EDP-514, a Novel Pangenotypic Class II Hepatitis B Virus Core Inhibitor Demonstrates Significant HBV DNA and HBV RNA Reductions in a Phase 1b Study in Viremic, Chronic Hepatitis B Infected Patients

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INTRODUCTION

Chronic hepatitis B (CHB) virus infection is a global public health challenge, with estimates of more than 296 million hepatitis B virus (HBV) carriers worldwide, of whom approximately 820,000 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.

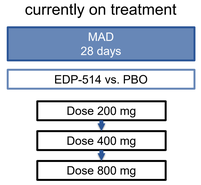
EDP-514 is a novel class II HBV core inhibitor. EDP-514 inhibits HBV replication with an *in vitro* EC_{50} of 18, 27 and 17 nM in HepAD38, HepDE19, and HepG2.2.15 cells, respectively, and a >4-log viral load reduction in HBV-infected chimeric mice with human liver cells. EDP-514 was shown to be generally safe and well tolerated over a broad range of single and multiple doses for up to 14 days in healthy adult subjects, and in multiple doses up to 28 days in nucleos(t)ide analog (NUC)-suppressed CHB patients. Here, we present results of a Phase 1b, 28-day study in non-cirrhotic, viremic, HBeAg(+) or (-) CHB patients not currently on any treatment.

METHODS

Study Design

Eight subjects per cohort were randomized 3:1 to receive multiple once-daily oral doses of either EDP-514 at 200, 400, and 800 mg or placebo QD for 28 days.

The first cohort received 200 mg of EDP-514 and cohort progression was determined by a Study Adjudication Committee after review of blinded safety and available PK data.



Key Objectives

- Primary
  - To evaluate the safety and tolerability of multiple doses of EDP-514
- Secondary
  - To evaluate the plasma PK of multiple doses of EDP-514
  - To evaluate the antiviral activity of multiple doses of EDP-514

Key Inclusion/Exclusion Criteria

- Inclusion Criteria:
  - Male and female subjects of any ethnic origin between the ages of 18 and 70 years
  - CHB subjects must have HBsAg detectable at screening and in most recent test at least 6 months prior
  - For HBeAg(+) subjects, screening HBV DNA ≥ 20,000 IU/mL and no HBV DNA < 1,000 IU/mL over previous 12 months
  - For HBeAg(-) subjects, screening HBV DNA ≥ 2,000 IU/mL and no HBV DNA < 1,000 IU/mL over previous 12 months
  - No anti-HBV treatment (ie, pegIFN and/or NUC) for 12 months prior to screening
- Exclusion Criteria:
  - Documented prior diagnosis of cirrhosis or current evidence of hepatic decompensation
  - Documented extensive bridging fibrosis or cirrhosis
  - Evidence of hepatocellular carcinoma by imaging or screening AFP ≥ 50 ng/mL
  - Meeting study defined safety laboratory parameters at screening
  - Coinfection with HIV, HAV, HCV, HDV, or HEV
  - Chronic liver disease of non-HBV etiology

Assessments

- Safety and tolerability assessments
  - Adverse events, clinical laboratory tests, physical examinations, vital signs, and electrocardiograms
- PK assessments
  - On Days 1 and 28, blood samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6 and 8 hours post-dose
  - On Days 3, 7, 14 and 21, blood samples were collected at pre-dose, 1-3 hrs post-dose and at least 1 hr after the first post-dose sample and prior to next dose
  - 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)
- Antiviral activity assessments
  - HBV DNA levels
  - Incidences of virologic failure defined as a confirmed increase in HBV DNA level ≥1.0 $\log_{10}$ IU/mL from nadir while receiving EDP-514

RESULTS

Subject Disposition and Demographics

- A total of 25 subjects were enrolled in the 200 mg, 400 mg, 800 mg and placebo cohorts. All subjects completed the study. Subjects were all Asian, more male, and HBeAg(-), with a mean age of ~46 years, mean HBV DNA of 5.12 $\log_{10}$ IU/mL, and mean HBV RNA of 3.49 $\log_{10}$ U/mL at baseline
- Subject demographics and disease characteristics for the 3 cohorts are summarized in **Table 1**

Table 1. Baseline Demographics and Disease Characteristics

	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=7)	Placebo (N=6)	Overall (N=25)
Sex [n (%)]					
Female	2 (33.3)	2 (33.3)	1 (14.3)	5 (83.3)	10 (40.0)
Male	4 (66.7)	4 (66.7)	6 (85.7)	1 (16.7)	15 (60.0)
Race [n (%)]					
Asian	6 (100)	6 (100)	7 (100)	6 (100)	25 (100)
Age (y)[a]	48.7 (42, 56)	42.8 (33, 51)	47.9 (35, 59)	45.5 (24, 60)	46.3 (24, 60)
BMI (kg/m^2)[a]	24.76 (19.3, 30.2)	26.41 (20.0, 34.7)	28.85 (23.6, 33.7)	22.87 (18.8, 28.1)	25.85 (18.8, 34.7)
HBeAg negative [n (%)]	6 (100)	5 (83.3)	5 (71.4)	5 (83.3)	21 (84.0)
HBV DNA (Log_{10} IU/mL)[a,b]	4.57 (3.6, 5.6)	5.37 (4.0, 8.4)	5.54 (3.8, 8.9)	4.91 (3.7, 7.5)	5.12 (3.6, 8.9)
HBV RNA (Log_{10} U/mL)[a,c]	3.22 (1.9, 4.5)	3.58 (0.8, 7.3)	3.77 (0.8, 7.4)	3.34 (0.0, 5.7)	3.49 (0.0, 7.4)

a. Presented as Mean (Min, Max), b. HBV DNA Limit of Detection = 20 IU/mL, c. HBV RNA Limit of Detection = 1.65 Log_{10} U/mL
BMI = Body Mass Index; QD = Once Daily, y = Year

Pharmacokinetics

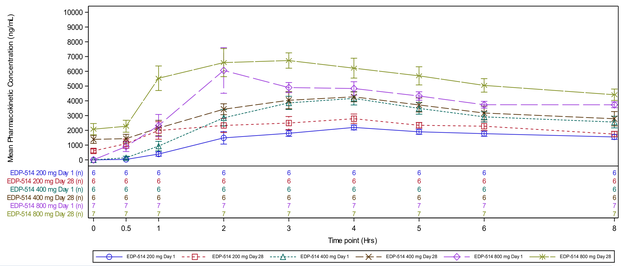
- EDP-514 exposure increased with dose, with time-linear pharmacokinetics (**Table 2, Figure 2**)
- EDP-514 exposure increased with multiple doses with an accumulation index of ~1.1-1.4
- PK is supportive of once-daily dosing, with median C_{trough} at Day 28 ~9-fold for 200 mg, ~20-fold for 400 mg and ~24-fold for 800 mg above the protein-adjusted EC_{50}

Table 2. EDP-514 Day 28 Plasma PK Parameters[a]

PK Parameters	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=7)
$AUC_{0\text{-last}}$ (ng/mL*hr)	17075 (26)	25315 (25)	42526 (22)
C_{max} (ng/mL)	3230 (29)	4717 (17)	8013 (14)
C_{trough} (ng/mL)	646 (377, 871)	1390 (789, 1790)	1700 (1580, 2340)

a. $AUC_{0\text{-last}}$, C_{max}, presented as Mean (%CV), C_{trough} is presented as median (interquartile range)

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



Antiviral Activity

- At Day 28, mean HBV DNA reductions of 2.9, 3.3, 3.5 and 0.2 logs IU/mL, and mean HBV RNA reductions of 2.9, 2.4, 2.0 and 0.02 logs U/mL were observed in the 200 mg, 400 mg, 800 mg and placebo groups, respectively (**Table 3, Figure 3, 4**)
- As expected, there were no discernible changes in HBeAg, HBcrAg, or HBsAg
- No instances of virologic failure in the EDP-514 arms were observed

Table 3. Antiviral Activity with 28-day Treatment[a]

	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=7)	Placebo (N=6)
HBV DNA (Log IU/mL)				
Baseline	4.57 (3.6, 5.6)	5.37 (4.0, 8.4)	5.54 (3.8, 8.9)	4.91 (3.7, 7.5)
Change at Day 28	-2.88 (-3.4, -2.2)	-3.26 (-4.2, -2.4)	3.35 (-4.0, -2.7)	-0.19 (-0.5, 0.3)
HBV RNA (Log U/mL)				
Baseline	3.22 (1.9, 4.5)	3.58 (0.8, 7.3)	3.77 (0.8, 7.4)	3.34 (0.0, 5.7)
Change at Day 28	-2.88 (-3.8, -1.9)	-2.39 (-4.8, -0.8)	-2.00 (-3.5, -0.8)	-0.02 (-1.9, 1.8)

a. Data presented in Mean (Range)

Figure 3. Antiviral Activity by HBV DNA Mean (±) Change from Baseline Over Time

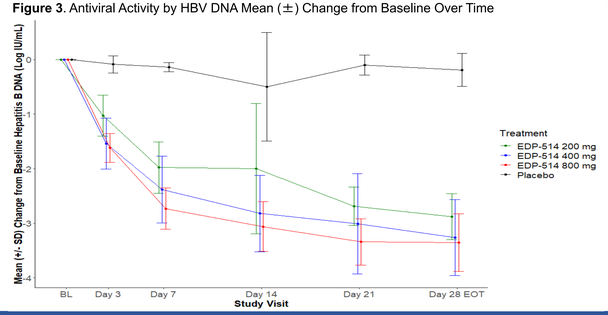
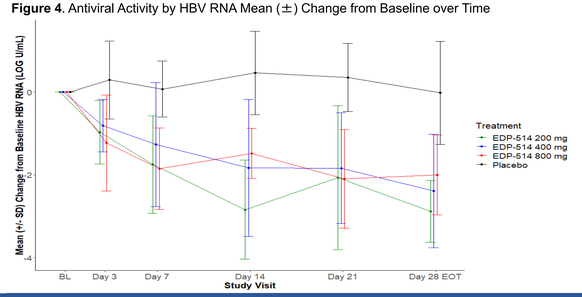


Figure 4. Antiviral Activity by HBV RNA Mean (±) Change from Baseline over Time



Safety

- Overall, EDP-514 was generally safe and well-tolerated (**Table 4**)
- Nine patients reported treatment emergent adverse events (TEAEs) and all were mild except for 4 moderate events, 2 in the same placebo subject (gastrointestinal disorder, urinary tract infection) and 2 in the same 200 mg subject (anemia, activated partial thromboplastin time prolonged); both of 200 mg subject's events were considered unlikely related to drug
- There were no severe or serious TEAEs and no discontinuations due to AEs
- There were no clinically significant laboratory abnormalities, grade 3 or 4 laboratory abnormalities, ALT/AST elevations or clinically relevant ECG or vital sign changes in the EDP-514 arms

Table 4: Summary of TEAEs Following Administration of EDP-514 in the MAD Phase

System Organ Class Preferred Term [n (%)]	200mg QD (N=6)	400mg QD (N=6)	800mg QD (N=7)	Placebo (N=6)	Overall (N=25)
Total Subjects with at Least One TEAE	2 (33.3)	3 (50.0)	2 (28.6)	2 (33.3)	9 (36.0)
Investigations					
aPTT prolonged	1 (16.7)	0	0	1 (16.7)	2 (8.0)
INR increased	1 (16.7)	0	0	1 (16.7)	2 (8.0)
Prothrombin time prolonged	1 (16.7)	0	0	0	1 (4.0)
Gastrointestinal disorders					
Flatulence	0	0	1 (14.3)	0	1 (4.0)
Gastrointestinal disorder	0	0	0	1 (16.7)	1 (4.0)
Tooth development disorder	0	1 (16.7)	0	0	1 (4.0)
Nervous system disorders					
Dizziness	1 (16.7)	0	1 (14.3)	0	2 (8.0)
Headache	0	1 (16.7)		0	1 (4.0)
Infections and infestations					
Nasopharyngitis	0	1 (16.7)	0	0	1 (4.0)
Urinary tract infection	0	0	0	1 (16.7)	1 (4.0)
Blood and Lymphatic System Disorders					
Anaemia	1 (16.7)	0	0	0	1 (4.0)
Skin and subcutaneous tissue disorders					
Dermatitis	0	1 (16.7)	0	0	1 (4.0)
Cardiac disorders					
Palpitations	0	0	0	1 (16.7)	1 (4.0)
Musculoskeletal and connective tissue disorders					
Myalgia	0	0	0	1 (16.7)	1 (4.0)
Neoplasms benign, malignant and unspecified					
Hepatic neoplasm	0	0	1 (14.3)	0	1 (4.0)
Respiratory, thoracic and mediastinal disorders					
Cough	0	0	1 (14.3)	0	1 (4.0)
Oropharyngeal pain	0	0	1 (14.3)	0	1 (4.0)

n = Number of Subjects, aPTT = activated partial thromboplastin time INR: international normalized ratio

CONCLUSIONS

- EDP-514 was generally safe and well-tolerated at 200, 400 and 800 mg QD for 28 days in viremic CHB patients
- EDP-514 exhibited PK supportive of once daily oral dosing, with C_{trough} up to ~24-fold above the $paEC_{50}$ with the 800 mg dose
- At Day 28, EDP-514 demonstrated antiviral activity with a mean reduction in HBV DNA of ~3 log, that was associated with a mean reduction in HBV RNA of up to ~3 log in patients who received 200, 400, and 800 mg QD of EDP-514 compared to reductions of 0.2 log and 0.02 log in HBV DNA and HBV RNA, respectively, in placebo

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DISCLOSURES

- GDLR, AA, EL, ALC and NA are employees and stockholders of Enanta Pharmaceuticals, Inc.