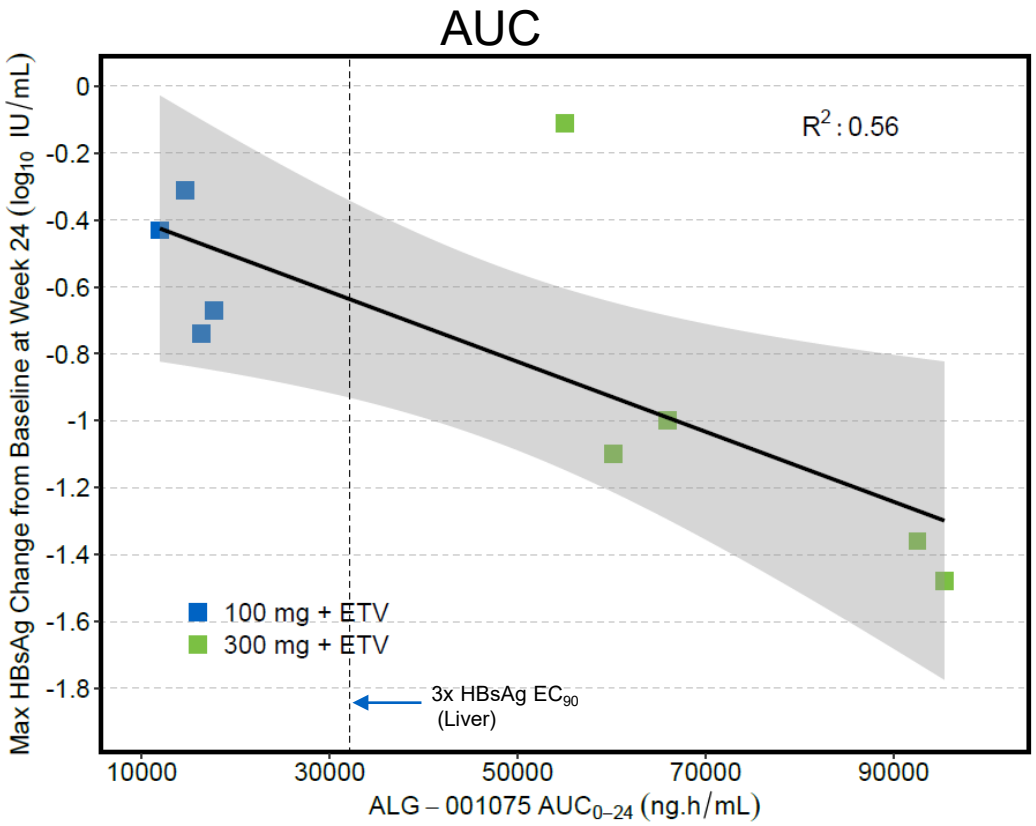
Part 4 Cohort 2 (300 mg ALG-00184 + ETV x 48 weeks)
HBsAg Declines In Subjects Receiving ALG-000184 x ≥12 Weeks

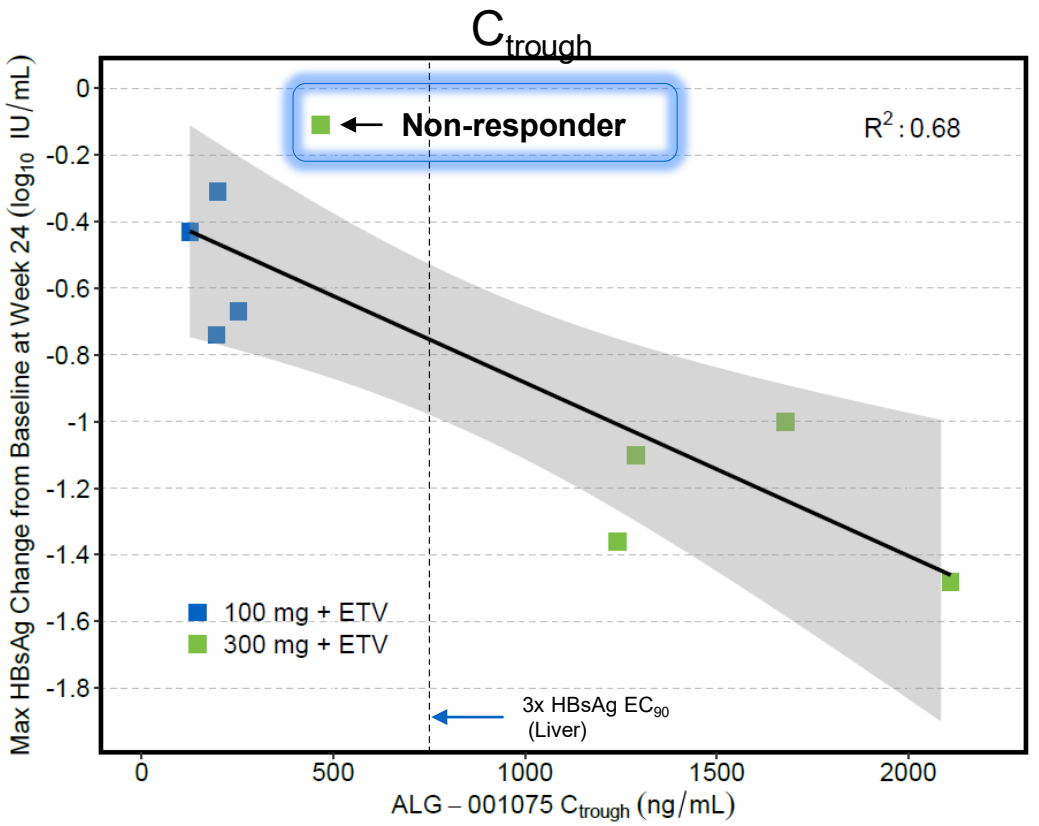


After 12 weeks, 6 of 7 subjects had HBsAg decline of ≥0.4 log_{10} IU/mL
After 24 weeks, 4 of 5 subjects had HBsAg decline of ≥1 log_{10} IU/mL

Maximum observed decline: 1.65 log_{10} IU/mL at Week 28

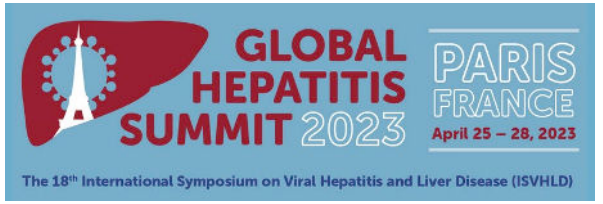
ALG-000184-201 Part 4
Change in HBsAg vs. PK (Week 24)





HBsAg declines appear to be correlated to plasma ALG-001075 PK (both AUC and C_{trough})
BID dosing (which raises C_{trough}) might further enhance HBsAg lowering – cohort planned

ALG-000184 Conclusions



- When combined with ETV for up to 28 weeks in HBeAg+ subjects not on treatment, ALG-000184 demonstrated:
  - Favorable safety profile
  - Superior reductions in HBV DNA compared to ETV alone
  - Substantial reductions in HBsAg (up to 1.65 $\log_{10}$ IU/mL)
    - >1 $\log_{10}$ IU/mL reduction in HBsAg in 4/5 patients dosed with 300mg x ≥24 weeks
    - This anti-viral effect appears to be related to exposure of active drug
- Longer dosing in ongoing and other cohorts (BID dosing) planned to further define safety, PK and antiviral activity of ALG-000184 + ETV
- ALG-000184 appears to have best in class properties and could contribute to enhanced rates of functional cure in combination with other antivirals and immunomodulators, including possibility of all oral regimens (e.g., oral PD-L1)

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    - Jilin University the 1st Hospital Phase 1 Unit
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