Safety, Pharmacokinetics (PK), and Antiviral Activity of the Capsid Assembly Modulator (CAM) ALG-000184 in Asian and non-Asian Subjects with Chronic Hepatitis B (CHB)

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INTRODUCTION

Worldwide, more than 296 million people are affected by Chronic Hepatitis B (CHB) and approximately 280,000 people per year die from cirrhosis and hepatocellular carcinoma (HCC) due to CHB. Long-term treatment with current standard of care for CHB, nucleotide analogues, suppresses HBV replication and reduces liver injury in most patients, but rarely results in functional cure, the goal of CHB treatment. Therefore, there is a significant medical need for novel approaches to enhance functional cure rates. ALG-000184 is a produg of ALG-000184, a novel, pan-genotypic Class 3 CAM (tide analogues), suppresses HBV replication and reduces liver injury in most patients, but rarely results in functional cure, the goal of CHB treatment.

AIM

To evaluate the safety, PK, and antiviral activity of multiple doses of ALG-000184 in Asian and non-Asian CHB subjects.

MATERIALS AND METHODS

ALG-000184-201 is a three-part, multicenter, double-blind, randomized, placebo-controlled Phase 1 study conducted in China, Hong Kong, New Zealand, Moldova, and United Kingdom (NCT01456337).

• Parts 1 and 2: all subjects have completed dosing and follow up
• Single oral doses up to 500 mg and multiple oral doses (7 days) up to 250 mg were evaluated in healthy volunteers (N=48) and were found to be well tolerated with dose dependent linear PK in both Asian and non-Asian subjects.
• Part 3 is ongoing and evaluating multiple cohorts (N=10/cohort; 8 active: 2 placebo) of currently not treated/treatment naive HBV negative or positive CHB subjects, who receive daily (QD) oral doses of ALG-000184 for 28 days, after which they are followed up for 8 weeks.
  - Key Inclusion Criteria: ALT and AST ≤ 5 x ULN; HBV DNA > 2000 IU/mL.
  - Key Exclusion Criteria: Liver fibrosis classified as Metavir Stage F3/F4 liver disease.
• Throughout the study, safety assessments (adverse events [AEs], vital signs, electrocardiogram [ECG] and laboratory abnormalities), PK, and vital markers were collected and analyzed.
• A Study Review Committee and ALF flare Committee (ACF) review safety and PK data on a regular basis for study oversight and determine dose escalation.
• Plasma concentrations of ALG-000184 (active moiety) are quantified using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS).
• PK parameters are determined by non-compartmental analysis using Phoenix WinNonLin.

RESULTS

SAFETY

Administration of 100 mg and 50 mg of ALG-000184/placebo QD for 28 days was generally well tolerated among both Asian and non-Asian subjects:
• An Asian subject with a history of sciatica experienced mild spinal lumbar pain.
• An Asian subject with a history of sciatica experienced mild spinal lumbar pain.
• A Grade 3 TEAE of ALT elevations during the follow up period. All three Grade 3 TEAEs were of ALT elevation.

BASLINE CHARACTERISTICS

Across the cohorts, Asian CHB subjects had a lower BMI, a higher prevalence of HBeAg positivity, a different predominant HBV genotype, and a higher mean HBV DNA and HBV RNA compared to non-Asian subjects.

ANTIVIRAL ACTIVITY

Similar rapid and substantial declines in HBV DNA and HBV RNA were observed at the 100 mg and 50 mg dose levels, regardless of HBV status (Fig. 1). The Asian vs non-Asian analysis was feasible for Cohort 2 only, as in Cohort 1 only one subject was Asian and all subjects in Cohort 4 were Asian.
• A similar rapid and significant HBV DNA and HBV RNA decline was observed in Asian and non-Asian subjects dosed with 50 mg dose level (Fig.2).

CONCLUSIONS

• No significant difference in exposures in body weight adjusted doses was observed between Asian and non-Asian subjects.
• Similar rapid declines in HBV DNA and HBV RNA were observed at both 50 mg and 100 mg dose levels with no clinical meaningful HCC benefit. No differences in antiviral activity were noted between Asian and non-Asian subjects receiving 50 mg ALG-000184 in Cohort 2. In Cohort 3 and 4, a total of 75% of subjects achieved HBV DNA and 100% of subjects had HBV RNA < 1,000 IU/mL.
• No significant difference in exposures by body weight adjusted doses was observed between Asian and non-Asian subjects.
• Dosing in additional cohorts is ongoing. A Phase 2 study to evaluate combinations of ALG-000184 with other novel therapies is planned.

DISCLOSURES

The authors have no financial relationships relevant to this study to disclose.

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