APASL2021 COLLABORATION AND CURE

ALIGOS THERAPEUTICS

Safety, Tolerability and Pharmacokinetics of Single Ascending Doses of ALG-000184, a Class II Capsid Assembly Modulator for the Treatment of Chronic Hepatitis B (CHB), in Healthy Volunteers (HV)

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INTRODUCTION

Chronic hepatitis B virus (cBV) infection is a serious global unmet medical need. Almost 300 million people worldwide have HBV, of whom an estimated 900,000 people die from complications of chronic hepatitis B (CHB), primarily cirrhosis and hepatocellular carcinoma (HCC).[1] To maintain suppression of HBV replication and reduce liver injury, life-long treatment with HBV nucleos(t)ide analogs (NAs) is necessary in most patients. This approach has very low rates of functional cure (the goal of CHB treatment) and is associated with non-adherence, which can result in life-threatening relapse and drug resistance.[2-7] With the persistently high global prevalence of HBV-associated mortality, the need for lifelong treatment and the low rate of functional cure with current treatments, there is a significant need for effective finite treatment regimens that achieve higher functional cure rates and improve long-term clinical outcomes (i.e., reduced mortality and morbidity from cirrhosis and HCC).[2,8,9]

Combinations of antiviral therapy targeting multiple steps in the HBV life cycle to suppress viral replication and immunosuppressive viral antigen production (e.g., hepatitis B surface antigen (HBsAg)) will likely be needed to achieve high rates of functional cure.

BACKGROUND

Capsid assembly modulators (CAMs) are a clinically validated class of antiviral compounds that inhibit hepatitis B virus (HBV) RNA encapsidation, leading to a reduction in circulating HBV DNA and RNA. ALG-000184 is a prodrug of ALG-001075, a novel class-II (normal, empty capsid formed) CAM with potentially best in-class preclinical characteristics[10] and excellent in vivo antiviral efficacy, demonstrated in a mouse adeno-associated virus-HBV model.[11]

Here we report preliminary results from Part 1 of the ongoing first-in-human (FIH) phase 1a/1b dose-ranging study, ALG-000184-201 (*ClinicalTrials.gov Identifier: NCT04536337*).

METHODS

Study Design

Part 1 of Study ALG-000184 was a double-blind, randomized, placebo-controlled evaluation of single ascending doses (SAD) that was conducted in HV at a single clinical pharmacology unit in New Zealand. For each SAD cohort:

- 8 HV were randomized to receive either a single oral dose of ALG-000184 (n=6) or placebo (n=2) in the fasted state and followed 1 week after the last dose
- At least 4 Asian subjects were enrolled into each cohort
- A sentinel group of 2 subjects was randomized to receive ALG-000184 or placebo (1:1 ratio) to allow for the assessment of any acute adverse events (AEs). The remaining 6 subjects (5 ALG-000184:1 placebo) were randomized and dosed at least 24 hours after the sentinel group following a review of available safety data by the Sponsor and Principal Investigator (PI)
- The dose for the first cohort was prespecified as 40 mg. For subsequent cohorts, doses were selected following a review of all available safety, tolerability and PK data during a Data Review Meeting conducted by a Study Review Committee (SRC), which included the Sponsor's Medical Monitor and the Principal Investigator (PI)
- Subjects in Cohort 2 received a single 100 mg dose of ALG-000184 in a fasted state followed by a second dose of 100 mg in a fed state (high-fat/high-calorie meal) after at least 1 week of washout, to assess the effect of food on the PK profile

Key Study Objectives

The primary objective of this part of the study was to evaluate the safety and tolerability of single doses of ALG-000184 in HV.

The secondary objectives were to evaluate:

- The plasma pharmacokinetics (PK) of ALG-000184 and ALG-001075 following single doses of ALG-000184
- The effect of food on the PK of ALG-000184 and ALG-001075 following a single dose of ALG-000184
- The effect of covariates such as ethnicity (Asian vs. non-Asian subjects) on safety and PK

Key Entry Criteria Included:

- Age 18-55 years
- Men or women of non child-bearing potential
- Body mass index (BMI) 18-32 kg/m^2 (inclusive)
- Absence of clinically significant health issues as determined by medical history and screening assessments, including electrocardiogram (ECG), laboratories, vital signs, and physical examination

Safety Assessments

- Safety assessments were conducted from screening through Day 8 post-dosing. The safety assessments included physical examinations, vital signs, 12-lead ECGs, collection of AEs, and laboratory safety tests

Pharmacokinetics Assessments

- Blood samples were collected to determine the concentrations of ALG-000184 and ALG-001075 at pre-specified time points from Day 1- Day 6 post-dosing
- Urine samples were collected to determine urinary excretion of ALG-001075 following dosing with ALG-000184 from Day 1- Day 6 post-dosing
- Plasma concentrations of ALG-000184 and ALG-001075 and urine concentrations of ALG-001075 were quantified using validated liquid chromatography–tandem mass spectrometry methods

STATISTICS

Safety data are summarized categorically or as continuous variables; no inferential statistics were performed. Placebo subjects' data were pooled across cohorts.

PK parameters were determined by non-compartmental analysis using Phoenix WinNonlin version 8.2. Comparison of PK in Asian vs. non-Asian subjects was done following stratification by body weight.

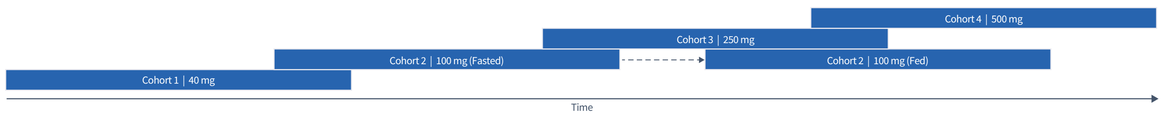
Projected efficacious dose determination was calculated using ALG-001075 antiviral activity EC_{90} values ranging from 1.84 to 8.56 nM (cellular assays and HBV-infected primary human hepatocytes) and the 40% human serum-shifted EC_{90} for HBV DNA inhibition (36.6 nM). The target efficacious exposure for total plasma was based on the serum-shifted in vitro EC_{90} for HBV DNA inhibition while the target free exposure in liver was based on the in vitro EC_{90} of primary human hepatocyte DNA inhibition. The minimum human efficacious exposure was projected using modeling and simulation analysis with the aim to maintain ALG-001075 plasma and liver concentrations at least 3-fold above the antiviral in vitro EC_{90} at C_{min}.

RESULTS

Dose Levels

Figure 1. **Part1: Phase 1a SAD (HV)**

Randomized, Double Blind, Placebo Controlled (6 ALG-000184:2 Placebo), 1 dose PO x 1 day



Following the initial dose of 40 mg, 100 mg, 250 mg and 500 mg were selected by the SRC for evaluation (Figure 1).

Demographics

Study subjects were male with a mean age range of 27-33 years and a mean BMI range of 22.3-27.0 kg/m^2. Half of subjects were Asian.

Table 1. **Demographics**

		40 mg n=6	100 mg n=6	250 mg n=6	500 mg n=6	Placebo n=8	Totals n=32
Age	Mean	27.3	30	27.8	32.5	27.9	29
	Min/Max	21/42	22/36	18/34	20/51	20/45	18/51
Sex	Male	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	8 (100.0%)	32 (100%)
BMI (kg/m^2)	Mean	22.6	24.2	22.6	22.3	27	24
	Min/Max	18.3/28.3	20.1/26.8	18.6/25.5	20/27.5	24.1/31.3	18.3/31.3
Race	Asian	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	4 (50.0%)	16 (50.0%)
	White	3 (50.0%)	3 (50.0%)	2 (33.3%)	3 (50.0%)	3 (37.5%)	14 (43.8%)
	Other	0 (00.0%)	0 (00.0%)	1 (16.7%)	0 (00.0%)	1 (12.5%)	2 (6.3%)

Pharmacokinetics

- At all dose levels, plasma ALG-000184 (prodrug) concentrations were low (ALG-000184 to ALG-001075 AUC ratio < 0.1 %), indicating rapid and efficient conversion from ALG-000184 to ALG-001075, the active moiety
- ALG-001075 exposures increased linearly with increased ALG-000184 dose and was similar with or without a high-fat, high calorie meal (Figures 2a, 2b, and Table 2)
- CLss/F ranged from 8.9-10.5 L/hr and Vz/F ranged from 93.2-107.0 L across all dose levels
- Half-life ranged from 6.9 - 8.0 hours, supporting QD dosing, and T_{max} ranged from 1–3.5 hours
- No clinically meaningful differences in PK parameters were observed between Asian and non-Asian subjects when stratified by body weight (Figure 3)
- Approximately 6.3 to 10.4% of an administered ALG-000184 dose was excreted as unchanged ALG-001075 in the urine over 120 hours post-dose
- Doses of 100 mg and above achieved plasma ALG-001075 exposures that are projected to result in antiviral activity in patients with CHB (Figure 4)

Figure 2a. **Mean (+SD) Plasma Concentration-Time Profiles of ALG-001075**

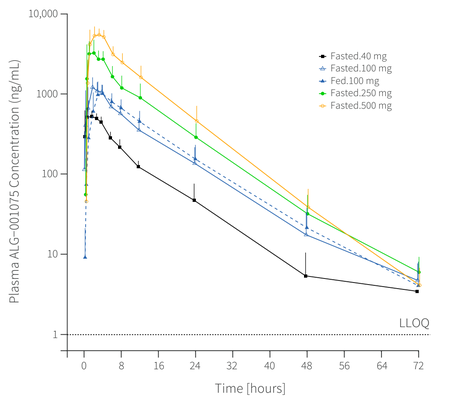
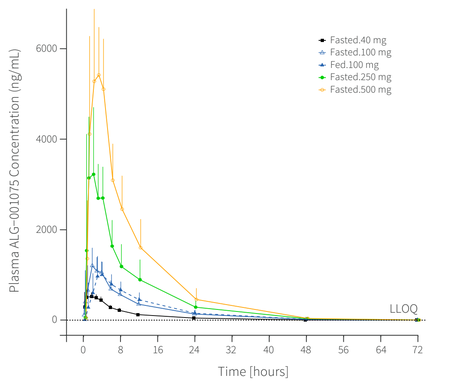


Figure 2b. **Mean (+SD) Plasma Concentration-Time Profiles of ALG-001075**



Safety

After single doses of up to 500 mg:

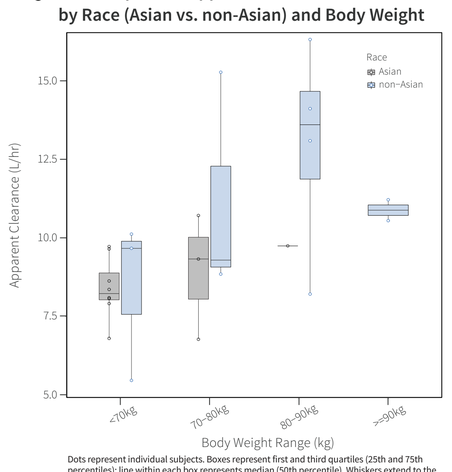
- There were no serious adverse events (SAEs) or dose-limiting toxicities
- All treatment emergent adverse events (TEAEs) were mild in severity (Grade 1). None were considered clinically significant
- No TEAE was reported in more than 1 subject
- All treatment-emergent laboratory abnormalities were Grade 1 with the exception of one subject in Cohort 1 with an exercise-related Grade 3 creatine kinase elevation
- There were no clinically significant physical examination, vital sign, or ECG abnormalities
- No clinically relevant differences were observed in the safety profile of ALG-000184 in Asian compared to non-Asian subjects

Table 2. **Geometric Mean (%CV) Plasma Pharmacokinetic Parameters of ALG-001075 Following a Single Oral ALG-000184 Dose in Healthy Volunteers**

ALG-000184 Dose (mg)	40 mg (Fasted)	100 mg (Fasted)	100 mg (Fed)	250 mg (Fasted)	500 mg (Fasted)
C_{max} (ng/mL)	611 (21.8)	1380 (24.3)	1110 (25)	4150 (37.4)	5920 (22.7)
$AUC_{0\text{-}24}$ (ng·h/mL)	4510 (18.3)	10700 (23.8)	10700 (27.7)	26400 (35.3)	47800 (25.6)
$AUC_{0\text{-}inf}$ (ng·h/mL)	5000 (23.5)	12100 (28.5)	12400 (30.9)	29300 (35.8)	51900 (27.5)
t_{max} (h)*	1 (0.5,3)	2 (0.5,4)	3.5 (2,6)	1 (0.5,3)	2 (1,4)
CLss/F (L/h)	8.87 (17.6)	9.35 (26.6)	9.36 (27.2)	9.46 (32.2)	10.5 (30.1)
Vz/F (L)	93.2 (21.3)	101 (26.2)	107 (26.6)	97.8 (29.7)	104 (33.7)
$t_{1/2}$ (h)**	7.45 (24.4)	7.63 (20.3)	8.04 (18.8)	7.27 (18.8)	6.88 (8.47)

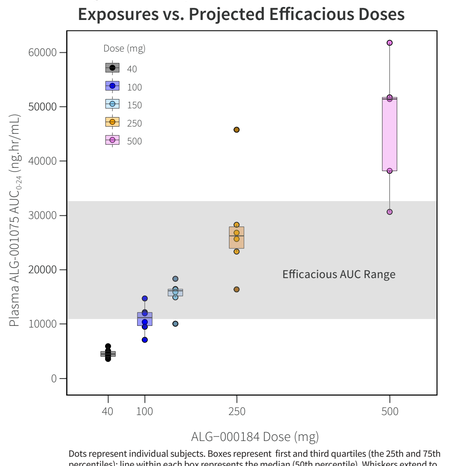
*median (min,max); **average (CV%), n=6

Figure 3. **Boxplots of Apparent Clearance of ALG-001075 by Race (Asian vs. non-Asian) and Body Weight**



Dots represent individual 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.

Figure 4. **Boxplots of Plasma ALG-001075 Exposures vs. Projected Efficacious Doses**



Dots represent individual subjects. Boxes represent first and third quartiles (the 25th and 75th percentiles); line within each box represents the median (50th percentile). Whiskers extend to the largest value no further than 1.5 * interquartile range from the hinges.

Predicted efficacious dose is projected to maintain liver ALG-001075 concentration in excess of at least 3-fold above the antiviral in vitro EC_{90} (1.84 to 8.56 nM).

CONCLUSIONS

- In healthy volunteers, ALG-000184 was safe, well tolerated and with no food effect, at single oral doses up to 500 mg
- ALG-001075 demonstrated desirable linear PK relationship which support once daily oral dosing with or without food.
- There were no clinically meaningful differences in the safety or PK profile of ALG-000184/ALG-001075 between Asian and non-Asian healthy volunteers.
- These findings support the continued evaluation of ALG-000184 given as multiple ascending doses in HV, and multiple doses in patients with CHB

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ACKNOWLEDGMENTS
We express our gratitude to all the study investigators, site staff, and healthy volunteers who participated in the study. This study was sponsored by Aligos Therapeutics.

DISCLOSURES
JY, KL, JN, CW, QZ, LB, SC, MM, and JF are employees at Aligos Therapeutics. JL is no longer an employee at Aligos Therapeutics. EG is an advisor and/or speaker for Gilead, AbbVie, Janssen and Roche. CS has no disclosures.