The Capsid Assembly Modulator ALG-000184 Dosed for 28 Days Was Well Tolerated and Rapidly Reduced Viral Markers in Subjects with Chronic Hepatitis B, Including HBsAg in a Subset of HBeAg Positive Subjects with Elevated Baseline ALT

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Disclosures

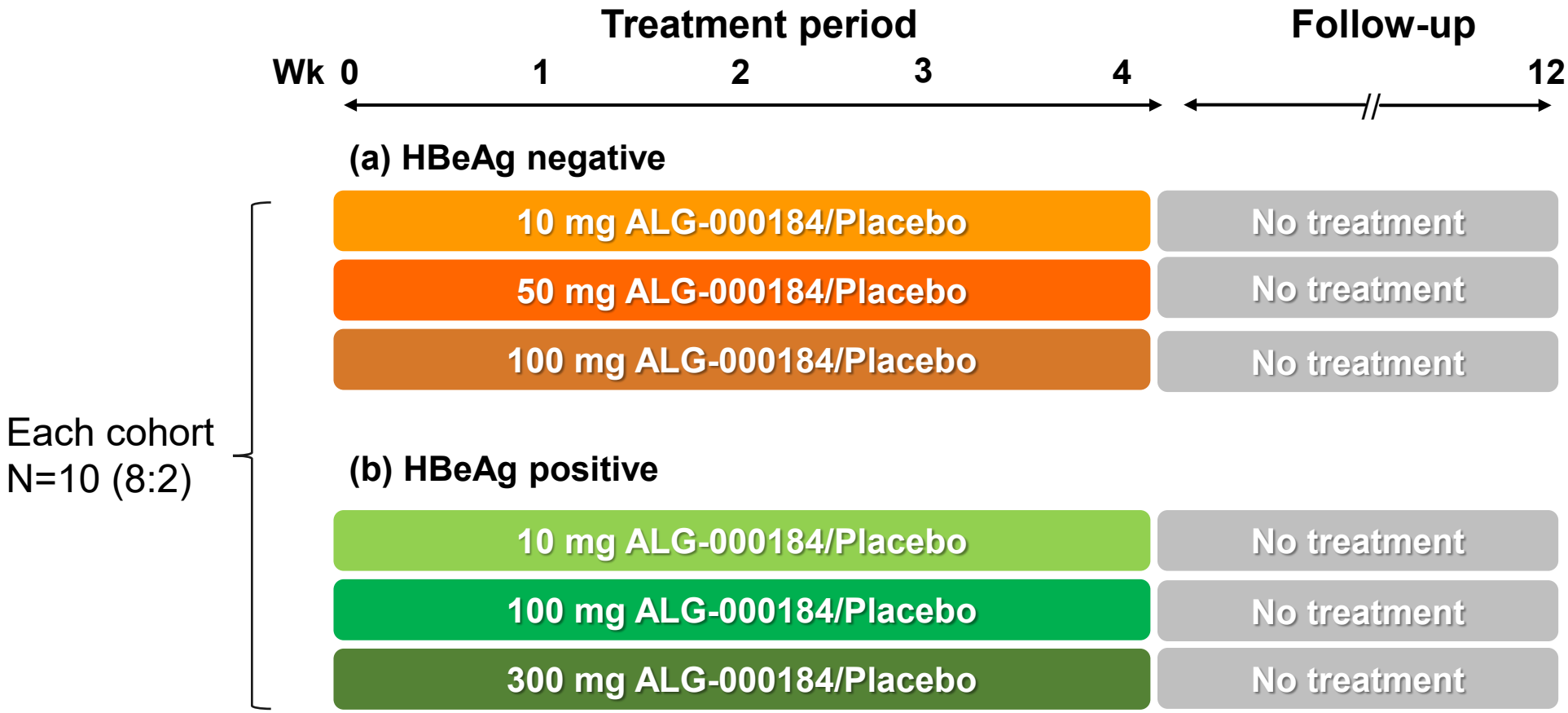
- Member of Scientific Advisory Board for AbbVie, Abbott Diagnostics, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, Enanta, Gilead Sciences, GlaxoSmithKline, Intellia, Janssen, Merck, Novartis, Genentech-Roche, Vaccitech, VIR Bio and Virion Therapeutics.
- Speaker for AbbVie, Abbott Diagnostics, Intellia
- Unrestricted grant support from AbbVie for the Hepatitis C Test and Treat pilot study in Auckland, New Zealand
- Associate Editor of the *Journal of Hepatology*
- Ministry of Health Chief Advisor for Chronic Viral Hepatitis

Background

- Long-term treatment with nucleos(t)ide analogues (NAs) improves outcomes in chronic hepatitis B (CHB), but rarely results in functional cure[1,2]
- ALG-000184, a prodrug of ALG-001075, is a pan-genotypic capsid assembly modulator – empty (CAM-E) with the potential to enhance functional cure rates
- ALG-000184 is currently being evaluated in a multipart, randomized, double-blind Phase 1 study (ALG-000184-201[3]), which:
  - Demonstrated favorable safety and dose-dependent pharmacokinetics (PK) after single (up to 500 mg) and multiple (up to 250 mg x 7 days) doses in healthy volunteers[4-5]
  - Recently completed evaluation of 28-day dosing in six cohorts of treatment naïve (TN) or currently not treated (CNT) CHB subjects (Part 3)

1. Lok A.S., J of Hepatology 2017. 2. Zhang et al. Chin Med J 2021.3 NCT04536337. 4. Gane E., APASL 2021. 5 Gane E., HBV-TAG 2021

ALG-000184-201
Study Design



Key Inclusion criteria

- Currently not treated/treatment naïve subjects
- ALT and AST ≤ 5 ULN
- HBV DNA > 2000 IU/mL

ALG-000184-201
Baseline Characteristics

Dose level	HBeAg Negative			HBeAg Positive		
	10 mg ALG-000184/PBO	50 mg ALG-000184/PBO	100 mg ALG-000184/PBO	10 mg ALG-000184/PBO	100 mg ALG-000184/PBO	300 mg ALG000184/PBO
N	N=9*	N=10	N=10	N=8*	N=10	N=12**
Age, years, mean (SEM)	45.4 (1.8)	42.7 (2.8)	44.7 (2.9)	36.8 (0.9)	30.2 (2.4)	31.9 (1.3)
Male, N (%)	4 (44.4)	4 (40.0)	5 (50.0)	3 (37.5)	8 (80.0)	6 (50)
White/Asian/Other, N (%)	3(33)/ 4(44)/2(22)	2(20)/ 7(70)/ 1(10)	9(90)/ 1(10)/ 0	0/8 (100)	0/ 10(100)/ 0	0/12 (100)/0
BMI, kg/m^2, mean (SEM)	26.2 (1.1)	24.3 (1.7)	26.7 (1.8)	23.2 (1.3)	21.8 (0.9)	22.4 (0.9)
HBeAg negative (%)	100	100	100	0	0	0
HBV Genotype: A/B/C/D/E (%)	A: 1 (11) B: 2 (22) C: 1 (11) D: 4 (44) E: 1 (11)	A: 1 (10) B: 6 (60) C: 1 (10) D: 2 (20)	A: 1 (10) B: 1 (10) D: 8 (80)	B:8 (100)	B: 4 (40) C: 6 (60)	B: 5 (42) C: 7 (58)
HBV DNA, $\log_{10}$ IU/mL, mean (SEM)	4.1 (0.1)	4.7 (0.4)	4.2 (0.3)	8.5 (0.1)	8.1 (0.3)	8.4 (0.2)
HBV RNA, $\log_{10}$ copies/mL, mean (SEM)	1.3 (0.3)	2.1 (0.3)	1.6 (0.3)	8.5 (0.1)	7.8 (0.4)	7.3 (0.2)
HBsAg, $\log_{10}$ IU/mL Mean (SEM)	3.2 (0.2)	3.0 (0.3)	3.4 (0.2)	4.8 (0.04)	4.5 (0.1)	4.5 (0.1)

PBO= Placebo. BMI= Body Mass Index. SEM= Standard Error of the Mean

*Enrollment in the 10 mg cohorts was considered completed before 10 subjects enrolled, in agreement with the Study Review Committee.** Two additional subjects enrolled to replace 2 subjects with incomplete data due to Covid-19 lockdown (China)

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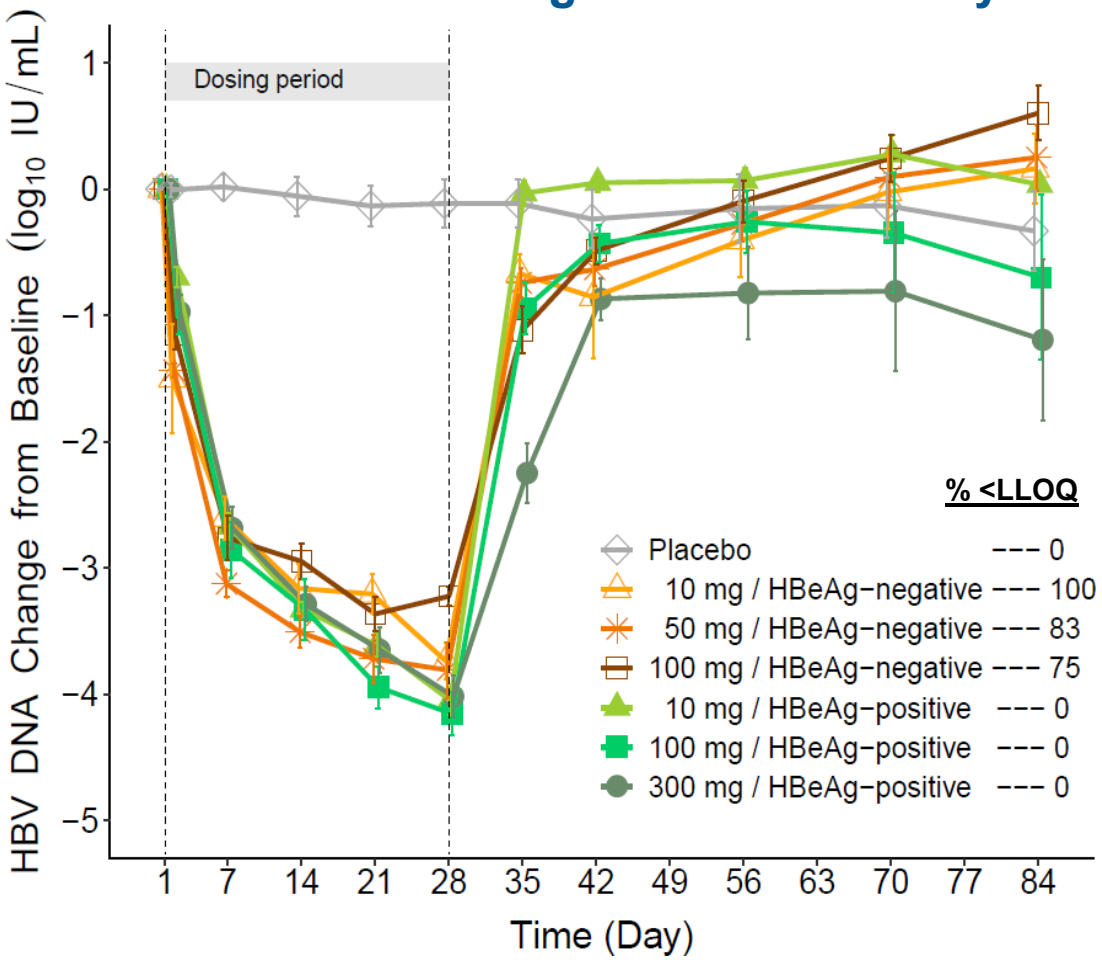
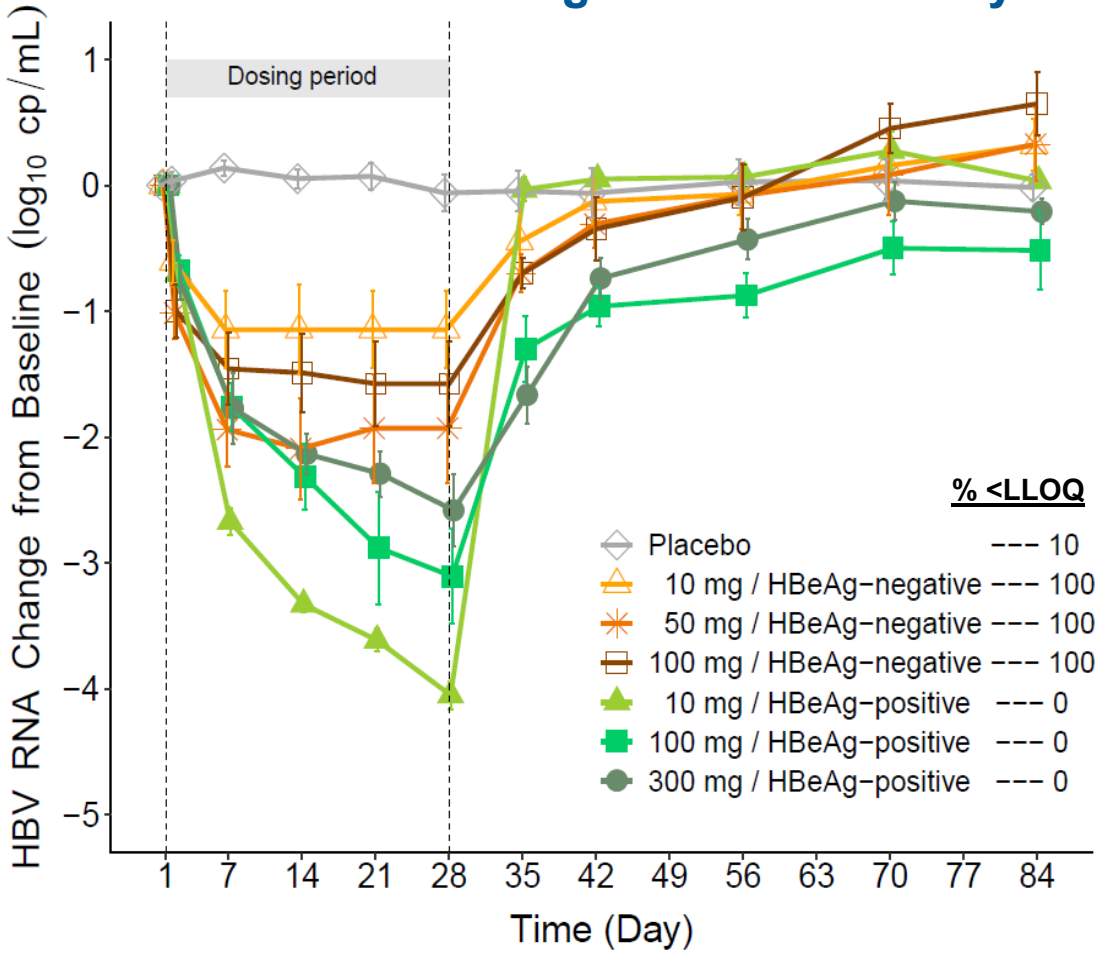
Change in HBV DNA and HBV RNA

(i) Mean (SEM) Serum HBV DNA Levels Change from Baseline Through the End of Study



(ii) Mean (SEM) Serum HBV RNA Levels Change from Baseline Through the End of Study



- HBV DNA Roche Cobas® assay: Sonic laboratory: Lower Limit of Quantification (LLOQ) = 10 IU/mL. Lower limit of detection (LLOD) = 2.8 IU/mL; KingMed laboratory: LLOQ=10 IU/mL and LLOD = 2.4 IU/mL
- HBV RNA Roche Cobas® assay. LLOQ = 10 copies/mL. LLOD = 3.3 copies/mL
- HBV RNA China local assay: LLOQ and LLOD = 200 copies/mL

ALG-000184-201
Antiviral Activity: HBV DNA

Dose level	HBeAg Negative			HBeAg Positive			Placebo Overall
	10 mg ALG-000184	50 mg ALG-000184	100 mg ALG-000184	10 mg ALG-000184	100 mg ALG-000184	300 mg ALG000184	
N	N=7	N=8	N=8	N=7	N=8	N=10	N=11
Baseline mean (SEM) log_{10} IU/mL	4.1 (0.1)	4.8 (0.4)	4.2 (0.4)	8.5 (0.1)	8.3 (0.3)	8.4 (0.2)	5.8 (0.6)
Change from BL mean (SEM) log_{10} IU/mL	-3.7 (0.1)	-3.8 (0.2)	-3.2 (0.1)	-4.1 (0.1)	-4.2 (0.2)	-4.0 (0.2)	-0.1 (0.2)
Subjects < LLOQ N (%)	7/7 (100)	5/6[a] (83)	6/8 (75)	0	0	0	0
Subjects < LLOD N (%)	3/7 (43)	1/6[a] (17)	2/8 (25)	0	0	0	0

Substantial declines in HBV DNA at all doses, regardless of HBeAg status

[a] Cohort 2 (50 mg ALG-000184/placebo in HBeAg negative): Two subjects had missing HBV DNA and RNA data due to early discontinuation for personal reasons (not safety related) (N=1) and because the subject did not attend Day 28 visit due to COVID lock down (N=1)

ALG-000184-201
Antiviral Activity: HBV RNA

Dose level	HBeAg Negative			HBeAg Positive			Placebo Overall
	10 mg ALG-000184	50 mg ALG-000184	100 mg ALG-000184	10 mg ALG-000184	100 mg ALG-000184	300 mg ALG000184	
N	N=7	N=8	N=8	N=7	N=8	N=10	N=11
Baseline mean (SEM) log_{10} copies/mL	1.2 (0.4)	2.1 (0.4)	1.7 (0.4)	8.5 (0.1)	7.8 (0.4)	7.4 (0.3)	4.3 (1.0)
Change from BL mean (SEM) log_{10} copies/mL	-1.1 (0.3)	-1.9 (0.4)	-1.6 (0.3)	-4.1 (0.1)	-3.1 (0.4)	-2.6 (0.3)	-0.1 (0.1)
Subjects < LLOQ N (%)	7/7 (100)	6/6[a] (100)	8/8 (100)	0	0	0	1/10[b,c] (10)
Subjects < LLOD N (%)	6/7 (86)	5/6[a] (83)	7/8 (88)	0	0	0	0/10 (0)

Substantial declines in HBV RNA at all doses, regardless of HBeAg status

[a.] Cohort 2 (50 mg ALG-000184/placebo in HBeAg negative): Two subjects had missing HBV DNA and RNA data due to early discontinuation for personal reasons (not safety related) (N=1) and because the subject did not attend Day 28 visit due to COVID lock down (N=1) [b] One subject missed Day 28 visit due to having Covid [C] One subject had HBV RNA <LLOQ at baseline

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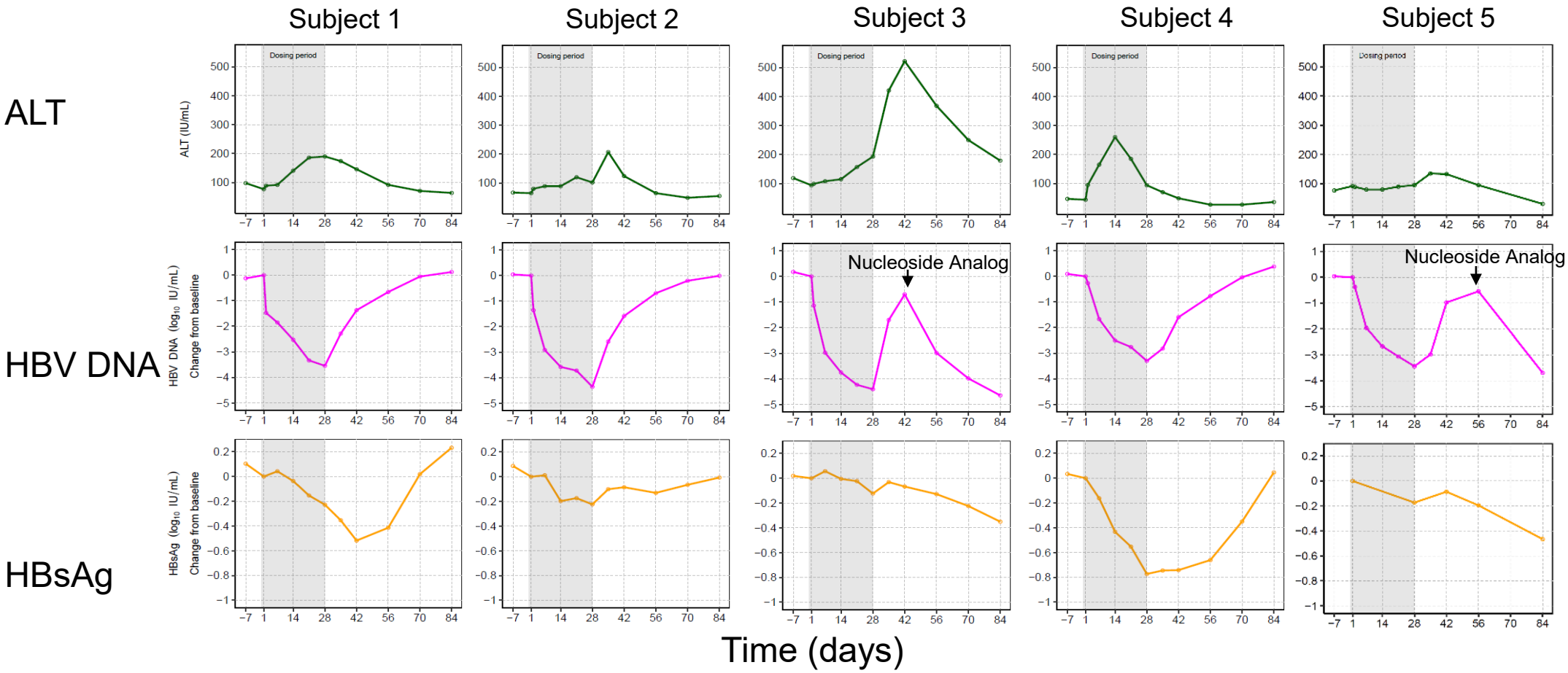
Individual Profiles for HBeAg Positive Subjects with Changes in HBsAg



- 4/8 subjects (#2-5) in 300 mg cohort had HBsAg reductions of up to 0.78 log10 IU/mL
- 1 subject in 100 mg cohort (#1) with exposures similar to 300 mg had HBsAg reduction of 0.5 log10 IU/mL
- No HBsAg changes observed in HBeAg-negative cohorts or HBeAg-positive subjects receiving 10 mg ALG-000184

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HBsAg, DNA, & ALT in HBeAg+ Subjects Receiving 100 or 300 mg ALG-000184

Subject #	Baseline ALT	HBV DNA Change From Baseline at Day 28 (log_{10} IU/mL)	Max HBsAg Change From Baseline (log_{10} IU/mL)
1 *	Elevated	-3.5	-0.5
2	Elevated	-4.4	-0.2
3	Elevated	-4.4	-0.35
4	Elevated	-3.3	-0.8
5	Elevated	-3.4	-0.5
6	Normal	-4.2	<0.1
7	Normal	-4.4	<0.1
8	Elevated	-3.6	<0.1
9	Normal	-4.3	<0.1
Placebo	Elevated	-0.2	<0.1
Placebo	Elevated	0.2	<0.1

All subjects with HBsAg declines received ALG-000184 and had elevated baseline ALT

- No HBsAg declines in subjects treated with ALG-000184 with normal baseline ALT
- No HBsAg declines in subjects receiving placebo with elevated baseline ALT levels

* 100 mg subject with ~300 mg exposure
Excludes subjects missing Day 28 data (N=2) due to COVID lockdown in China

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Safety

	HBeAg negative			HBeAg positive		
Dose level	**10 mg ALG-000184/PBO**	**50 mg ALG-000184/PBO**	**100 mg ALG-000184/PBO**	**10 mg ALG-000184/PBO**	**100 mg ALG-000184/PBO**	**300 mg ALG-000184/PBO**
N subject with	**N=9**	**N=10**	**N=10**	**N=8**	**N=10**	**N=12**
TEAE (Total)	2 (22)	6 (60)	6 (60)	0	10 (100)	10 (83.3)
TEAE (Related)	0	4 (40)	3 (30)	0	3 (30)	6 (50)
Worst reported grade TEAE						
TEAE Grade 1	2 (22)	5 (50)	4 (40)	0	10 (100)	10 (83)
TEAE Grade 2	0	3 (30)	2 (20)	0	4 (40)	5 (42)
TEAE Grade 3*	0	0	1 (10)	0	2 (20)	4 (33)
TEAE Grade 4*	0	0	0	0	0	1 (8)
TEAE leading to study drug discontinuation	0	0	0	0	0	0
SAE	0	0	1 back pain, not related (Grade 1)	0	0	1 Pneumo-thorax, unlikely related (Grade 3)

10 mg to 300 mg ALG-000184 for 28 days was well tolerated

*Except for the Grade 3 TEAE of pneumothorax, the other 7 Grade ≥3 TEAEs were ALT elevations which occurred during HBV DNA rebound after stopping drug (N=5) or during HBsAg/HBV DNA declines (N=2). None were associated with clinically relevant changes in liver synthetic function, or considered suggestive of drug toxicity by the ALT Flare Committee

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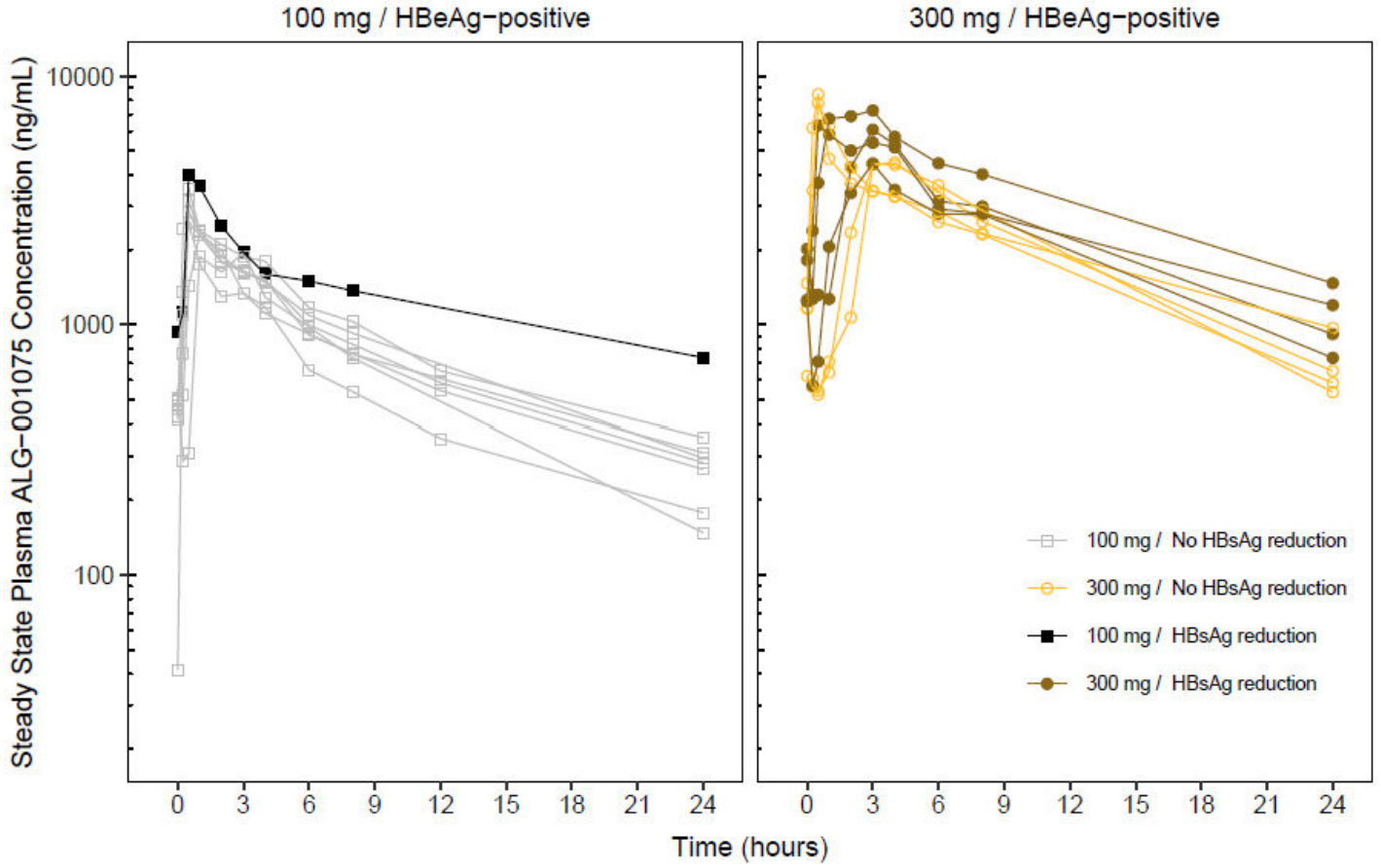
Pharmacokinetics of ALG-001075



PK profile: dose proportional with low variability
Patients who had reduction in HBsAg levels generally had higher steady state plasma ALG-001075

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Conclusions

- Oral daily dosing with 10-300 mg of ALG-000184 for 28 days
  - Was well tolerated
  - Resulted in substantial declines in HBV DNA and RNA at all doses, regardless of HBeAg status
  - Resulted in HBsAg declines up to 0.8 $\log_{10}$ IU/mL at 100 mg and 300 mg dose. The 5 HBeAg-positive subjects with changes in HBsAg also had elevated ALT levels at baseline and generally had higher plasma exposures
- Longer duration (≤48 weeks) cohorts evaluating ALG-000184 ± ETV
  - Preliminary (up to 24 weeks) data presented by Prof Hou (Abstract #FP03-17)
- ALG-000184 has best in class antiviral efficacy and may have a role in future combination regimens for functional cure of chronic hepatitis B

ALG-000184-201
Acknowledgments

The authors wish to thank the following for their contributions:

- The subjects and their families for their participation
- The clinical investigational study teams:
  1. New Zealand Clinical Research, New Zealand
  2. University of Hong Kong, Hong Kong
  3. Institute of Liver Studies, Kings College Hospital, United Kingdom
  4. ARENSIA Exploratory Medicine, Republican Clinical Hospital and Nicolae Testemitanu State University of Medicine and Pharmacy, Moldova
  5. Nanfang Medical University
  6. Nanfang Hospital Infectious Disease Department
  7. Jilin University the 1st Hospital Phase 1 Unit
- Our collaborators: Novotech, Sonic, TigerMED and KingMED for study conduct
- Aligos internal team members: John Fry, Min Wu, Chris Westland, Maida Maderazo, Kim Steel and Genevieve Harrington for their leadership and aid in the conduct of the study