EDP-514, a Novel Penangotenic Type II Hepatitis B Virus Core Inhibitor: Final Results of a Phase 1 Study in Healthy Adult Subjects

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a global public health challenge, with estimates of more than 240 million HBV carriers worldwide, of whom approximately 500,000 die annually from HBV-related liver disease. There is an unmet medical need for curative therapy, i.e., a true treatment which yields a sustained post-treatment response.

EDP-514 is a novel class II HBV core inhibitor. EDP-514 inhibits HBV replication with an in vitro EC50 of 18, 27 and 17 nm on HepG2, HepG2D1, and HepG2-2.15 cells, respectively, and a -4 log10 viral load reduction in HBV-infected chimeric mice with human liver cells. Here, we present final PK and safety results of single ascending doses (SAD) and multiple ascending doses (MAD) in a phase 1 study of EDP-514 in healthy adult subjects (HDS).

METHODS

Study Design (Figure 1)

- In the SAD phase, subjects per cohort were randomized 3:1 (10:4, T in food effect (FE) cohort) to receive a single oral dose of either EDP-514 or placebo under fasted (50, 100, 200, 400, 600, and 800 mg) or fed (400 mg high fat meal) conditions.
- In the MAD phase, subjects per cohort were randomized 3:1 to receive multiple once-daily oral doses of either EDP-514 or placebo for 14 days under fasted (200, 400, and 800 mg) or fed (400 mg; standard meal) conditions.

Key Objectives

- To evaluate the safety and tolerability of a single dose and multiple doses of EDP-514 administered to healthy subjects
- To evaluate the PK of single and multiple doses of EDP-514 in plasma and urine in healthy subjects
- To evaluate the effect of intake on the PK of EDP-514 following single and multiple doses in healthy subjects

Key Inclusion/Exclusion Criteria

- Inclusion Criteria:
  - An informed consent document signed and dated by the subject
  - Male or female, age ≥ 18 years
  - Body mass index (BMI) of 18 to 30 kg/m² with a minimum body weight of 50 kg
  - ELRRIA suppressed patients and viremic patients

- Exclusion Criteria:
  - Clinically relevant evidence of history of illness or disease
  - Pregnancy or nursing females
  - History of HCV, HBV, or HIV infection
  - History of drug abuse or dependence
  - Systematic disease, including diabetes, hypertension, asthma, and multiple dosing
  - History of allergies or anaphylaxis
  - History of significant hepatic, renal, pulmonary, or cardiac disease
  - History of smoking

- Assessments:
  - Safety and tolerability assessments evaluated throughout study conduct included adverse events, clinical laboratory, physical examination, vital signs, and electrocardiographic evaluations
  - PK parameters determined using non-compartmental methods in Phoenix WinNonlin (Pharsight Corporation version 6.3)

RESULTS

Subject Disposition and Demographics

- A total of 82 subjects enrolled: n= 50 in SAD; n=32 in MAD
- Two subjects discontinued the study (withdrawal by subject): n=1 in MAD 100 mg cohort
- In the SAD phase, subjects were mostly male of White or Black/African American race, with a mean (range) age of 42.1 (18-65) year and mean (range) BMI of 26.5 (20-38.3) kg/m²
- Demographics for the MAD phase are summarized in Table 1

Pharmacokinetics

- In the SAD phase (Table 2, Figure 2), EDP-514 exposure increased with increasing single doses in an approximately dose-proportional manner, up to 600 mg
- In the MAD phase (Table 3, Figure 3), EDP-514 exposure increased with increasing multiple doses in an approximately dose-proportional manner, up to 400 mg QD
- Exposures of EDP-514 increased with multiple dosing with a geometric mean accumulation index of 1.4 to 1.6
- Geometric mean half-life ranged between 15.7 and 20.4 hours following multiple dosing, supporting QD dosing
- Steady state achieved to be reached for the 2nd day of dosing of EDP-514
- MAD 400 mg fasted (high fat) and MAD 400 mg fasted (standard meal) data demonstrated a moderate food effect
- Across the SAD cohorts, the geometric mean plasma concentration (Cmax) ranged from 2.3- to 15-fold higher than the in vitro serum protein adjusted EC50 (pEC50) of 71 ng/mL under fasted conditions and 14.2-fold higher when administered with a high-fat meal
- Across the MAD cohorts, the geometric mean Cmax ranged from 5.8- to 93-fold higher than the pEC50 under fasted conditions and 22.1-fold higher when administered with a high-fat meal

Safety

- Overall, EDP-514 was well-tolerated with all treatment emergent adverse events (TEAEs) being of mild severity (Table 2, MAD Safety)
- There were 8 TEAEs in SAD in 7 subjects (n=5 in EDP-514 and n=2 in placebo) and 13 TEAEs in MAD in 7 subjects (n=6 in EDP-514 and MAD (n=3, n=3 in EDP-514)
- There were no severe or serious TEAEs and no discontinuations due to AE
- There were no significant individual lab data findings or pattern of lab abnormalities

CONCLUSIONS

- EDP-514 was generally safe and well-tolerated over a broad range of single and multiple doses for up to 14 days
- EDP-514 was rapidly absorbed and EDP-514 exposure increased with increasing single and multiple dosing
- EDP-514 exhibited PK suitable for once daily oral dosing
- Following multiple dosing with EDP-514 (when administered with and without a standard meal), the Cmax was several folds above the pEC50, suggesting that EDP-514 can be administered without regard to meals
- Phase 1b studies are ongoing to evaluate multiple ascending doses of EDP-514 in patients with chronic HBV infection (non-suppressed patients and viremic patients)

REFERENCES

- EDP-514, a novel HBV core inhibitor with potent antiviral activity both in vitro and in vivo M Vaney, et al. J Hepatology, VOLUME 70, ISSUE 1, SUPPLEMENT, E474-E475

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DISCLOSURES

- KIL, AA, EC, TM, JC, and NA are employees of Enanta Pharmaceuticals, Inc. and may be stockholders.
- CD is an employee of PRA Health Sciences, which was contracted by Enanta Pharmaceuticals, Inc. to conduct the study

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