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

Man-Fung Yuen[1], Wan-Long Chuang[2], Cheng-Yuan Peng[3], Wen-Juei Jeng[4,5], Wei-Wen Su[6], Ting-Tsung Chang[7,8], Chi-Yi Chen[9], Yao-Chun Hsu[10], Guy De La Rosa[11], Alaa Ahmad[11], Ed Luo[11], Annie L. Conery[11], Nathalie Adda[11]

[1]Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, [2]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [3]Center for Digestive Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan, [4]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Branch, Taiwan, [5]College of Medicine, Chang Gung University, Taiwan, [6]Department of Gastroenterology and Hepatology, Changhua Christian Hospital, Taiwan, [7]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [8]Infectious Disease and Signaling Research Center, National Cheng Kung University, Tainan, Taiwan, [9]Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan, [10]Center for Liver Diseases and School of Medicine, E-Da Hospital/I-Shou University, Kaohsiung, Taiwan, [11]Enanta Pharmaceuticals, Inc., Watertown, Massachusetts, USA

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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, and in multiple doses up to 28 days in nucleos(t)ide analog (NUC)-suppressed Chronic Hepatitis B (CHB) patients. Here, we present preliminary results for the 200 mg and 400 mg cohorts of a Phase 1b, 28-day study in non-cirrhotic, viremic, HBeAg(+) or (-) CHB patients not currently on treatment. Additionally, preliminary results for antiviral activity only for the 800 mg cohort are presented here.

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

CHB viremic subjects not currently on treatment

MAD
28 days

EDP-514 vs. PBO

Dose 200 mg
Dose 400 mg
Dose 800 mg

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 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 a confirmed increase in HBV DNA level ≥1.0 log10 IU/ml from nadir while receiving EDP-514

RESULTS

Subject Disposition and Demographics

- A total of 16 subjects were enrolled in the 200 mg and 400 mg cohorts. All subjects completed the study. Subjects were all Asian, mostly male, HBeAg(-), with a mean age of 45 years, mean HBV DNA of 4.87 log IU/mL, and mean HBV RNA of 3.45 log U/mL at baseline
- Subject demographics and disease characteristics for the 200 mg and 400 mg cohorts are summarized in **Table 1**

Table 1. Baseline Demographics and Disease Characteristics

	200 mg QD (N=6)	400 mg QD (N=6)	Placebo (N=4)	Overall (N=16)
Sex [n (%)]				
Female	2 (33.3)	2 (33.3)	3 (75.0)	7 (43.8)
Male	4 (66.7)	4 (66.7)	1 (25.0)	9 (56.3)
Race [n (%)]				
Asian	6 (100)	6 (100)	4 (100)	16 (100)
Age (y)[a]	48.7 (42, 56)	42.8 (33, 51)	43.8 (24, 60)	45.3 (24, 60)
BMI (kg/m^2)[a]	24.76 (19.3, 30.2)	26.41 (20.0, 34.7)	23.23 (18.8, 28.1)	25.00 (18.8, 34.7)
HBeAg negative [n (%)]	6 (100)	5 (83.3)	4 (100)	15 (93.8)
HBV DNA (Log IU/mL)[a,b]	4.57 (3.6, 5.6)	5.37 (4.0, 8.4)	4.56 (4.2, 5.2)	4.87 (3.6, 8.4)
HBV RNA (Log U/mL)[a,c]	3.22 (1.9, 4.5)	3.58 (0.8, 7.3)	3.59 (2.7, 4.4)	3.45 (0.8, 7.3)

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

Pharmacokinetics

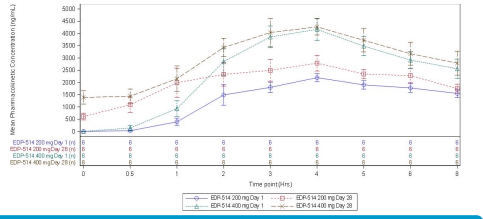
- EDP-514 exposure increased with 200 or 400 mg dose, with time-linear pharmacokinetics (**Table 2, Figure 2**)
- EDP-514 exposure increased with multiple dosing of 200 or 400 mg with an accumulation index of ~1.1-1.4
- Based on the 200 and 400 mg cohorts, PK is supportive of once daily dosing, with median C_{trough} at Day 28 ~9-fold for 200 mg and ~20-fold for 400 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)
AUC_{tau} (ng/mL*hr)	17230 (26)	25629 (25)
C_{max} (ng/mL)	3230 (29)	4717 (17)
C_{trough} (ng/mL)	646 (377, 871)	1390 (789, 1790)

a. AUC_{tau}, 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

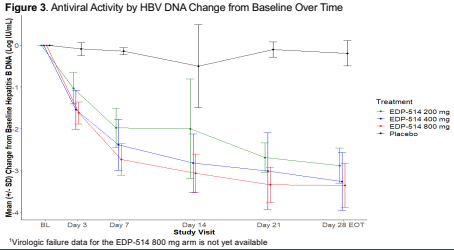
- At Day 28, mean HBV DNA reductions of 2.9, 3.3, 3.4 and 0.2 logs IU/mL, and mean HBV RNA reductions of 2.9, 2.4, 2.0 and 0.02 logs IU/mL were observed in the 200 mg, 400 mg, 800 mg and placebo groups, respectively (**Table 3, Figure 3, 4**)
- As expected, there were no discernible changes in HBeAg, HBcrAg, and HBsAg
- No instances of virologic failure in the EDP-514 arms of the 200 and 400 mg cohorts were observed[1]

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

	200 mg QD (N=6)	400 mg QD (N=6)	800 mg QD (N=6)	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)

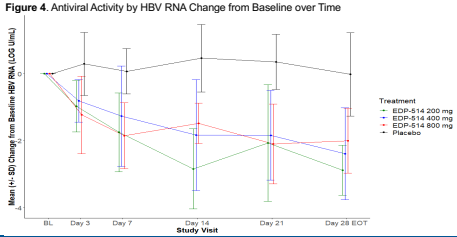
a. Data presented in Mean (Range)

Figure 3. Antiviral Activity by HBV DNA Change from Baseline Over Time



[1]Virologic failure data for the EDP-514 800 mg arm is not yet available

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



Safety

- Overall, EDP-514 was generally safe and well-tolerated at 200 mg and 400 mg doses (**Table 4**)
- Six 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)	Placebo (N=4)	Overall (N=16)
Total Subjects with at Least One TEAE	2 (33.3)	3 (50.0)	1 (25.0)	6 (37.5)
Blood and Lymphatic System Disorders				
Anaemia	1 (16.7)	0	0	1 (6.3)
Skin and subcutaneous tissue disorders				
Dermatitis	0	1 (16.7)	0	1 (6.3)
Nervous system disorders				
Dizziness	1 (16.7)	0	0	1 (6.3)
Headache	0	1 (16.7)	0	1 (6.3)
Gastrointestinal disorders				
Gastrointestinal disorder	0	0	1 (25.0)	1 (6.3)
Tooth development disorder	0	1 (16.7)	0	1 (6.3)
Infections and infestations				
Nasopharyngitis	0	1 (16.7)	0	1 (6.3)
Urinary tract infection	0	0	1 (25.0)	1 (6.3)
Cardiac disorders				
Palpitations	0	0	1 (25.0)	1 (6.3)
Investigations				
Activated partial thromboplastin time prolonged	1 (16.7)	0	1 (25.0)	2 (12.5)
International normalised ratio increased	1 (16.7)	0	1 (25.0)	2 (12.5)
Prothrombin time prolonged	1 (16.7)	0	0	1 (6.3)

n = Number of Subjects

CONCLUSIONS

- EDP-514 was generally safe and well-tolerated for 28 days in viremic CHB patients
- EDP-514 exhibited PK supportive of once daily oral dosing, with C_{trough} up to ~20-fold the $paEC_{50}$
- 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 doses of EDP-514 compared to 0.2 log and 0.02 log, respectively, in placebo

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
- EDP-514, a novel pangenotypic class II hepatitis B virus core inhibitor: preliminary results of a phase 1 study in healthy adult subjects. K Larson, et al. J Hepatology, VOLUME 73, SUPPLEMENT 1, S871

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DISCLOSURES

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