Phase 1 Trial of the Safety, Pharmacokinetics, and Antiviral Activity of EDP-514 in Untreated Viremic Chronic Hepatitis B Patients


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Conflicts of Interest/Disclosures
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**Author Contributions**

GDLR, AA, EL, ALC contributed to data analysis, interpretation, and manuscript preparation. All other authors conducted the clinical study and contributed to data interpretation. All authors critically reviewed and approved the final manuscript.
ABBREVIATIONS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; CV, coefficient of variation; cccDNA, covalently closed circular DNA; CpAMs, core protein allosteric modulators; EC50, concentration that is 50% effective; HAV, hepatitis A virus; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HEV, hepatitis E virus; NRTI, nucleos(t)ide reverse transcriptase inhibitors; NUC, nucleos(t)ide analogue; NUC-suppressed CHB patients, patients who had sustained HBV DNA suppression after long-term therapy with NUC; PT, prothrombin time; PTT, partial thromboplastin time; pegIFN, pegylated interferon alpha; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

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Study Highlights
Chronic hepatitis B (CHB) is a major cause of morbidity and mortality worldwide. Oral EDP-514 is a potent core protein inhibitor of hepatitis B virus (HBV). This study tested the safety, tolerability, pharmacokinetics (PK) and antiviral activity of EDP-514. EDP-514 was well tolerated with a favorable safety and PK profile. EDP-514 reduced HBV DNA and HBV RNA in untreated viremic CHB patients.
ABSTRACT

**Background & Aims:** Oral EDP-514 is a potent core protein inhibitor of hepatitis B virus (HBV) replication, which produced a >4-log viral load reduction in HBV-infected chimeric mice with human liver cells. This study evaluated the safety, pharmacokinetics (PK), and antiviral activity of three doses of EDP-514 in treatment naïve viremic patients with HBeAg-positive or -negative chronic HBV infection.

**Methods:** Patients with HBsAg detectable at screening and at least 6 months previously were eligible. HBeAg-positive and -negative patients had a serum/plasma HBV DNA level ≥20,000 and ≥2,000 IU/mL, respectively. Twenty-five patients were randomized to EDP-514 200 (n=6), 400 (n=6) or 800 mg (n=7) or placebo (n=6) once daily for 28 days.

**Results:** A dose-related increase in EDP-514 exposure (AUC last and C max) was observed across doses. At Day 28, mean reductions in HBV DNA were -2.9, -3.3, -3.5 and -0.2 log10 IU/mL with EDP-514 200 mg, 400 mg, 800 mg, and placebo groups, respectively. The corresponding mean change from baseline for HBV RNA levels was -2.9, -2.4, -2.0, and -0.02 log10 U/mL. No virologic failures were observed. No clinically meaningful changes from baseline were observed for HBsAg, HBeAg or HBcrAg. Nine patients reported treatment emergent adverse events (TEAEs) of mild or moderate severity with no discontinuations, serious AEs or deaths.

**Conclusions:** In treatment-naïve viremic patients, oral EDP-514 was generally safe and well-tolerated, displayed PK profile supportive of once-daily dosing, and markedly reduced HBV DNA and HBV RNA.

**Key Words:** chronic hepatitis B; hepatitis B virus; core inhibitor; core protein inhibitor; core protein allosteric modulator, capsid assembly modulator; pharmacokinetics; pharmacodynamics; safety
INTRODUCTION

Infection with hepatitis B virus (HBV) is a common cause of hepatic cirrhosis and the most common cause of hepatocellular carcinoma.\(^1\) Worldwide, almost 300 million people are estimated to be chronically infected with HBV, and 1.5 million new infections/year are reported resulting in >800,000 deaths annually.\(^2\) HBV infection can be prevented with widely available HBV vaccines,\(^3,4\) however, the majority of people are unvaccinated, especially in lower- and middle-income countries. Standard treatment for HBV infection includes pegylated interferon (pegIFN) and nucleos(t)ide reverse transcriptase inhibitors (NUCs). These effectively suppress the infection through immunomodulation and inhibition of viral replication, respectively. NUCs are associated with an excellent safety/tolerability profile and potent antiviral activity for suppressing hepatitis B DNA levels but is needed to be taken long-term, whereas, pegIFN provides a satisfactory response in a very limited number of patients.\(^3,4\)

Hence, a need exists for treatments providing a sustained clinical response and functional cure, which is defined as a sustained loss of hepatitis B surface antigen (HBsAg), with or without acquisition of anti-HBs, and undetectable HBV DNA 6 months after completing treatment.\(^5,6\) Current therapies only achieve functional cure in a limited number of patients. Treatment with pegIFN achieves functional cure in approximately 11% of patients after 3 years,\(^4\) and treatment with NUC produces a functional cure in \(\leq 10\%\) of patients after 5 years of treatment.\(^7,8\) As a result, patients with HBV infection frequently require lifelong maintenance therapy, which imparts a substantial economic burden and may be associated with a risk of breakthrough drug resistance and drug toxicity.\(^9,10\) Further, the risk of hepatocellular carcinoma is reduced but not eliminated with these currently available treatments.\(^11,12\)
Novel drugs, which offer the potential for a functional cure, are in early clinical development for HBV infection including viral entry inhibitors, drugs for epigenetic control of cccDNA, immune modulators, RNA interference agents, ribonuclease H inhibitors, and core protein inhibitors. Two types of core protein inhibitors are recognized, both of which accelerate the kinetics of core protein interactions. Treatment with Type I inhibitors *in vitro* leads to the intracellular core protein aggregation and degradation, while *in vitro* treatment with Type II inhibitors results in production of empty capsids that lack the RNA polymerase complex-required for HBV replication. Interestingly, in addition to suppressing replication by preventing pgRNA encapsidation, inhibitors of both these classes have been described to prevent de novo formation of cccDNA by preventing delivery of intact capsids to the nucleus. Treatment with core protein inhibitors in patients with HBV infection demonstrated a 2 to 3 log₁₀ IU/ml reduction in the mean HBV DNA concentrations in viremic CHB patients.

EDP-514 is a novel HBV core protein inhibitor that is in clinical development to treat CHB infection. EDP-514 is a Type II core protein inhibitor that stimulates core assembly and prevents encapsulation of viral pregenomic RNA to block HBV replication resulting in the production of empty capsids (Figure 1). EDP-514 potently inhibited encapsidation of viral RNA and production of viral DNA in stable cell lines expressing HBV and prevented HBV cccDNA establishment in cell lines or primary human hepatocytes when present at the time of viral infection. EDP-514 was equally active across HBV genotypes (A to H) and NUC-resistant variants with no cytotoxicity and exhibited a promising safety and pharmacological profile in nonclinical studies. In a first-in-human study of the safety and pharmacokinetics (PK) of oral EDP-514 in healthy
volunteers and nucleos(t)ide analogs (NUC)-suppressed patients with CHB, EDP-514 was well-tolerated, exhibited a PK profile supportive of once daily dosing, and reduced antiviral activity in NUC-suppressed CHB patients.\textsuperscript{18}

This study evaluated the safety, PK, and antiviral activity of three doses of oral EDP-514 in treatment naïve, viremic patients with either hepatitis B e-antigen (HBeAg)-positive or -negative chronic HBV infection. The inclusion of patients with CHB who are viremic and not currently on treatment provides an opportunity to evaluate initial safety and efficacy for EDP-514 in CHB patients. In addition, the present study would provide supportive data allowing for adequate dose selection and choice of appropriate endpoints for future studies in patients with CHB including those receiving NUC therapy.

**MATERIALS AND METHODS**

The present study was conducted in compliance with the International Conference on Harmonisation- Good Clinical Practices guidelines, the Declaration of Helsinki, and national regulations for clinical trials. The study protocol and informed consent were reviewed and approved by Institutional Review Boards of participating institutions. Written informed consents were obtained from all participants prior to any study procedures. This study was registered at clinicaltrials.gov: NCT04470388.

**Study Design**

This was a randomized, double-blind, placebo-controlled, Phase 1b study. The study consisted of three cohorts of viremic patients with CHB not currently on treatment. Each cohort enrolled
patients who were randomized to EDP-514 200 mg, 400 mg or 800 mg or placebo once daily for 28 days. A safety follow-up was conducted 2 and 8 weeks after the last dose of study drug. Following dosing for the initial 200 mg cohort with EDP-514, subsequent cohorts were dosed following review of available blinded safety and PK data from the previous cohort.

**Patient Selection**

Men or women aged 18 to 70 years with a body mass index (BMI) of 18 to 35 kg/m² were eligible if they had HBsAg detectable in serum/plasma at screening and in the most recent HBsAg serum/plasma testing within the past 6 months. At screening, all patients who were HBeAg-positive had a screening serum/plasma HBV DNA level ≥20,000 IU/mL or for those who were HBeAg-negative, a screening serum/plasma HBV DNA level ≥2,000 IU/mL, and no HBV DNA serum/plasma test values <1,000 IU/mL over the previous 12 months. Patients were not taking prescribed anti-HBV treatment, specifically pegIFN and/or NUC therapy for at least 12 months prior to screening.

Patients were excluded if there was a prior diagnosis of cirrhosis or history of hepatic decompensation (ascites, encephalopathy or variceal hemorrhage) or documented extensive bridging fibrosis or cirrhosis defined by any one of the following: a) Metavir ≥3 or Ishak fibrosis score ≥4 by a prior liver biopsy; or b) FibroSure at Screening with a score of ≥0.48 and aspartate aminotransferase (AST) to platelet ratio index ≥0.45; or c) FibroScan with a result ≥9 kPa at screening or within 6 months of screening. Patients also were excluded if they had coinfection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis A virus (HAV) or hepatitis E virus (HEV); prior history of hepatocellular carcinoma,
evidence of hepatocellular carcinoma, by imaging in the past 3 months or screening alpha-fetoprotein $\geq 50$ ng/mL without imaging. Patients also were excluded if there were usage of any prescription medication or St. John’s Wort or receipt of any vaccine or investigational drugs within 28 days or 5 half-lives prior to the first dose of study drug; or use of nonprescription drugs, dietary or herbal supplements, hormone replacement therapy or cytochrome P450 3A4 or p-glycoprotein inducers or inhibitors within 14 days of study drug. Full eligibility criteria are provided in Supplementary Material A.

**Study Assessments**

Safety was assessed by physical examination, vital signs (heart rate, blood pressure, respiratory rate, body temperature), clinical laboratory testing (chemistry, hematology, urinalysis), 12-lead electrocardiogram (ECG), and reports of adverse events (AEs). Partial thromboplastin time (PTT), prothrombin time (PT), and international normalized ratio (INR) were measured at each study visit. Patients were assessed at screening for the presence of HAV, HDV, HCV, HEV, and HIV. HBV DNA, HBsAg, hepatitis B core-related antigen (HBcrAg), HBeAg, and HBV RNA were assessed at each study visit. The lower limits of quantification (LLOQ) for HBV DNA, HBsAg, HBcrAg, HBeAg, and HBV RNA were $1.3 \log_{10}$ IU/ml, 0.05 IU/mL, $2.75 \log_{10}$ U/mL, 0.59 PEI-U/mL, and $1.65 \log_{10}$ U/mL, respectively. Serious AEs, Grade 3 or 4 AEs considered at least possibly related to the study drug, all clinically significant Grade 3 or 4 laboratory abnormalities, alanine aminotransferase (ALT) $\geq 2 \times$ baseline with signs of hepatic decompensation and/or laboratory changes suggestive of worsening hepatic function, ALT elevations $>3 \times$ upper limit of normal (ULN) and $\geq 2 \times$ baseline, and ALT elevations $>10 \times$ ULN were monitored and managed according
to protocol-specific guidelines (Supplementary Materials B). AEs and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

Blood samples were collected for PK analysis on Day 1 and Day 28 (or EOT) predose and at 0.5, 1, 2, 3, 4, 5, 6, and 8 hours postdose, and on Days 3, 7, 14, and 21 predose and at 1 to 3 hours postdose and at least 1 hour later but before administration of the next dose.

Statistical Analysis

No formal sample size calculations were performed. A total of 24 viremic CHB patients not currently on treatment were planned to be enrolled, which was considered sufficient to characterize the efficacy, safety, tolerability, and PK for each EDP-514 dose level.

For safety data, no formal statistical analyses were performed. Plasma PK parameters for each dose level were calculated from the concentrations of EDP-514 and its major metabolites measured in predose and postdose plasma samples. For each EDP-514 dose level, descriptive statistics (sample size, arithmetic means, geometric means, standard deviation, % coefficient of variation (CV), % geometric CV, minimum, median, and maximum) were reported. Dose proportionality was assessed using a linear regression. PK parameters included $C_{\text{max}}$, $C_{\text{trough}}$, and $AUC_{0-\text{last}}$ for plasma EDP-514 and its major metabolites.

For each EDP-514 dose cohort, HBV-specific biomarkers were evaluated at baseline, on treatment through Day 28, and at 2 and 8 weeks posttreatment. The primary antiviral endpoint was HBV
DNA levels through Day 28. HBV DNA levels were summarized by treatment using descriptive statistics. The percentage of patients with virologic failure/viral breakthrough defined as a confirmed increase in serum/plasma HBV DNA level ≥1.0 log_{10} IU/ml from nadir while receiving EDP-514 would be reported. For all patients with virologic failure, resistance testing was attempted if HBV DNA levels were adequate. Other antiviral parameters assessed over time included HBsAg, HBeAg, HBcrAg, and HBV RNA levels (log_{10} U/mL). Additionally, HBsAg (reflex anti-HBs) and HBeAg (reflex anti-HBe in patients who were HBeAg-positive at baseline) were assessed serologically at the end of treatment.

The safety population included all patients who received at least one dose of study drug, the PK population consisted of all patients who received active study drug and had any measurable plasma concentration of study drug, and the antiviral population was all patients who received at least one dose of study drug and had any on-treatment HBV DNA data.

**RESULTS**

Twenty-five patients were randomized to treatment and completed the study. Patients were mostly male (60.0%) and all were Asian. The mean age was 46.3 years (range: 24 to 60 years), and the mean BMI was 25.8 kg/m² (range: 18.8 to 34.7 kg/m²) (Table 1). Baseline HBV DNA and HBV RNA levels were similar in all EDP-514 treatment groups and placebo. All patients had detectable HBsAg and the baseline levels were variable in all groups. Two patients in the 800 mg group, one patient each in the EDP-514 400 mg and placebo groups, and no patient in the 200 mg group were HBeAg-positive.
Pharmacokinetics

Following once daily oral administration, mean EDP-514 plasma concentrations increased with dose from 200 mg to 800 mg at most time points on Day 1 and Day 28, respectively (Figure 2). EDP-514 was absorbed within approximately 2.0 to 4.0 hours post dose, with median $T_{\text{max}}$ between approximately 2.9 to 4.0 hours across all doses on Day 1 and between 2.0 to 3.4 hours across all doses on Day 28. A dose-related increase in EDP-514 exposure ($\text{AUC}_{\text{last}}$ and $C_{\text{max}}$) was observed on both Day 1 and Day 28 (Table 2). Exposures on Day 28 were higher than on Day 1 indicating some evidence for accumulation with multiple daily dosing. The PK profile was supportive of once daily dosing, with median $C_{\text{trough}}$ at Day 28 ~9-fold for 200 mg, ~20-fold for 400 mg, and ~24-fold for 800 mg doses above the protein-adjusted EC$_{50}$ (71 ng/mL) (Figure 3).

Antiviral Activity

EDP-514 showed both dose- and time-dependent decreases in HBV DNA levels when administered to viremic CHB patients not currently on treatment (Figure 4 and Supplementary Figure 1). Mean HBV DNA levels decreased with increasing EDP-514 dose at all measurements between Day 3 and Day 28, with the greatest decrease in the EDP-514 800 mg at all time points. At Day 28, mean reductions in HBV DNA levels were -2.9, -3.3, -3.5, and -0.2 log$_{10}$ IU/mL in the 200 mg, 400 mg, 800 mg, and placebo groups, respectively. Once treatment was discontinued, HBV DNA levels returned to near baseline levels for all EDP-514 treatment groups. No virologic failures were observed.

22 patients had quantifiable HBV RNA levels at baseline (200 mg, n=6; 400 mg, n=5; 800 mg, n=6; placebo, n=5) (Table 1). EDP-514 also showed increasing inhibition of HBV RNA levels.
with increasing duration of treatment, but no clear dose-dependent effects were observed (Figure 5 and Supplementary Figure 2). By Day 28, mean change from baseline for HBV RNA levels was -2.9, -2.4, -2.0, and -0.02 log_{10} U/mL with the 200 mg, 400 mg, 800 mg, and placebo groups, respectively. Following discontinuation of study treatments, HBV RNA levels increased to approach baseline levels in all treatment groups.

No clinically meaningful changes from baseline were observed in patients with quantifiable levels at baseline for HBsAg, HBeAg (n=4) or HBcrAg (n=21) (Table 1 and Supplementary Figures 3 and 4).

**Safety/Tolerability**

No discontinuations, serious AEs or deaths were reported with EDP-514 treatment. Overall, nine patients reported treatment emergent adverse events (TEAEs) (Table 3). All TEAEs were mild or moderate, and none were severe. No individual TEAE occurred more than once with any dose of EDP-514. One patient in the placebo group experienced gastrointestinal disorder, activated partial thromboplastin time prolonged, and INR increased that were considered possibly related to placebo therapy. Clinical laboratory findings were generally normal with no clinically relevant changes in the EDP-514 treatment groups except for one patient who experienced activated partial thromboplastin time prolonged and INR increased and one patient who experienced prothrombin time prolonged, both in the EDP-514 200 mg group. Mean change from baseline of ALT, AST, gamma glutamyl transferase, bilirubin, triglycerides, and cholesterol are shown in Supplementary Figures 5, 6, 7, 8, 9 and 10. No ALT elevations indicative of HBV viral flares was observed in
the study. No clinically relevant changes in the physical examination, vital signs or ECG were observed with EDP-514.

DISCUSSION

The HBV core protein plays an indispensable role in the viral life cycle by packaging the viral pregenomic RNA along with the viral polymerase into capsids. This packaging enables the reverse transcription of pregenomic RNA into relaxed circular DNA to produce the infectious form of the viral genome. The core protein itself also displays limited sequence polymorphisms across HBV genotypes, which coupled with the critical role of the protein in producing infectious virus and sustaining the viral cccDNA pool, makes it an important target for novel antivirals to treat HBV infection.19,20

In this Phase 1b study of EDP-514, positive data were obtained from all three dose cohorts in patients with viremic CHB infection not currently treated with pegIFN or NUC. The incidence of mild or moderate AEs was similar between EDP-514 groups and placebo with no dose-related increase in AEs. No AEs occurred more than once in any patient, and no patients discontinued the study for an AE. EDP-514 displayed a PK profile demonstrating a dose-related increase in exposure and supporting once-daily dosing, with median C\text{trough} at Day 28 ~9-fold for 200 mg, ~20-fold for 400 mg, and ~24-fold for 800 mg doses above the protein-adjusted EC\text{50} (71 ng/mL). Marked reductions in HBV DNA and HBV RNA levels occurred rapidly with all three EDP-514 doses compared with placebo, and levels returned to baseline after discontinuing study treatment. Overall, these results were consistent with a previous study of EDP-514 in healthy patients.18 At Day 28 in the study reported here, mean reductions in HBV DNA levels were -2.9, -3.3, and -3.5
with the 200 mg, 400 mg, and 800 mg doses of EDP-514, and mean reductions in HBV RNA levels were -2.9, -2.4, and -2.0. The lack of dose proportional response in HBV RNA may be due to potentially attaining the maximal effect in HBV RNA reduction with 200 mg, the small number of patients evaluated, or that the majority of patients were HBeAg negative whose HBV RNA levels are typically low. The lack of dose proportional response in HBV RNA may be due to potentially attaining the maximal effect in HBV RNA reduction with 200 mg, the small number of patients evaluated, or that the majority of patients were HBeAg negative whose HBV RNA levels are typically low.21 As a whole, other studies of drug therapy for treatment naïve patients with HBV reported similar findings.13,15,22-24 While the clinical significance of circulating HBV RNA remains unknown, it has been suggested HBV RNA levels may be a marker for treatment response and cccDNA activity in patients with chronic HBV infection.25-29. This viral biomarker is one that remains largely unchanged with short term NUC therapy and highlights the differentiated mechanism of action of EDP-514. The addition of a potent core protein inhibitor such as EDP-514 to NUC treatment could potentially lower HBV DNA and RNA levels more rapidly and profoundly, which may result in a lower incidence of hepatocellular carcinoma. The addition of an early generation core protein inhibitor vebicorvir to patients taking NUCs further suppressed HBV DNA and HBV RNA more than with NUCs alone (24,30). In this manner, an EDP-514 and NUC combination treatment may have clinical benefit in treatment naïve highly viremic HBeAg-positive patients where NUC treatment takes longer than a year to achieve undetectable HBV DNA levels and NUC-treated patients with residual HBV DNA and HBV RNA are detectable in circulation by highly sensitive assays.

In the present study of 4 weeks dosing of EDP-514, a reduction in HBsAg was not observed. Recently, another core protein inhibitor ALG-000184 demonstrated an HBsAg reduction beginning at approximately 4 weeks to 36 weeks of treatment.31 According to the present study, EDP-514 appears to have a similar potency of HBV DNA and HBV RNA suppressions when
compared with ALG-000184 (mean HBV DNA and HBV RNA reductions of 3.8 log10 IU/mL and 1.9 log10 copies/mL after 4 weeks of treatment, respectively).\textsuperscript{32} Whether a longer treatment duration of EDP-514 than 4 weeks could also show an HBsAg reduction would be interesting to explore in the future.

Limitations to this study included a small sample size, a short treatment duration, and limited diversity in the patient population. However, this study was specifically designed to evaluate safety, PK, and antiviral activity in a previously untreated population with CHB and help to confirm results from an earlier study that evaluated EDP-514 in healthy subjects and NUC-suppressed patients.\textsuperscript{18} Studies enrolling larger numbers of more diverse patients with HBV infections with longer treatment duration and follow-up will be necessary to further elucidate the role of EDP-514 for treating CHB.

Overall, these results demonstrate that EDP-514, a novel oral HBV core protein inhibitor, was well tolerated and had a favorable safety profile for viremic, treatment naïve CHB patients. In this population of patients with chronic HBV infection, EDP-514 for 28 days resulted in a mean reduction in both HBV DNA and HBV RNA of 2 to 3.5 log10 that is highly suggestive of antiviral activity as a potent HBV core protein inhibitor. These results encourage continued investigation of EDP-514 for viremic, treatment naïve patients with CHB.
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Conflicts of Interest/Disclosures

Man-Fung Yuen: Advisory/consultant for AbbVie, Aligos Therapeutics, AiCuris, Antios Therapeutics, Assembly Biosciences, Arbutus Biopharma, Bluejay Therapeutics, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Hoffmann-La Roche, Vir Biotechnology; grant/research supports from AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Arbutus Biopharma, Bristol Myer Squibb, Dicerna Pharmaceuticals, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Merck Sharp and Dohme, Hoffmann-La Roche; sponsored lectures for Menarini, Gilead Sciences, Janssen

Wan-Long Chuang: Consultant for Gilead Sciences, AbbVie, Bristol Myers Squibb, Roche, Vaccitec, PharmaEssentia; Speaker for Gilead Sciences, AbbVie, Bristol Myers Squibb, Roche, PharmaEssentia; Sponsored lectures for Gilead Sciences, AbbVie, Bristol Myers Squibb, Roche, PharmaEssentia

Cheng-Yuan Peng: Advisory board for AbbVie, Bristol Myers Squibb, Gilead Sciences and Hoffman-La Roche

Wen-Juei Jeng: Speaker for Bristol Myers Squibb and Gilead Sciences; Grants from Chang Gung Medical Foundation; National Science Council, Taiwan

Wei-Wen Su: Speaker for Gilead Sciences, Eisai, AbbVie
Ting-Tsung Chang: Nothing to disclose

Chi-Yi Chen: Nothing to disclose

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Annie L. Conery, Alaa Ahmad, Ed Luo, Guy De La Rosa: Employee and stockholder for Enanta Pharmaceuticals, Inc. Watertown, MA at the time the work was performed.

Author Contributions

GDLR, AA, EL, ALC contributed to data analysis, interpretation, and manuscript preparation. All other authors conducted the clinical study and contributed to data interpretation. All authors critically reviewed and approved the final manuscript.

Data Sharing Statement

All relevant data for this study are reported in the manuscript. Additional data may be available with written request due to privacy/ethical restrictions.

Role of Funding Source

The study was funded by Enanta Pharmaceuticals, Inc. and was designed in conjunction with the authors. Enanta was involved in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study, participated in drafting and editing the manuscript and were responsible for the decision to submit for publication.
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31. Hou J, Yanhua D, Junqi N, Xie’er L, Massetto B, Le K, et al. ALG-000184, a capsid assembly modulator, dosed with entecavir for up to 28 weeks is well tolerated and resulted in substantial declines in surface antigen levels in untreated hepatitis B e antigen positive subjects with chronic hepatitis. Poster LBP-18 presented at the 2023 European Association for the Study of the Liver, Vienna, Austria.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
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<th>EDP-514</th>
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<tr>
<td></td>
<td>200 mg</td>
<td>400 mg</td>
<td>800 mg</td>
<td>Placebo</td>
<td>Total</td>
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<td></td>
<td>(n=6) b</td>
<td>(n=6) b</td>
<td>(n=7) b</td>
<td>(n=6) b</td>
<td>(n=25)</td>
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<td>Age, years a</td>
<td>48.7 ±4.8</td>
<td>42.8 ±6.6</td>
<td>47.9 ±8.0</td>
<td>45.5 ±12.0</td>
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<tr>
<td>Male, n (%)</td>
<td>4 (66.7)</td>
<td>4 (66.7)</td>
<td>6 (85.7)</td>
<td>1 (16.7)</td>
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<td>Asian, n (%)</td>
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<td>6 (100)</td>
<td>7 (100)</td>
<td>6 (100)</td>
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<tr>
<td>HBV Genotype</td>
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<tr>
<td>B, n (%)</td>
<td>6 (100)</td>
<td>5 (83.3)</td>
<td>5 (71.4)</td>
<td>5 (83.3)</td>
<td>21 (84)</td>
<td></td>
</tr>
<tr>
<td>C, n (%)</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
<td>2 (28.6)</td>
<td>1 (16.7)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>HBV DNA levels, log₁₀ IU/mL a</td>
<td>4.57 ±0.75</td>
<td>5.37 ±1.59</td>
<td>5.54 ±1.70</td>
<td>4.91 ±1.38</td>
<td>5.12 ±1.38</td>
<td></td>
</tr>
<tr>
<td>HBV RNA &gt; LLOQ, n (%)</td>
<td>6 (100)</td>
<td>5 (83.3)</td>
<td>6 (85.7)</td>
<td>5 (83.3)</td>
<td>22 (88)</td>
<td></td>
</tr>
<tr>
<td>HBV RNA Levels (log₁₀ U/mL) a</td>
<td>3.22 ±0.95</td>
<td>3.58 ±2.30</td>
<td>3.77 ±2.17</td>
<td>3.34 ±1.97</td>
<td>3.49 ±1.82</td>
<td></td>
</tr>
<tr>
<td>HBsAg levels, IU/mL a</td>
<td>1384.25 ±1316.87</td>
<td>23874.62 ±46178.28</td>
<td>6972.28 ±14771.62</td>
<td>2601.11 ±4827.76</td>
<td>8638.63 ±24189.61</td>
<td></td>
</tr>
<tr>
<td>HBeAg positive, n (%)</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
<td>2 (28.6)</td>
<td>1 (16.7)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>HBeAg levels, PEI-U/mL a</td>
<td>0.30 ±0.00</td>
<td>398.39 ±975.14</td>
<td>45.24 ±118.02</td>
<td>11.21 ±26.73</td>
<td>111.04 ±478.74</td>
<td></td>
</tr>
<tr>
<td>HBcrAg &gt; LLOQ, n (%)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>5 (71.4)</td>
<td>4 (66.7)</td>
<td>21 (84)</td>
<td></td>
</tr>
<tr>
<td>HBcrAg levels (log₁₀ U/mL) a</td>
<td>3.6 ±0.7</td>
<td>4.9 ±1.9</td>
<td>4.1 ±2.6</td>
<td>3.5 ±2.4</td>
<td>4.0 ±2.0</td>
<td></td>
</tr>
</tbody>
</table>

a Mean ±standard deviation; b The n applies to all values show in the table including HBV DNA, HBV RNA, HBsAg, HBeAg and HBcrAg levels, but excluding instances where a specific n is shown (ie, to demonstrate the number of patients with values below LLOQ); LLOQ: lower limit of quantification.
Table 2. Geometric mean plasma PK parameters for EDP-514 at Day 1 and Day 28

<table>
<thead>
<tr>
<th>EDP-514</th>
<th>200 mg (n=6)</th>
<th>400 mg (n=6)</th>
<th>800 mg (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-last}$, ng/mL*h</td>
<td>11815 (11)</td>
<td>21325 (23)</td>
<td>30746 (17)</td>
</tr>
<tr>
<td>C$_{max}$, ng/mL</td>
<td>2387 (19)</td>
<td>4246 (21)</td>
<td>6806 (40)</td>
</tr>
<tr>
<td>T$_{max}$, h</td>
<td>3.8 (43.2)</td>
<td>3.8 (47.3)</td>
<td>2.7 (31.8)</td>
</tr>
<tr>
<td><strong>Day 28</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-last}$, ng/mL*h</td>
<td>16617 (26)</td>
<td>24600 (27)</td>
<td>41669 (22)</td>
</tr>
<tr>
<td>C$_{max}$, ng/mL</td>
<td>3115 (31)</td>
<td>4660 (17)</td>
<td>7947 (14)</td>
</tr>
<tr>
<td>C$_{trough}$, ng/mL</td>
<td>482.7 (106.9)</td>
<td>1250.6 (54.8)</td>
<td>1900.3 (47.1)</td>
</tr>
<tr>
<td>T$_{max}$, h</td>
<td>2.7 (62.4)</td>
<td>3.3 (32.4)</td>
<td>2.3 (52.0)</td>
</tr>
</tbody>
</table>

All values presented as geometric mean (% geometric coefficient of variation).
Table 3. Incidence of treatment-emergent adverse events (TEAEs) with EDP-514

<table>
<thead>
<tr>
<th></th>
<th>EDP-514</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg (n=6)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation for TEAE</td>
<td>0</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>0</td>
</tr>
<tr>
<td>Individual TEAEs</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time prolonged</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic neoplasm</td>
<td>0</td>
</tr>
<tr>
<td>International normalized ratio increased</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
</tr>
<tr>
<td>Prothrombin time prolonged</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Tooth development disorder</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
</tr>
</tbody>
</table>

m=number of total AEs; N=number of patients per measurement; n=number of patients per treatment group.
**Figure 1.** Mechanism of action of core inhibitors in the HBV life cycle. EDP-514 is a type II core protein inhibitor that suppresses HBV replication by modulating the kinetics of capsid assembly and disassembly. This prevents both pgRNA encapsidation and delivery of rcDNA to the nucleus, resulting in suppression of rcDNA and de novo cccDNA formation. rcDNA: relaxed circular DNA, cccDNA: covalently closed circular DNA, pgRNA: pregenomic RNA, mRNAs: messenger RNAs.
Figure 2. Mean plasma EDP-514 concentration-time curves on Day 1 and Day 28.
Figure 3. Mean (standard error) EDP-514 trough plasma concentrations.
Figure 4. Mean (standard deviation) change from baseline in HBV DNA concentrations over time.
Figure 5. Mean (standard deviation) change from baseline in HBV RNA concentrations over time.
Supplementary Material

A. Subject Eligibility Criteria

Inclusion Criteria
1. An informed consent form (ICF) signed and dated by the subject;
2. Male and female subjects of any ethnic origin between the ages of 18 and 70 years, inclusive (or national legal age of consent);
3. CHB subjects must have HBs-Ag detectable in serum/plasma at Screening and in the most recent HBs-Ag serum/plasma testing at least six months previously;
4. HBV DNA levels:
   • For subjects who are HBe-Ag positive at Screening, a Screening HBV DNA level in serum/plasma that is ≥20,000 IU/ml; or
   • For subjects who are HBe-Ag negative at Screening, a Screening HBV DNA level in serum/plasma that is ≥2,000 IU/mL; and
   • For all subjects, no HBV DNA serum/plasma test values <1,000 IU/ml over the previous 12 months (using an approved test).
5. CHB subjects must not have been on prescribed anti-HBV treatment, specifically pegIFN and/or NUC therapy for at least 12 months prior to Screening;
6. Negative serum β-human chorionic gonadotropin for women of childbearing potential;
7. A woman of childbearing potential who is sexually active with a male must agree to use two effective methods of contraception from the date of Screening until 30 days after her last dose of EDP-514. Effective methods of contraception are defined as:
   • A condom with or without spermicide for the male partner and at least one of the following for the female subject:
     o Intrauterine device;
     o Occlusive cap (diaphragm or cervical/vault caps);
     o Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive.
   Note: The above does not apply to a female subject who has a vasectomized male as the sole partner or who is of nonchildbearing potential (ie, physiologically incapable of becoming pregnant) as defined below:
   • Has had a complete hysterectomy ≥3 months prior to dosing; or
   • Has had a bilateral oophorectomy (ovariectomy); or
   • Has had a bilateral tubal ligation or fallopian tube inserts; or
   • Is postmenopausal (a total cessation of menses for at least 2 years; subjects with a cessation of menses between 1 to 2 years and a follicle-stimulating hormone [FSH] level of >35 mIU/mL will also be considered to be postmenopausal).
8. A male subject who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after their last dose of study drug. Effective contraception is defined as a condom with or without spermicide and at least one of the following for a female partner:
   - Intrauterine device;
   - Occlusive cap (diaphragm or cervical/vault caps);
   - Oral, injectable, implantable, transdermal, or intravaginal contraceptive;
   
   For a male subject who has had a vasectomy, use of a condom with or without spermicide will still be required.

9. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug;

10. Screening electrocardiogram (ECG) without clinically significant abnormalities and with QTcF interval (QT corrected using Fridericia’s formula) ≤450 msec for males and ≤470 msec for females;

11. Body mass index (BMI) of at least 18 kg/m² but ≤35 kg/m²;

12. Subject must be willing and able to adhere to the assessments, visit schedule, prohibitions, and restrictions, as described in this protocol.

Exclusion Criteria

1. A documented prior diagnosis of cirrhosis or any history or current evidence of clinical hepatic decompensation (ascites, encephalopathy, or variceal hemorrhage);

2. Documented extensive bridging fibrosis or cirrhosis as defined by any one of the following:
   a. Metavir ≥3 or Ishak fibrosis score ≥4 by a prior liver biopsy; or
   b. FibroSure at Screening with a score of ≥0.48 and AST to platelet ratio index ≥0.45; or
   c. FibroScan with a result ≥9 kPa at Screening or within 6 months of Screening.

3. Subjects meeting any of the following laboratory parameters at Screening:
   a. Hemoglobin <12 g/dL (for males), <11 g/dL (for females);
   b. White blood cell count <2,500 cells/mm³;
   c. Neutrophil count <1500 cells/mm³ (or <1000 cells/mm³ if considered a physiological variant in a subject of African descent);
   d. ALT values >2.5 × upper limit of normal (ULN);
   e. Direct bilirubin >1.2 × ULN;
   f. International normalized ratio [INR] >ULN;
   g. Albumin <3.9 g/dL;
   h. Platelet count <150,000/μL;
i. At screening, estimated serum creatinine clearance of <90 mL/min (as calculated by Cockcroft-Gault method).

4. Pregnant or nursing females;

5. Coinfection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis A virus (HAV), or hepatitis E virus (HEV);

6. Prior history of hepatocellular carcinoma or screening alpha-fetoprotein ≥50 ng/mL without imaging:
   - Evidence of lack of hepatocellular carcinoma by imaging in the past 3 months, or alpha-fetoprotein <50 ng/mL at Screening without imaging is required.

7. Malignancy within 5 years prior to Screening, with the exception of specific cancers that are cured by surgical resection (eg, basal cell skin cancer). Subjects under evaluation for possible malignancy are not eligible;

8. Significant cardiovascular, pulmonary, gastrointestinal, hematologic, autoimmune, psychiatric or neurological disease, or other significant medical conditions;

9. Chronic liver disease of a non-HBV etiology (eg, hemochromatosis, Wilson’s disease, alpha-1 antitrypsin deficiency, cholangitis); coexisting liver or biliary diseases, such as primary sclerosing cholangitis, choledocholithiasis, acute or chronic hepatitis, autoimmune hepatitis, alcoholic liver disease, acute infection of bile duct system or gall bladder, history of gastrointestinal bleeding (secondary to portal hypertension). A prior diagnosis of nonalcoholic steatohepatitis will exclude a subject. A diagnosis of hepatic steatosis (fatty liver) is not considered exclusionary;

10. Received solid organ or bone marrow transplant;

11. Received prolonged therapy with systemic immunomodulators (eg, corticosteroids) within 3 months of Screening:
   - Prolonged therapy with systemic immunomodulators is defined as administration for more than 1 week in the 3 months prior to Screening;
   - Nonsystemic immunomodulators, such as corticosteroids administered topically, inhaled, ophthalmologically, or nasally, are allowed.

12. Use of any prohibited concomitant medications, including CYP3A4 and P-gp inhibitors and inducers within 14 days prior to the first dose of study drug and for the duration of the study;

13. Use of St John’s Wort within 28 days prior to first dose of study drug and for the duration of the study;

14. Prior to the first dose of study drug, subject has received any vaccine, an investigational agent, or a biological product within 28 days or 5 times the t½, whichever one is longer;
   - Note: this includes agents administered during clinical trial participation. Recent receipt of influenza vaccine is not exclusionary.

15. History of regular alcohol consumption exceeding 7 drinks/week for females and 14 drinks/week for males within 6 months of Screening and for the duration of the study. One
drink is defined as 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor;

16. History of substance abuse and in the judgment of the Investigator, the subject would not be suitable for participation in the study;

17. Consumption of grapefruit or grapefruit containing products within 14 days prior to the first dose of study drug and for the duration of the study;

18. Clinically significant history of drug sensitivity or allergy, as determined by the Investigator.
B. Protocol-defined Management of TEAEs

1. Individual Subject Stopping Rules

- If a subject receiving EDP-514 experiences an SAE considered at least possibly related to the study drug, then the study drug should be permanently discontinued for that subject.
- In the case of a Grade 3 or 4 AE considered at least possibly related to the study drug, the Investigator should contact the Sponsor’s Medical Monitor and the study drug will be permanently discontinued for that subject.
- All clinically significant laboratory abnormalities of Grade 3 or 4 and regardless of the relationship to the study drug should be confirmed by repeat testing within up to 48 hours of receipt of results. If the clinically significant laboratory abnormality is confirmed and considered at least possibly related to the study drug, the Investigator should contact the Sponsor’s Medical Monitor and the study drug should be permanently discontinued for that subject.
- A subject with unacceptable toxicity or other circumstance (eg, intercurrent illness, study drug noncompliance) for which treatment discontinuation is considered by the SAC to be in the best interest of the subject should be discontinued from further dosing.

2. Dose Escalation Stopping Rules. Dose escalation will be placed on hold and based on full review by the SAC of all available clinical safety data, may be permanently discontinued if any of the following occurs:

- One or more subjects in the same dose cohort, receiving EDP-514 experience a Grade 4 or higher AE or confirmed treatment emergent laboratory abnormality (except ALT elevation*) regardless of causality attribution to drug.
- Two or more subjects, in the same dose cohort, receiving EDP-514, experience a Grade 3 drug-related AE or confirmed treatment emergent drug-related laboratory abnormality (except ALT elevation*).
- One or more subjects receiving EDP-514 in any cohort experiences an SAE at least possibly related to the study drug (except ALT elevation*).

*ALT elevations are managed separately by specific guidelines.

3. Subject Management of ALT Elevations Occurring While Receiving EDP-514

- For ALT values >3 and ≤10 × ULN and which are ≥2 × baseline value but the liver function tests (LFTs; ie, bilirubin, albumin and INR) are within the normal range and without clinical signs of hepatic decompensation, the subject should return to the study site as soon as possible and ideally no more than 3 days after the previous visit.
- A repeat clinical assessment of the subject should be performed, and repeat laboratory parameters tested (including ALT, AST, prothrombin time [PT], INR, albumin and, if available, lactate levels) by the local and central laboratories;
  - If the isolated ALT elevation is confirmed to be >3 and ≤10 × ULN:
- The subject should be monitored every 3 days until ALT returns to ULN or lower value;
- Study drug dosing may be withheld by the Investigator after discussion with Sponsor’s Medical Monitor who will in turn inform the SAC;
- Subsequent dosing with the study drug may be considered following a consultation with the SAC;
- If an alternate etiology is suspected by the Investigator, the Investigator in collaboration with the SAC will determine if subsequent dosing will be allowed for the subject within an acceptable timeframe (ie, within 3 days);
- The subject should be queried on potential clinically relevant causes for ALT elevation;
- Appropriate testing for HBV (DNA [serum/plasma], HBe Ag and HBs Ag [and reflex if negative]), HDV, HEV, HAV, and HCV should be performed.

- For ALT values >10 × ULN but with LFTs that are within normal range and without clinical signs of hepatic decompensation, the subject should return to the study site as soon as possible and ideally no more than 3 days after the previous visit:
  - A repeat clinical assessment of the subject should be performed, and repeat laboratory parameters tested (including ALT, AST, PT, INR, albumin and, if available, lactate levels) by the local and central laboratories;
  - If the isolated ALT elevation >10 × ULN is confirmed:
    - The subject should continue to be monitored frequently, at least every 3 days, until ALT returns to ULN or lower value;
    - Study drug dosing should be withheld by the Investigator who should immediately discuss with the Sponsor’s Medical Monitor who will in turn inform the SAC;
    - Subsequent dosing with the study drug may be considered following a consultation with the SAC;
    - If an alternate etiology is suspected by the Investigator, the Investigator in collaboration with the SAC will determine if subsequent dosing will be allowed for the subject within an acceptable timeframe (ie, within 3 days);
    - The subject should be queried on potential clinically relevant causes for ALT elevation;
    - Appropriate testing for HBV (DNA [serum/plasma], HBe Ag and HBs Ag [and reflex if negative]), HDV, HEV, HAV, and HCV should also be performed.

- For confirmed ALT values ≥2 × Baseline with a) and/or b) below:
  a) Signs of hepatic decompensation, eg, new onset ascites and/or confusion; and/or
  b) Confirmed changes outside of the normal range in other laboratory parameters which are suggestive of worsening hepatic function such as:
- Total bilirubin ≥2 mg/dL above Baseline (excluding a bilirubin elevation that is predominantly indirect); and/or
- PT ≥2 seconds or INR ≥0.5 over Baseline; and/or
- Serum albumin ≥1 g/dL below Baseline; and/or
- Elevated serum lactate levels (if available), defined as 2 × ULN.

  - In this setting study drug should be permanently discontinued;
  - The subject should receive additional medical management as appropriate;
  - Additionally, the subject should be queried on potential clinically relevant causes for ALT elevation;
  - Appropriate testing for HBV (DNA [serum/plasma], HBe Ag and HBs Ag [and reflex if negative]), HDV, HEV, HAV, and HCV should also be performed;

4. Study Management of ALT Elevations

- After confirmation of an ALT elevation considered related to the study drug in one dose level, no further subject enrollment into the respective dose cohort or higher dose level cohorts will occur until all subjects currently in the respective dose cohort and higher dose cohorts have completed dosing and the postdose safety follow-up visit unless otherwise approved by the SAC.

- If another ALT elevation occurs subsequently within a dosing cohort and which is considered related to the study drug, then further dosing of study drug and further subject enrollment will be suspended until a review of all safety data to date is conducted by the SAC.

- If an ALT elevation is considered unrelated to EDP-514, currently enrolled subjects will be allowed to remain on study drug and receive subsequent dosing as applicable. Further enrollment into the study will be allowed if no further ALT elevations occur on study which are considered related to the study drug.

5. Monitoring for Virologic Failure and Potential HBV Drug Resistance

- There will be regular viral monitoring, including assays to measure serum HBV DNA, HBsAg levels, and other HBV-specific assays. Virologic failure is defined as a confirmed increase in serum/plasma HBV DNA level ≥1.0 log10 IU/ml from nadir while receiving EDP-514. If a subject receiving EDP-514 is determined to have met a virologic failure criterion through confirmatory testing, then the subject should be instructed to discontinue EDP-514 and genotypic resistance testing should be performed, if possible.
C. Supplementary HBV Figures

Supplementary Figure 1. Change in Baseline in HBV DNA (log IU/mL) in Individual Patients

A. EDP-514 200 mg

B. EDP-514 400 mg

C. EDP-514 800 mg

D. Placebo
Supplementary Figure 2. Change in Baseline in HBV RNA (log U/mL) in Individual Patients

A. EDP-514 200 mg

B. EDP-514 400 mg

C. EDP-514 800 mg

D. Placebo
Supplementary Figure 3. Change in Baseline in HBcrAg (log U/mL) in Individual Patients

A. EDP-514 200 mg

B. EDP-514 400 mg

C. EDP-514 800 mg

D. Placebo
Supplementary Figure 4. Change in Baseline in HBsAg (IU/mL) in Individual Patients

A. EDP-514 200 mg

B. EDP-514 400 mg

C. EDP-514 800 mg

D. Placebo
D. Supplementary Safety Laboratory Figures

Supplementary Figure 5. Mean (standard deviation) change from baseline in ALT over time
Supplementary Figure 6. Mean (standard deviation) change from baseline in AST over time

Study Visit

-10 0 10

Mean (+/- SD) Change from Baseline in Aspartate Aminotransferase (U/L)

EDP-514 200 mg  EDP-514 400 mg  EDP-514 800 mg  Placebo
Supplementary Figure 7. Mean (standard deviation) change from baseline in Gamma Glutamyl Transferase over time.
Supplementary Figure 8. Mean (standard deviation) change from baseline in Bilirubin over time

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>BL</th>
<th>D3</th>
<th>D7</th>
<th>D14</th>
<th>D21</th>
<th>D28EOT</th>
<th>EOT2W</th>
<th>EOT8W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (+/- SD) Change from Baseline in Bilirubin (umol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>EDP-514 200 mg</td>
<td>EDP-514 400 mg</td>
<td>EDP-514 800 mg</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Visit:
- BL: Baseline
- D3, D7, D14, D21, D28EOT, EOT2W, EOT8W: Days or Visits after Baseline
Supplementary Figure 9. Mean (standard deviation) change from baseline in Triglycerides over time.

Study Visit

Mean (+/- SD) Change from Baseline in Triglycerides (mmol/L)

-0.5 0.0 0.5 1.0 1.5

BL D3 D7 D14 D21 D28EOT EOT2W EOT8W

EDP-514 200 mg  EDP-514 400 mg  EDP-514 800 mg  Placebo
Supplementary Figure 10. Mean (standard deviation) change from baseline in Cholesterol over time

![Graph showing mean cholesterol changes over time for different treatment groups.](image_url)