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

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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 a viral cure. As such, there is a need for novel approaches which can enhance functional cure rates.

 dbovamyos,g at the goal of therapy. To access such, there is a need for novel approaches which can enhance functional cure rates. ALG-000184 is being developed as a potential component of a finite duration combination regimen approach designed to achieve lower rates of functional cure.

OBJECTIVES
• To evaluate the safety & PK of multiple ALG-000184 doses in HVs
• To evaluate the safety, PK, and 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 (1:1 ratio).
• In Part 3, evaluating multiple cohorts (N=10/cohort; 8 active:2 placebo) of currently not treated (C/T) naive treatment naïve (TN) hepatitis B virus (HBV) positive CHB subjects receiving PO QD doses of ALG-000184/placebo for 28 days.

SAFETY
Multiple (7 or 14) doses of ALG-000184 were well tolerated in HVs and C/T in 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-PD PREDICTIONS
The PK-PD model predicts that daily ALG-000184 doses ≥100 mg will achieve steady state free liver concentrations ≥3xC90 and will result in antiviral activity in CHB subjects.

RESULTS
DOSE LEVELS EVALUATED
In Part 2, 7 daily oral doses of 150 mg (cohort 1) and 250 mg (cohort 2) were evaluated.
In Part 3, 28 daily doses of 100 mg were being evaluated.

BASELINE CHARACTERISTICS
The baseline characteristics were similar across treatment groups and are typical for a HV and CHB population, respectively.

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.

SAFETY
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  - Asian compared to non-Asian subjects.
  - HVs compared to CHB subjects.

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

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

Figure 2: Primary Efficacy Endpoint: Mean Change from Baseline in HBV DNA at Day 14

Figure 3: Mean (+SD) Plasma Concentration-Time Profiles of ALG-000184 following 100mg ALG-000184 PO QD in CHB subjects

Figure 4: Primary Efficacy Endpoint: Mean Change from Baseline in HBV DNA at Day 14