Phase 1a Study of the Safety, Tolerability and Pharmacokinetics of ABI-H2158, a Novel Second-Generation HBV Core Inhibitor, In Healthy Volunteers

E.J. Gane, C. Schwabe, M. Evanchik, E. Ruby, R. Colombo, K. Alves, S. Liaw, and U. Lopatin
Clinical Trial Unit, Auckland Clinical Studies, Auckland, New Zealand; Assembly Biosciences, Inc., San Francisco, California, USA

INTRODUCTION

Despite broad implementation of hepatitis B virus (HBV) vaccination programs, new cases of HBV continue to occur. Block establishment of cccDNA. CIs are being developed for the treatment of patients with viral life cycle with a small molecule direct-acting antiviral. CIs can inhibit formation of new virions, as well as prevent trafficking of incoming nucleocapsids to the nucleus and block establishment of cccDNA. CIs are being developed for the treatment of patients with chronic HBV infection.

BACKGROUND

ABI-H2158 is a novel second-generation CI with activity against all genotypes tested (A-E). It has a favorable pharmaceutical and pharmacokinetic (PK) properties in preclinical models, and potent antiviral activity against HBV replication (EC90 of 69 ng/mL) in primary human liver cells.

METHODS


Primary

To assess the dose-related safety and tolerability of orally administered ABI-H2158 in healthy volunteers following single (Part 1) and multiple (Part 2) doses.

Secondary

To evaluate the PK of ABI-H2158 in plasma following single doses and 10-day multiple doses in healthy volunteers (Parts 1 and 2).

STUDY DESIGN

Key Inclusion/Exclusion Criteria

- Able and willing to provide informed consent prior to screening
- Male or female between 18 and 55 years of age, BMI ≤ 30 kg/m² with a minimum weight of 50 kg
- No positive serology for HIV, hepatitis C virus, hepatitis B surface antibody, and/or hepatitis B core antibody at screening
- In good health, in the judgement of the investigator, as determined by clinical and laboratory assessments (no clinically significant abnormalities at screening)
- No ongoing illness at time of screening or within 30 days prior to study start
- No medical condition that may interfere with the absorption, distribution, or elimination of study drug or with the clinical and laboratory assessments in this study
- No participation in a study of another investigational agent in the last 60 days

- Eight healthy volunteers per cohort were randomized (6 to active, 2 to placebo) to receive single (SAD) and multiple (MAD) dose regimens.
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- Plasma concentrations of ABI-H2158 were determined using a validated liquid chromatography tandem mass spectrometry method.
- PK parameters were determined by noncompartmental analysis using Phoenix WinNonLin

Summary

- Mean BMI (min, max), (fasted)
- Mean BMI (min, max), (fed)
- PK parameters were determined by noncompartmental analysis using Phoenix WinNonLin

Figure 1. SAD

Figure 2. MAD

PK Summary

- ABI-H2158 concentrations increased in a roughly dose-proportional fashion between 5 mg and 500 mg
- In the MAD cohort, steady-state concentrations were achieved quickly, with an accumulation ratio of 1.5-fold at steady state
- No significant change in exposure was seen when ABI-H2158 was administered with a standard high-fat meal

Table 1. Pharmacokinetic Parameters Following Single and Multiple Doses of ABI-H2158

PK Parameters

Table 2. Anticipated Exposures in Excess of 1 ng/mL

CONCLUSIONS

- In this phase 1a dose-ranging study of ABI-H2158 in healthy human volunteers, ABI-H2158 was safe and well tolerated following single ascending doses of 5 mg, 25 mg, 100 mg (fasted and fed), 300 mg, and 500 mg PO QD (SAD) and 300 mg PO QD (MAD).
- No significant food-effect was seen when ABI-H2158 300 mg PO was administered with a standardized high-fat meal.
- There was no increase in the number or severity of TEAES with increase in dose, and no pattern of clinical safety or laboratory abnormalities was observed within or across any cohorts.
- There were no serious AEs reported in any cohorts.
- Treatment-emergent adverse events were mild (grade 1) and generally mild.

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DISCLOSURES

Katia Alves, MD, kalia@assemblybio.com

REFERENCES