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:
     - Intrauterine device;
     - Occlusive cap (diaphragm or cervical/vault caps);
     - 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 non-childbearing potential (i.e., 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/m^2 but ≤35 kg/m^2;

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/mm^3;
   c. Neutrophil count <1,500 cells/mm^3 (or <1,000 cells/mm^3 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 (e.g., 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 (e.g., 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 (e.g., 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;

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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 (e.g., 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; i.e., 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 (i.e., 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 (i.e., 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, e.g., 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 $\log_{10}$ 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.