Inclusion criteria

Potential study participants must meet the following criteria for study entry:

1. Adult male and female patients, 18 to 60 years of age (inclusive) at the time of signing the informed consent form (ICF).
2. A body mass index (BMI) between 18 to 32 kg/m$^2$ inclusive.
3. Chronic hepatitis B (CHB) infection, defined as positive test for HBsAg or HBV DNA (including qualitative, quantitative, and genotype testing) or positive HBeAg for more than 6 months prior to screening.
4. HBsAg >250 IU/mL at screening.
5. For Cohorts only enrolling NUC-suppressed CHB patients (e.g., Cohort A), patients must qualify for the following criteria:
   a) Patients treated with a single NUC (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate) for ≥12 months. Patients must be on the same NUC therapy for at least 3 months before screening.
   b) At least one result showed HBV DNA <60 IU/mL at least 6 months prior to screening; and HBV DNA <20 IU/mL at screening by Roche Cobas assay.
   c) ALT ≤2xULN (upper limit of normal) at screening and at Day -1 (can be checked by local lab result).
6. For Cohorts only enrolling anti-HBV treatment-naïve and immune-active patients (e.g., Cohort B and Cohort C), patients must qualify for the following criteria:
   a) Previous anti-HBV treatments for <30 days in total, and did not receive any anti-HBV treatments within 3 months prior to the first study dose.
   b) HBV DNA at screening ≥2x10$^4$ IU/mL for HBeAg positive patients, or ≥2x10$^3$ IU/mL for HBeAg negative patients.
   c) ALT at screening between 1–5 (exclusive)xULN and ALT <5xULN at Day -1 (can be checked by local lab result).
7. Screening laboratory values (haematology, chemistry [other than liver function test], urinalysis) obtained up to 28 days prior to first study treatment within acceptable range or judged to be not clinically significant by the Investigator and the Medical Monitor.
8. Liver biopsy, Fibroscan, or equivalent test obtained within the past 6 months demonstrating liver disease consistent with chronic HBV infection with absence of extensive bridging fibrosis and absence of cirrhosis (cutoff for Fibroscan is liver stiffness measurement ≤8.5 kPa for treatment-naïve patients and ≤7.4 kPa for NUC-suppressed CHB patients, or Metavir fibrotic Stage <3, or other equivalent staging systems).
9. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:
   a) Men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
10. For women of childbearing potential: agree to use two methods of contraception, with at least one method considered as highly effective during the study and for at least 6 months after the last dose of study drug.
    a) A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    b) Contraceptive methods considered as highly effective (failure rate <1% per year when used consistently and correctly):
        - Combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation
        - intrauterine device (IUD)
        - intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study treatment and at least 6 months after the last dose of study drug. In such case, there is no need to use two contraceptive methods. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

c) Contraceptive methods NOT considered as highly effective (failure rate >1% per year):
- Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)
- Male or female condoms with or without spermicide
- Cap, diaphragm, or sponge with spermicide

11. Informed of, willing and able to comply with all of the protocol requirements and the investigational nature of the study, and have signed an informed consent form (ICF) in accordance with institutional and regulatory requirements.

Exclusion criteria

Potential study participants who meet any of the following criteria were excluded from study entry:
1. Pregnant (positive pregnancy test) or lactating women.
2. History or other evidence of bleeding from oesophageal varices.
3. Evidence of liver cirrhosis or decompensated liver disease such as ascites, oesophageal or gastric varices, splenomegaly, nodular liver, jaundice, and hepatic encephalopathy.
4. One or more of the following laboratory abnormalities at screening:
   a) Total serum bilirubin >ULN (exception Gilbert’s disease)
   b) International normalized ratio (INR) >1.1 ULN
   c) Serum albumin <3.0 g/dL (<30 g/L)
   d) Platelet count <140,000 cells/mm³
   e) Haemoglobin <12 g/dL (females) or <13 g/dL (males)
   f) White blood cell count <2,500 cell/mm³
   g) Neutrophil count <1,500 cell/mm³ (<1,200 cell/mm³ if considered a physiological variant in a patient of African descent)
5. History or other evidence of a medical condition associated with chronic liver disease other than HBV infection (e.g., haemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, nonalcoholic steatohepatitis, etc.).
6. History of thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], and free thyroxin [FT4]) at screening.
7. Documented history or other evidence of metabolic liver disease within one year of screening.
8. Positive test for hepatitis A (IgM anti-HAV), hepatitis C, hepatitis D, hepatitis E virus (HEV) or human immunodeficiency virus (HIV).
9. Expected to need systemic antiviral therapy other than that provided by the study at any time during their participation in the study, with the exception of oral therapy for herpes simplex virus (HSV) I or HSV II.
10. Diagnosed or suspected hepatocellular carcinoma (HCC) as evidenced by screening alpha-fetoprotein (AFP) ≥100 ng/mL. If AFP >ULN, absence of mass/findings suspicious for HCC must be demonstrated by ultrasound or computed tomography (CT) scanning or magnetic resonance imaging (MRI) within the screening period.
11. History of significant gastrointestinal disease (including but not limited to gastric ulcers).
12. History of clinically significant cardiovascular, endocrine, renal, ocular, pulmonary, psychiatric, or neurological disease.
13. Evidence of active or suspected cancer or a history of malignancy other than adequately treated basal cell carcinoma.
15. Participation in an investigational drug or device study within 30 days prior to screening.
16. Taking any drugs or nutrients listed in prohibited medications and prohibited foods.
17. Significant acute infection (e.g., influenza, local infection) or any other clinically significant illness within 2 weeks of screening.
18. ECG at screening with clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia’s formula) ≥450 msec for males and ≥470 msec for females.
19. Abnormal renal function, including serum or plasma creatinine > ULN or glomerular filtration rate (eGFR; using CKD-Epi equation) <60 mL/min.
20. Donation or loss of blood over 500 mL within 3 months prior to screening.
21. Administration of any blood product within 3 months prior to screening.
22. History of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink=10 grams of alcohol) and/or drug abuse within one year of randomization; positive test result for drugs of abuse or alcohol breath test at screening.
23. Subjects under judicial supervision, guardianship, or curatorship.

Medical or social conditions that would potentially interfere with the subject’s ability to comply with the study visit schedule or the study assessments.

Measurements of HBV genotype and viral markers

Plasma HBV DNA was quantitatively assessed at Q2 Solutions (Singapore) using the COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0 (Roche Diagnostics) with an LLOQ of 20 IU/mL at all sites other than China. For the patients in the sites from China, plasma HBV DNA was quantitatively assessed at Q2 Solutions (China) by a Real-Time PCR assay (Roche) using the COBAS® HBV kit with a LLOQ of 10 IU/mL. Blood samples for HBV genotype determination were collected at baseline. For the NUC-suppressed patients in Cohort A, HBV genotype was determined at DDL Diagnostic Laboratory by HBV RNA sequencing, and for the treatment-naïve patients in Cohorts B and C, HBV genotype based on HBV DNA was determined at Q2 Solutions using the INNO-LiPA® HBV genotyping assay (Fujirebio). Serum HbcAg was quantitatively assessed at DDL Diagnostic Laboratory (for non-Chinese sites) and KingMed Centre for Clinical Lab (for China) using the Lumipulse® G HbcAg assay (Fujirebio). Samples with an HbcAg value above the upper limit of quantification (7-0 log10 U/mL) were retested after a 1:100 dilution, therefore expanding the quantification range up to 9-0 log10 U/mL. Quantitative and/or qualitative serum levels of HBsAg, anti-HBs, HBeAg, and anti-HBe were assessed at Q2 Solutions (Asia Pacific) using the respective Elecsys® assays as described by the manufacturer (Roche Diagnostics): HBsAg II, HBsAg II quant II, Anti-HBs II, HBeAg, Anti-HBe. Serum HBeAg was qualitatively assessed at Q2 Solutions (Asia Pacific) using the Elecys HBeAg assay with a cutoff index=1. Serum anti-HBc was qualitatively assessed at Q2 Solutions (Asia Pacific) (for non-Chinese sites) or Q2 Solutions (for China) using the Elecsys® Anti-HBc II assay.