Safety, Tolerability, Pharmacokinetics (PK), and Antiviral Activity of Multiple Doses of ALG-000184 in Healthy Volunteers (HV) and Subjects with Chronic Hepatitis B (CHB)

E. Gane[1], MF Yuen[2], A Jucov[3], K Le[4], J Nguyen[4], C Westland[4], C Schwabe[5], K Agarwal[6], J Yogaratnam[4], Q Zhang[4], L Blatt[4], S Chanda[4], M McClure[4], J Fry[4]

[1]University of Auckland, New Zealand; [2]University of Hong Kong, Hong Kong; [3]Nicolae Testemitanu State University of Medicine and Pharmacy, Moldova; [4]Aligos Therapeutics, United States; [5]Auckland Clinical Studies, New Zealand; [6]Institute of Liver Studies, Kings College Hospital, United Kingdom

INTRODUCTION

Chronic Hepatitis B affects >250 million people worldwide. Long term complications of the disease result in an annual mortality rate of ~900,000 (WHO HBV fact sheet 2020). Treatment with the most commonly used drugs, nucleos(t)ide analogs, rarely results in functional cure, the goal of therapy. As such, there is a significant need for novel approaches which can enhance functional cure rates. ALG-000184 is a prodrug of a novel, potent, pan-genotypic Class II capsid assembly modulator, ALG-001075. ALG-000184 is being developed as a potential component of a finite duration combination regimen approach designed to achieve higher rates of functional cure.

OBJECTIVES

- To evaluate the safety & PK of multiple ALG-000184 doses in HVs
- To evaluate the safety, PK, & antiviral activity of multiple ALG-000184 doses in CHB subjects

METHODS

This is a three-part, multicenter, double-blind, randomized, placebo-controlled study (NCT04536337):

- In Part 1, single oral doses of ALG-000184 in HVs were found to be well tolerated with dose-dependent, linear PK at doses up to 500 mg (Gane E, APASL 2021)
- In Part 2, two cohorts of 8 HVs (≥3 Asian subjects/cohort) received 7 daily (QD) oral (PO) doses of ALG-000184 or placebo (3:1 ratio)
- Part 3 is evaluating multiple cohorts (N=10/cohort; 8 active:2 placebo) of currently not treated (CNT)/treatment naïve (TN) hepatitis B e antigen (HBeAg) negative CHB subjects receiving PO QD doses of ALG-000184/placebo for 28 days
- Assessments include adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECG), laboratories, PK, and hepatitis B virus viral markers (Part 3). HBV DNA was assessed at a central laboratory using the Roche Cobas® HBV Assay (lower limit of quantification (LLOQ) <10 IU/mL)

PK-PD model

- Plasma concentrations of ALG-001075 quantified using a validated LC-MS/MS method
- PK modeling conducted using PK data from humans and animal (mouse, rat, dog, monkey) plasma/liver PK data
- The model assumed that >3-fold EC_{90} free liver or serum-shifted plasma concentration for HBV DNA inhibition at steady state is required to achieve antiviral activity
- PK simulations performed using individual PK parameters of study subjects and body weight ranges

For clinical data, continuous data are presented as mean (standard deviation(SD) or standard error of the mean (SEM)). Categorical data are presented as percentages.

Reported here are preliminary safety and PK data from Part 2 and preliminary safety, PK, and antiviral activity (i.e., HBV DNA) data through 14 days from the first cohort of Part 3.

RESULTS

DOSE LEVELS EVALUATED

In Part 2, 7 daily oral doses of 150 (cohort 1) and 250 mg (cohort 2) were evaluated

In Part 3, 28 daily doses of 100 mg are being evaluated

BASELINE CHARACTERISTICS

The baseline characteristics were similar across treatment groups and are typical for a HV and CNT/TN CHB population, respectively

Characteristic	Part 2		Part 3
	Cohort 1	Cohort 2	Cohort 1
N	8	8	10
Age, years	32.6 (11.9)	33.9 (9.4)	44.7 (9.3)
% Male	88%	88%	60%
% Asian	75%	63%	10%
BMI, kg/m²	25.0 (1.6)	24.5 (2.9)	26.7 (5.7)
Baseline HBV DNA, IU/mL Mean (SD) Median	N/A	N/A	4.2 (1.0) 3.9

N/A = not applicable

SAFETY

Multiple (7 or 14) doses of ALG-000184 were well tolerated in HVs and CNT/TN CHB subjects:

- No serious adverse events
- Treatment emergent adverse events (TEAEs)
  - No TEAEs led to study drug discontinuation
  - All TEAEs were mild except one case of moderate back pain in a CHB subject (considered unlikely related to study drug)
  - The most commonly reported (≥2 subjects) TEAEs were back pain, dry mouth and headache (2 subjects/each) and nausea (3 subjects)
- No Grade ≥2 treatment emergent laboratory abnormalities
- No clinically concerning laboratory, ECG, vital sign or physical examination findings
- No clinically significant differences observed in the safety profile for
  - Asian compared to non-Asian subjects
  - HVs compared to CHB subjects

PK

- Dose-dependent, linear PK (ALG-001075 exposures) observed in HVs with low intersubject variability (CV ~20%)
- Minimal accumulation (~30%) seen with repeat dosing
- No clinically significant differences observed in the PK profile for Asian compared to non-Asian subjects or HVs compared to CHB subjects

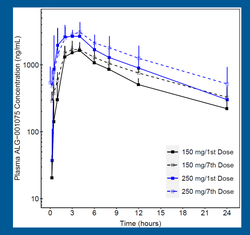

Figure 1: Mean (+SD) Plasma Concentration-Time Profiles of ALG-01075 following 150-250mg ALG-000184 PO QD in HVs

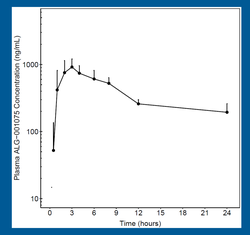

Figure 2: Mean (+SD) Plasma Concentration-Time Profiles of ALG-01075 following 100mg ALG-000184 PO QD in CHB subjects

Dose* (mg)	Dose #	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{n,24h}$ (ng.hr/mL)
		Part 2 (HVs)		
150	1st dose	1740 (11.5)	4 (2,4)	15100 (18.4)
	7th dose	1850 (21.1)	3 (2,4)	19100 (24.6)
250	1st dose	2840 (15.9)	3 (2,4)	24400 (27.7)
	7th dose	3370 (35.7)	3 (2,4)	30900 (42.3)
		Part 3 (CHB)		
100	1st dose	912 (17)	2 (1,3)	8150 (13.9)

Values represent Geometric Mean (Coefficient of Variation [CV]%), except T_{max}: median (minimum, maximum) and $t_{1/2}$: average (SD)

PK-PD PREDICTIONS

The PK-PD model predicts that daily ALG-000184 doses ≥100 mg will achieve steady state free liver concentrations ≥3xEC_{90} and will result in antiviral activity in CHB subjects

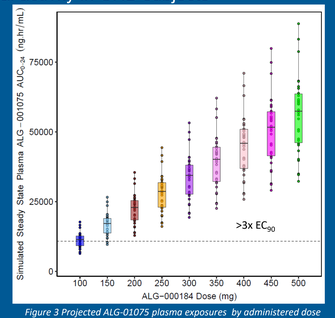

Figure 3 Projected ALG-01075 plasma exposures by administered dose

Dots represent simulated PK with different doses for individual study subjects. Boxes represent first and third quartiles (25th and 75th percentiles); line within each box represents median (50th percentile). Whiskers extend to the largest value no further than 1.5 * interquartile range from the hinges. The dotted line represents the mean efficacious plasma exposure needed to achieve ≥3xEC_{90} for HBV DNA reduction for a typical subject (75 kg).

HBV DNA

PK-PD modelling results were confirmed. Administration of 100 mg of ALG-000184 for 14 days resulted in antiviral activity:

- Rapid, substantial reductions in HBV DNA levels (mean (SEM) reduction of 2.9 (0.2) log_{10} IU/mL at Day 14)
- HBV DNA concentrations were below the LLOQ in 4 of 8 (50%) subjects

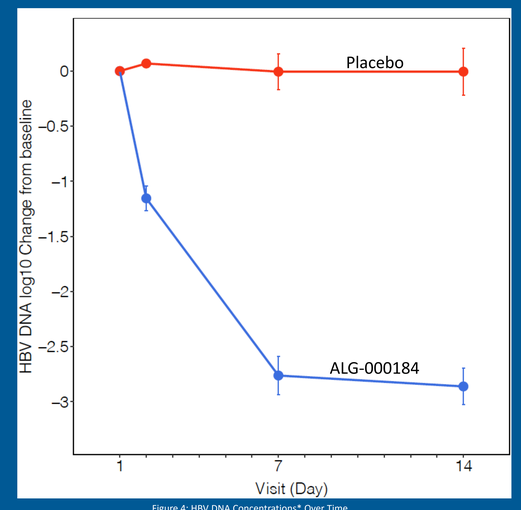

Figure 4: HBV DNA Concentrations* Over Time

*Roche COBAS; LLOQ <10 IU/mL

CONCLUSIONS

ALG-000184 was well tolerated after 7 and 14 daily oral doses in HVs and CHB subjects, respectively. Exposures increased in a dose proportional manner with low variability and no differences across ethnicities. As predicted by the PK-PD model, when given for 14 days, the 100 mg dose demonstrated rapid, substantial HBV DNA reductions with half of subjects' values being <LLOQ. Completion of 28 days' dosing in the 100 mg cohort and recruitment in a subsequent cohort are both ongoing.

ACKNOWLEDGEMENTS

The authors wish to thank the subjects for participating in this clinical study. We are also grateful to the staff at Auckland Clinical Studies and Novotech for assisting in the conduct of this study. We also wish to thank Certara for assisting with the PK-PD modelling.

CONTACT INFORMATION

Matt McClure - mmcclure@aligos.com