EDP-514, a Novel Pangenotypic Class II Hepatitis B Virus Core Inhibitor: Results of a 28-day Phase 1b Study in NUC-suppressed CHB Patients

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a global public health challenge, with estimates of more than 296 million 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. Here, we present results of a Phase 1b, 28-day study in non-cirrhotic, HBeAg(+) or (-) Chronic Hepatitis B (CHB) patients virologically suppressed on Nucleos(t)ide (NUC) therapy.

METHODS

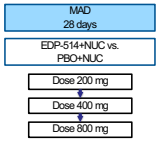
Study Design

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 doses or placebo 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.

Study Design

NUC-suppressed CHB Patients



Key Objectives

- Primary
  - To evaluate the safety and tolerability of multiple doses of EDP-514 administered to NUC-suppressed CHB patients
- Secondary
  - To evaluate the plasma PK of multiple doses of EDP-514 of NUC-suppressed CHB patients
  - To evaluate the antiviral activity of multiple doses of EDP-514 in NUC-suppressed CHB patients

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
  - Screening HBV DNA < LLOQ and no HBV DNA ≥ LLOQ over previous 12 months
  - No change in HBV NUC treatment regimen for 12 months prior to screening
- Exclusion Criteria:
  - Documented prior diagnosis of cirrhosis
  - Documented extensive bridging fibrosis or cirrhosis
  - Evidence of hepatocellular carcinoma by imaging or screening AFP ≥ 50 ng/mL
  - Meeting 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 predose and at 0.5, 1, 2, 3, 4, 5, 6 and 8 hours postdose
  - On Days 3, 7, 14 and 21, blood samples were collected at predose, 1-3 hrs postdose and at least 1 hr after the first postdose 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 HBV DNA level ≥LLOQ and which is confirmed to be ≥LLOQ on repeat testing

RESULTS

Subject Disposition and Demographics

- A total of 24 subjects were enrolled in the study
  - One subject from the EDP-514 200 mg arm discontinued from the study due to an adverse event of upper abdominal pain
  - Subjects were mostly male, Asian, HBeAg(-), with a mean age of 45 years, mean HBV DNA of 1.67 IU/mL, and mean HBV RNA of 1.13 log U/mL at baseline
- Subject demographics and disease characteristics 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=6)	Placebo (N=6)	Overall (N=24)
Sex [n (%)]					
Female	4 (66.7)	0	4 (66.7)	1 (16.7)	9 (37.5)
Male	2 (33.3)	6 (100)	2 (33.3)	5 (83.3)	15 (62.5)
Race [n (%)]					
White	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	6 (25.0)
Black or African American	0	2 (33.3)	0	0	2 (8.3)
Asian	5 (83.3)	3 (50.0)	5 (83.3)	3 (50.0)	16 (66.7)
Ethnicity [n (%)]					
Not Hispanic or Latino	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)
Age (y)[a]	43.2 (25, 62)	41.8 (34, 52)	43.0 (31, 49)	52.7 (45, 61)	45.2 (25, 62)
BMI (kg/m^2)[a]	24.46 (18.3, 31.1)	27.22 (23.5, 34.6)	26.81 (24.8, 31.0)	28.09 (23.0, 34.4)	26.64 (18.3, 34.6)
HBeAg negative [n (%)]	5 (83.3)	5 (83.3)	5 (83.3)	6 (100)	21 (87.5)
HBV DNA (IU/mL)[a,b]	2.50 (0.0, 10.0)	2.50 (0.0, 5.0)	1.67 (0.0, 5.0)	0.00 (0.0, 0.0)	1.67 (0.0, 10.0)
HBV RNA (Log U/mL)[a,c]	1.18 (0.0, 2.5)	1.57 (0.0, 3.7)	0.83 (0.0, 4.2)	0.96 (0.0, 2.1)	1.13 (0.0, 4.2)
HBV RNA < LOD [n (%)][c]	3 (50.0)	2 (33.3)	5 (83.3)	4 (66.7)	14 (58.3)
Tenofovir (TAF/TDF) [n (%)]	5 (83.3)	5 (83.3)	6 (100)	6 (100)	22 (91.7)

a. Presented as Mean (Min, Max), b. HBV DNA Limit of Detection = 10 IU/mL, c. HBV RNA Limit of Detection = 1.65 Log U/mL
BMI = Body Mass Index; QD = Once Daily, y = Year, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate

Pharmacokinetics

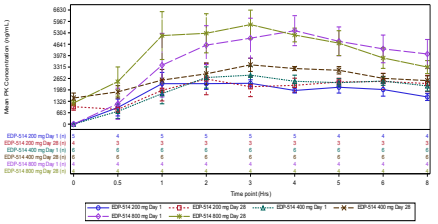
- EDP-514 exposure increased with increasing multiple doses, with time-linear pharmacokinetics (**Table 2, Figure 2**)
- Exposures of EDP-514 increased with multiple dosing with an accumulation index of ~1.3
- PK supportive of once daily dosing, with median C_{trough} at Day 28 ~16-fold for 200 mg, ~18-fold for 400 mg, and ~21-fold for 800 mg the protein-adjusted EC_{50}

Table 2. EDP-514 Day 28 Plasma PK Parameters

PK Parameters	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=6)
$AUC_{0\text{-last}}$ (ng/mL*hr)[a]	17498 (11.8)	22438 (19.5)	39331 (19.8)
C_{max} (ng/mL)[a]	3405 (11.5)	4048 (14.9)	7495 (21.9)
C_{trough} (ng/mL)[b]	1110 (860-1150)	1245 (1080-1700)	1465 (1100-2850)

a. Data presented as Mean (%CV)
b. Data presented as Median (Interquartile Range)
N=6, except for 200 mg $AUC_{0\text{-last}}$, C_{max}, N=4 and C_{trough} N=5

Figure 2. Mean Plasma PK Concentrations vs. Time Following Oral Administration of EDP-514 at Day 1 and Day 28



Safety

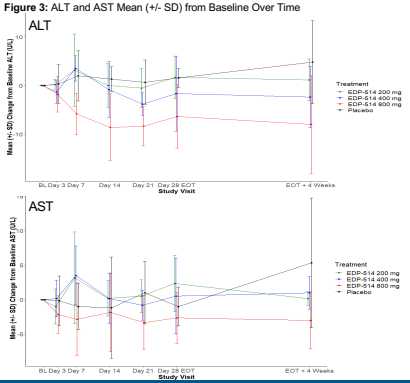
- Overall, EDP-514 was generally safe and well-tolerated in 200, 400 and 800 mg doses (**Table 3**)
- Eight patients reported treatment emergent adverse events (TEAEs); all were mild except for 1 moderate event (upper abdominal pain) in the EDP-514 200 mg arm that led to study drug discontinuation, and 1 severe event (drug hypersensitivity [allergic reaction to aloe cream]) in the EDP-514 800 mg arm that was unrelated to study drug
- There were no Grade 4 or serious TEAEs
- There were no clinically significant laboratory abnormalities, including no clinically significant ALT/AST elevations or notable differences in mean (+/- SD) change from baseline of all arms (**Figure 3**), and no clinically meaningful changes in ECG or vital signs

Table 3: Summary of TEAEs Following Administration of EDP-514 in the MAD Phase

System Organ Class Preferred Term [n (%)]	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=6)	Placebo (N=6)	Overall (N=24)
Total Subjects with at Least One TEAE	5 (83.3)	1 (16.7)	2 (33.3)	0	8 (33.3)
Gastrointestinal disorders					
Nausea	1 (16.7)*	1 (16.7)	0	0	2 (8.3)
Abdominal pain upper	1 (16.7)*	0	0	0	1 (4.2)
Diarrhoea	1 (16.7)*	0	0	0	1 (4.2)
Investigations					
Blood creatine phosphokinase increased	0	0	2 (33.3)^	0	2 (8.3)
Neutrophil count decreased	0	0	1 (16.7)^	0	1 (4.2)
White blood cell count decreased	0	0	1 (16.7)^	0	1 (4.2)
Nervous system disorders					
Dizziness	1 (16.7)	0	0	0	1 (4.2)
Headache	0	1 (16.7)	0	0	1 (4.2)
Respiratory, thoracic and mediastinal disorders					
Hyperventilation	1 (16.7)	0	0	0	1 (4.2)
Rhinorrhoea	1 (16.7)	0	0	0	1 (4.2)
General disorders and administration site conditions					
Fatigue	1 (16.7)	0	0	0	1 (4.2)
Immune system disorders					
Drug hypersensitivity	0	0	1 (16.7)	0	1 (4.2)
Infections and infestations					
Urinary tract infection	1 (16.7)	0	0	0	1 (4.2)
Skin and subcutaneous tissue disorders					
Pruritus	1 (16.7)	0	0	0	1 (4.2)
Vascular disorders					
Flushing	1 (16.7)*	0	0	0	1 (4.2)

n = Number of Subjects
*Occurred in same subject, ^Occurred in same subject

Figure 3: ALT and AST Mean (+/- SD) from Baseline Over Time



Antiviral Activity

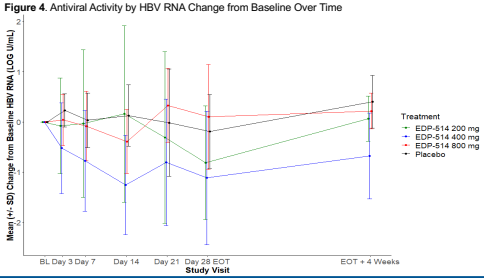
- At Day 28, mean HBV RNA change of -0.81, -1.12, 0.10, and -0.19 log U/mL were observed in the 200 mg, 400 mg, 800 mg and placebo groups, respectively (**Table 4, Figure 4**)
- EDP-514 led to a maximum HBV RNA reduction of 2.3 log in HBeAg(-) and 2.8 log in HBeAg(+) subjects in EDP-514 arms compared to 1.2 log in placebo
- For the EDP-514 800 mg subjects, 5 of 6 subjects had either non-detectable or very low levels of HBV RNA at baseline; consequently, the effect of EDP-514 on HBV RNA could not be assessed in these subjects
- As expected in this NUC-suppressed patient population, there were no discernible changes in HBV DNA, and also, no changes in HBeAg, HBcrAg, and HBsAg
- There were no instances of virologic failure were reported

Table 4. HBV RNA (Log U/mL) Change with 28-day Treatment[a]

	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=6)	Placebo (N=6)
Baseline	1.18 (0.0, 2.5)	1.57 (0.0, 3.7)	0.83 (0.0, 4.2)	0.96 (0.0, 2.1)
Change at Day 28	-0.81 (-2.3, 0.0)[b]	-1.12 (-2.8, 0.2)	0.10 (-1.9, 0.8)*	-0.19 (-1.2, 0.8)

a. Data presented in Mean (Range)
b. n = 5
*5 of 6 subjects had HBV RNA < LOD at baseline and the effect of EDP-514 on HBV RNA could not be assessed in these subjects

Figure 4. Antiviral Activity by HBV RNA Change from Baseline Over Time



CONCLUSIONS

- EDP-514 was generally safe and well-tolerated at 200, 400 and 800 mg doses for 28 days in NUC-suppressed CHB patients
- EDP-514 was rapidly absorbed and EDP-514 exposure increased with increasing multiple doses
- EDP-514 exhibited PK suitable for once daily oral dosing, with Ctrough concentrations reaching up to ~20-fold above the $paEC_{50}$
- At Day 28, EDP-514 demonstrated reductions in circulating HBV RNA levels, consistent with its mechanism of action as an HBV core inhibitor

REFERENCES

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DISCLOSURES

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