EDP-514, a Novel Pangenotypic Class 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 600,000 die annually from HBV-related liver disease. There is an unmet medical need for curative therapy, i.e., a finite treatment which yields a sustained post-treatment response.

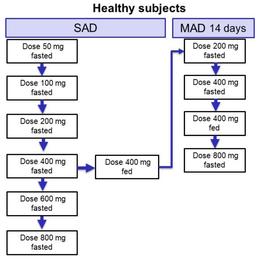
EDP-514 is a novel class II HBV core inhibitor. EDP-514 inhibits HBV replication with an *in vitro* EC_{50} of 18, 27 and 17 nM in HepAD38, HepDE19, and HepG2.2.15 cells, respectively, and a >4-log viral load reduction in HBV-infected chimeric mice with human liver cells. Here, we present final pharmacokinetic (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 (HS).

METHODS

Study Design (Figure 1)

- In the SAD phase, 8 subjects per cohort were randomized 3:1 (N=10, 4:1 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, 8 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.

Figure 1. Study Design



Key Objectives

- Primary
  - To evaluate the safety and tolerability of a single dose and multiple doses of EDP-514 administered to healthy subjects
- Secondary
  - To evaluate the PK of single and multiple doses of EDP-514 in plasma and urine in healthy subjects
  - To evaluate the effect of food 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
  - Healthy male and female subjects of any ethnic origin between the ages of 18 and 65 years, inclusive, BMI of 18 to 30 kg/m^2 with a minimum body weight of 50 kg
- Exclusion Criteria:
  - Clinically relevant evidence or history of illness or disease
  - Pregnant or nursing females
  - History of febrile illness within 7 days prior to the first dose of study drug or subjects with evidence of active infection
  - A positive urine drug screen at screening or Day -1
  - Current tobacco smokers or use of tobacco within 3 months prior to screening
  - Any condition possibly affecting drug absorption (e.g., gastrectomy, cholecystectomy)
  - History of regular alcohol consumption
  - Receipt of any vaccine, an investigational agent, or biological product within 28 days or 5 times the t½, whichever one is longer, prior to first dose. This includes agents administered during clinical trial participation

Assessments

- Safety and tolerability assessments evaluated throughout study conduct included:
  - Adverse events, clinical laboratories, physical examination, vital signs, and electrocardiographic evaluations
- PK assessments
  - SAD phase: Blood samples were collected from time 0 to 120 hours
  - MAD phase: Blood samples were collected from time 0 to 24 hours on Days 1 and 14, pre-dose on Days 3 through 13, and 48, 72, and 96 hours post last dose
  - Urine samples were collected in the SAD phase
  - Concentrations of EDP-514 and its metabolites were measured using a validated method
  - PK parameters were 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 SAD 100 mg, and n=1 in MAD 800 mg cohorts
  - 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 26.1 (19.3-29.9) kg/m^2 across all cohorts
- Demographics for the MAD phase are summarized in **Table 1**

Table 1. Demographics of Subjects in the MAD Phase

	200 mg QD (N=6)	400 mg QD (fasted, N=6)	400 mg QD (fed, N=6)	800 mg QD (N=6)	Placebo (N=8)	Overall (N=32)
Male, n (%)	3 (50.0)	4 (66.7)	6 (100.0)	2 (33.3)	6 (75.0)	21 (65.6)
Race						
White	3 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)	5 (62.5)	17 (53.1)
Black or African American	3 (50.0)	3 (50.0)	2 (33.3)	3 (50.0)	2 (25.0)	13 (40.6)
Asian	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Other	0	0	1 (16.7)	0	1 (12.5)	2 (6.3)
Ethnicity						
Hispanic or Latino, n (%)	1 (16.7)	0	1 (16.7)	2 (33.3)	0	4 (2.5)
Age (y)[a]	45.0 (28, 65)	42.3 (21, 59)	39.5 (32, 46)	42.2 (24, 56)	37.1 (21, 62)	41.0 (21, 65)
BMI (kg/m^2)[a]	25.65 (21.9, 29.2)	24.13 (20.2, 29.9)	28.07 (24.6, 29.4)	24.87 (22.3, 27.9)	25.69 (22.2, 28.6)	25.68 (20.2, 29.9)

All doses were administered fasted unless otherwise indicated
[a]presented as mean (min, max)
BMI: body mass index; QD: once daily

Pharmacokinetics

- In the SAD phase (**Table 3, 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 4, Figure 3**), EDP-514 exposure increased with increasing multiple doses in an approximately dose-proportional manner, up to 400 mg
- 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 appeared to be reached after the 2nd day of dosing of EDP-514
- SAD 400 mg fasted/fed (high fat) and MAD 400 mg fasted/fed (standard meal) data demonstrated a moderate food effect
- Across the SAD cohorts, the geometric mean plasma concentration at 24 hr (C_{24}) ranged from 2.3- to 10.3-fold higher than the *in vitro* serum protein adjusted EC_{50} ($paEC_{50}$) 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 C_{24} ranged from 5.8- to 9.3-fold higher than the $paEC_{50}$ under fasted conditions and 22.1-fold higher when administered with a standard meal

Table 3. EDP-514 Plasma PK Parameters Following Oral Administration of Single Doses of EDP-514 (values presented as geometric mean (%GCV) except as noted)

PK Parameters	50 mg fasted (N=6)	100 mg fasted (N=6)	200 mg fasted (N=6)	400 mg fasted (N=8)	400 mg fed (N=8)	600 mg fasted (N=6)	800 mg fasted (N=6)
$AUC_{0\text{-}inf}$ (ng/mL*hr)	10200 (31.6)	15900 (30.3)	19700 (17.7)	32400 (35.2)	56400 (18.4)	52800 (34.0)	51100 (37.2)
C_{max} (ng/mL)	551 (17.8)	796 (55.4)	1010 (21.2)	2060 (45.1)	3350 (21.5)	2750 (49.9)	2490 (26.0)
C_{24} (ng/mL)	162 (38.8)	227 (39.1)	327 (27.6)	459 (39.7)	1010 (35.3)	729 (31.0)	620 (32.7)
T_{max} (hr)	3.0 (1.0-5.0)	3.0 (1.0-5.0)	3.5 (2.0-4.0)	3.0 (2.0-4.0)	6.0 (5.0-10.0)	2.5 (2.0-3.0)	2.0 (1.0-5.0)
$T_{1/2}$ (hr)	17.2 (9.2)	24.4 (40.0)	15.6 (16.9)	17.5 (35.4)	15.5 (24.4)	19.2 (45.0)	26.1 (53.7)
CL/F (L/hr)	4.91 (31.6)	6.31 (30.5)	10.1 (17.6)	12.4 (35.2)	7.09 (18.3)	11.4 (33.9)	15.7 (37.2)
Vd/F (L)	122 (27.2)	222 (36.9)	228 (27.2)	311 (49.4)	159 (28.4)	315 (49.4)	590 (38.9)

* T_{max} presented as median (range)

Table 4. EDP-514 Day 14 Plasma PK Parameters Following Oral Administration of Multiple Doses of EDP-514 (values presented as geometric mean (%GCV) except as noted)

PK Parameters	200 mg fasted (N=6)	400 mg fasted (N=6)	400 mg fed (N=6)	800 mg fasted (N=6)
$AUC_{0\text{-}tau}$ (ng/mL*hr)	22000 (29.0)	37500 (38.7)	64500 (22.3)	37900 (39.2)
C_{max} (ng/mL)	2160 (41.5)	3720 (51.8)	5430 (28.1)	3990 (49.7)
C_{24} (ng/mL)	414 (18.1)	624 (60.7)	1570 (47.8)	663 (36.5)
T_{max} (hr)	2.5 (2.0 – 4.0)	3.0 (2.0-3.0)	4.0 (2.0-4.0)	3.0 (1.0-3.0)
$T_{1/2}$ (hr)	16.0 (33.3)	15.7 (16.9)	17.8 (12.2)	20.4 (22.9)

* T_{max} presented as median (range)

Figure 2. EDP-514 Mean Plasma PK Concentrations vs Time Following Oral Administration of Single Doses of EDP-514

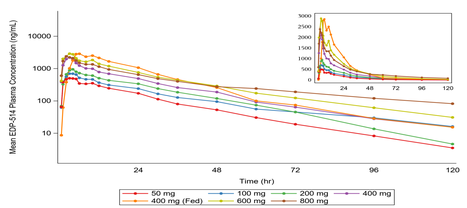
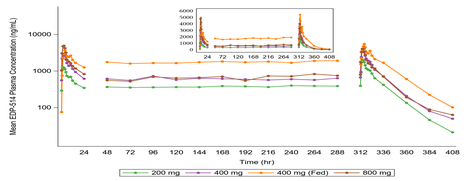


Figure 3. EDP-514 Mean Plasma PK Concentrations vs Time Following Oral Administration of Multiple Doses of EDP-514



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 (all in EDP-514)
  - Headache was the most frequent TEAE in both SAD (n=4 including n=2 in EDP-514) and MAD (n=3, all 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

Table 2: Summary of Treatment-emergent AEs Following Administration of EDP-514 in the MAD Phase

System Organ Class Preferred Term	Placebo Fasted (N=6) n (%)	Placebo Fed (N=2) n (%)	EDP-514 200 mg Fasted (N=6) n (%)	EDP-514 400 mg Fasted (N=6) n (%)	EDP-514 400 mg Fed (N=6) n (%)	EDP-514 800 mg Fasted (N=6) n (%)	Overall (N=32) n (%)
Total Subjects with at Least One TEAE	0	0	2 (33.3)	2 (33.3)	3 (50.0)	0	7 (21.9)
Gastrointestinal disorders	0	0	0	1 (16.7)	2 (33.3)	0	3 (9.4)
Nausea	0	0	0	0	2 (33.3)	0	2 (6.3)
Constipation	0	0	0	1 (16.7)	0	0	1 (3.1)
Injury, poisoning and procedural complications	0	0	2 (33.3)	0	0	0	2 (6.3)
Skin laceration	0	0	1 (16.7)	0	0	0	1 (3.1)
Skin abrasion	0	0	1 (16.7)	0	0	0	1 (3.1)
Musculoskeletal and connective tissue disorders	0	0	0	1 (16.7)	0	0	1 (3.1)
Back pain	0	0	0	1 (16.7)	0	0	1 (3.1)
Nervous system disorders	0	0	1 (16.7)	2 (33.3)	3 (50.0)	0	6 (18.8)
Headache	0	0	1 (16.7)	0	2 (33.3)	0	3 (9.4)
Neuralgia	0	0	0	1 (16.7)	0	0	1 (3.1)
Nerve compression	0	0	0	1 (16.7)	0	0	1 (3.1)
Dizziness	0	0	0	0	1 (16.7)	0	1 (3.1)
Skin and subcutaneous tissue disorders	0	0	0	1 (16.7)	0	0	1 (3.1)
Rash vesicular	0	0	0	1 (16.7)	0	0	1 (3.1)

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 C_{24} was several folds above the $paEC_{50}$, 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 (nuc-suppressed patients and viremic patients)

REFERENCES

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

ACKNOWLEDGEMENT

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DISCLOSURES

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