**Official Title:** A Randomized, Placebo-controlled,Observer-blinded Study, to Evaluate Safety,Tolerability, Pharmacokinetics and Pharmacodynamics of RO7239958 in Healthy Volunteers and Patients With Chronic Hepatitis B Virus Infection

**NCT Number:** NCT03762681

**Document Date:** Protocol Version 4: 18-February-2020

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED STUDY, TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7239958 IN HEALTHY VOLUNTEERS AND PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION** |
| **PROTOCOL NUMBER:** | NP40520 |
| **VERSION:** | 4 |
| **EUDRACT NUMBER:** | 2018-003530-32 |
| **TEST PRODUCT:** | RO7239958 |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | Version 1: 01 October 2018 |
| **DATE AMENDED:** | Version 2: 08 February 2019<br>Version 3: *24 April 2019*<br>*Version 4: See electronic stamp below* |

## FINAL PROTOCOL APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 18-Feb-2020 17:42:59 | Company Signatory | [redacted] |

## PROTOCOL ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED STUDY, TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7239958 IN HEALTHY VOLUNTEERS AND PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION** |
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| **TEST PRODUCT:** | RO7239958 |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**I agree to conduct the study in accordance with the current protocol.**

_____

Principal Investigator's Name (print)

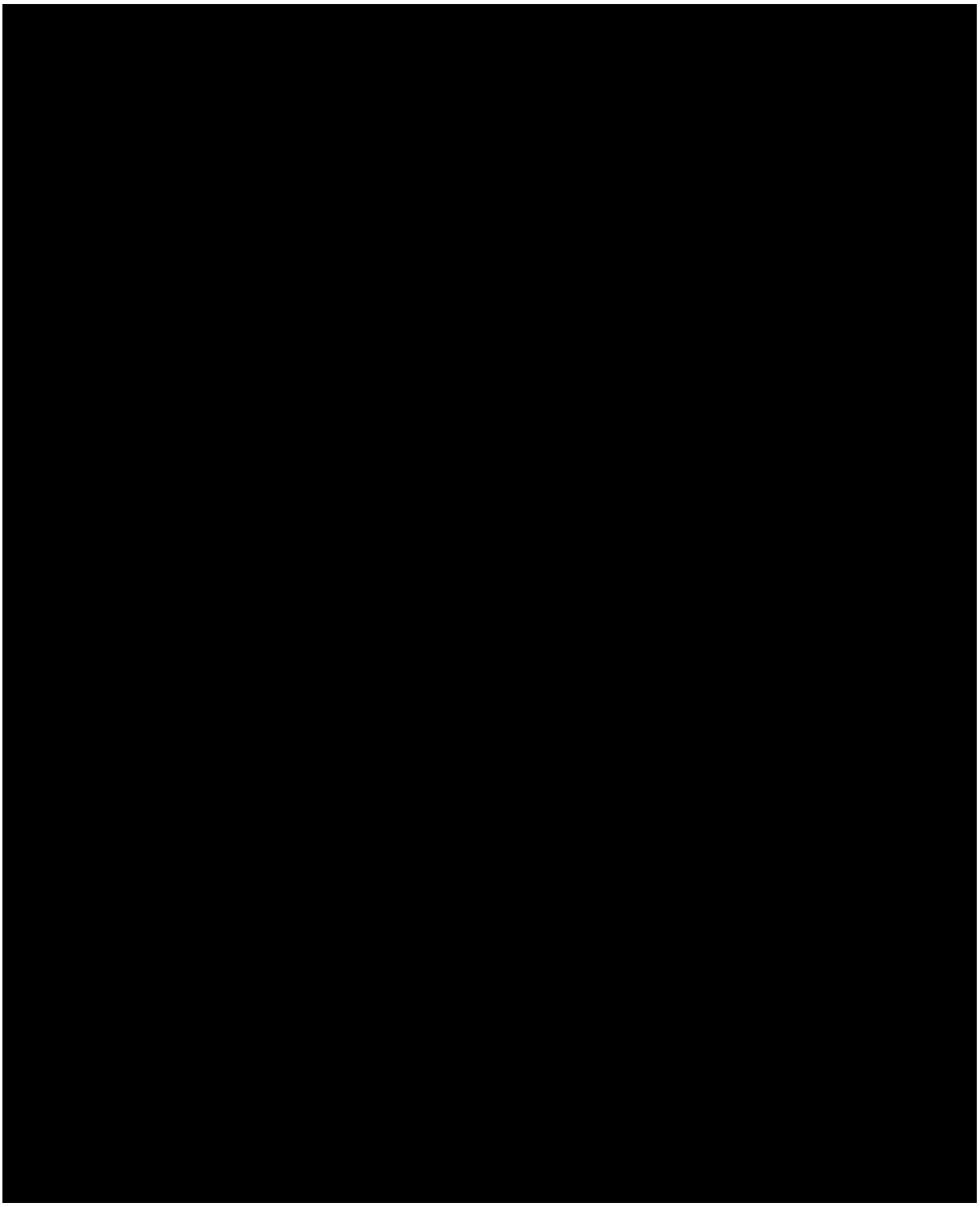
_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

## PROTOCOL AMENDMENT, VERSION 4:

## RATIONALE



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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| **ADA** | Anti-drug antibody |
| **AE** | Adverse event |
| **ALT** | Alanine aminotransferase |
| **aPTT** | Activated partial thromboplastin time |
| **AST** | Aspartate aminotransferase |
| **AUC** | Area under the curve |
| **BP** | Blood pressure |
| **ccc DNA** | Covalently closed circular DNA |
| **CL** | Clearance |
| **CL/F** | Apparent clearance |
| **CLU** | Clusterin |
| **CMC** | Chemistry manufacturing and control |
| **CNS** | Central nervous system |
| **CRO** | Contract research organization |
| **CSAP** | Clinical statistical analysis plan |
| **CSR** | Clinical study report |
| **CTCAE** | Common terminology criteria for adverse events |
| **CTD** | Common technical document |
| **CYS-C** | Cystatin-C |
| **DDI** | Drug-drug interaction |
| **DILI** | Drug-induced liver injury |
| **DLAE** | Dose-limiting adverse event |
| **DNA** | Deoxyribonucleic acid |
| **DRF** | Dose range finding |
| **EC** | Ethics Committee |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic case report form |
| **EDC** | Electronic data capture |
| **ESF** | Eligibility screening form |
| **EU** | European Commission |
| [redacted] | [redacted] |
| **FDA** | Food and Drug Administration |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| **GGT** | Gamma-glutamyl transferase |
| **GLP** | Good Laboratory Practice |

| | |
|---|---|
| **HBcAb** | Total hepatitis B core antibody |
| **HBeAg** | Hepatitis B envelope antigen |
| **HBsAg** | Hepatitis B surface antigen |
| **HCV** | Hepatitis C Virus |
| **HED** | Human equivalent dose |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HIV** | Human immunodeficiency virus |
| **IB** | Investigator's Brochure |
| **ICH** | International Conference on Harmonisation |
| **IFN** | Interferon |
| **IEC** | Independent Ethics Committee |
| **IMC** | Internal Monitoring Committee |
| **IMP** | Investigational medicinal product |
| **IND** | Investigational New Drug (application) |
| **INR** | International normalized ratio |
| **IRB** | Institutional Review Board |
| **IRF** | Independent review facility |
| **IRC** | Independent Review Committee |
| **ISR** | Injection Site Reaction |
| **IUD** | Intrauterine device |
| **IxRS** | Interactive (voice/web) response system |
| **KIM-1** | Kidney injury molecule-1 |
| **LDH** | Lactate dehydrogenase |
| **LLQ** | Lower Limit of Quantification |
| **LNA** | Locked nucleic acid |
| **LPLV** | Last participant, last visit |
| **MAD** | Multiple-ascending doses |
| **MD** | Multiple doses |
| **NAG** | N-acetyl-beta-D-glucosamin*i*dase |
| **NCI** | National Cancer Institute |
| **NGAL** | Neutrophil gelatinase-associated lipocalin |
| **NHP** | Non-human primate |
| **NOAEL** | No-observed-adverse-effect level |
| **NSAESI** | Non-serious adverse event of special interest |
| **NUC** | Nucleoside/nucleotide analogues |
| **OTC** | Over-the-counter |
| **OPN** | Osteopontin |
| [redacted] | [redacted] |

| | |
|---|---|
| [redacted] | [redacted] |
| **PD** | Pharmacodynamic |
| **PK** | Pharmacokinetic |
| **PT** | Prothrombin time |
| **QRS** | QRS complex |
| **QT** | QT interval |
| **QTc** | QT corrected for heart rate |
| **QTcF** | QT corrected for heart rate using the Fridericia's correction factor |
| **RBR** | Research biosample repository |
| **RNA** | Ribonucleic acid |
| **RR** | RR interval |
| [redacted] | [redacted] |
| **SAD** | Single-ascending dose |
| **SAE** | Serious adverse event |
| **SD** | Single dose |
| **SoA** | Schedule of activities |
| **SOP** | Standard operating procedure |
| **SPA** | Statistical Programmer |
| **SSO** | Single stranded oligonucleotide |
| **SUSAR** | Suspected unexpected serious adverse reaction |
| **TQT** | Thorough QT |
| **ULN** | Upper limit of normal |
| **US** | United States |
| **V** | Volume |
| **VAS** | Visual analogue scale |
| **V/F** | Apparent volume of distribution |
| **WBC** | White blood cell |

# 1. PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **PROTOCOL TITLE:** | **A RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED STUDY, TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7239958 IN HEALTHY VOLUNTEERS AND PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION** |
| **SHORT TITLE** | **SAD/ DRF Study to Evaluate Safety, PK, PD of RO7239958 in Healthy Volunteers and Patients with Chronic Hepatitis B** |
| **PROTOCOL NUMBER:** | NP40520 |
| **VERSION:** | 4 |
| **TEST PRODUCT:** | RO7239958 |
| **PHASE:** | I |

**RATIONALE**

This is the first study with RO7239958 in humans, designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending doses in healthy participants and participants diagnosed with chronic hepatitis B (CHB). Data collected in this study will be critical to define optimal doses and dosing regimens to be studied in Phase II clinical trials in CHB patients.

[redacted]

**OBJECTIVES AND ENDPOINTS**

| | Objectives | Endpoints |
|---|---|---|
| **Primary** | | |
| **All parts** | **Safety** | |
| | • To assess the safety and tolerability of RO7239958 compared to placebo after single subcutaneous (SC) ascending doses in healthy participants and multiple SC ascending doses in CHB patients on stable NUC therapy. | • Incidence, severity, and causal relationship of adverse events (AEs).<br>• Changes in vital signs, physical findings and electrocardiogram (ECG) findings, and clinical laboratory results during and following RO7239958 administration.<br>• Incidence of injection site reactions (ISRs). |
| **Secondary** | | |
| **All Parts** | **Pharmacokinetics (PK)** | |
| | • To assess plasma and urine pharmacokinetics (PK) of RO7239958 after single ascending SC doses in healthy participants and after multiple SC doses in CHB patients on stable NUC therapy. | • Plasma and urine PK parameters determined using non-compartmental analysis (NCA).<br>• The following plasma PK parameters will be calculated:<br>o Time to maximum concentration ($T_{max}$).<br>o Maximum plasma concentration observed ($C_{max}$).<br>o Area under the curve (AUC) for various time intervals post-dose.<br>• Additional PK parameters may be calculated in plasma (e.g., apparent clearance [CL/F], terminal half-life [$t_{1/2}$], K [elimination rate constant]).<br>• Additional urine parameters may be calculated, e.g., cumulative amount of drug excreted in urine over defined time periods ($A_e$). |
| **Part 2a and 2b** | **Pharmacodynamics (PD)**<br>• To assess the antiviral activity of RO7239958 after multiple ascending SC doses in CHB patients on stable NUC therapy. | • Time course profile of HBsAg levels and maximum decline from baseline.<br>• Time course profile of hepatitis B surface antibody (anti-HBs) levels. |

**OBJECTIVES AND ENDPOINTS (CONT.)**

| | | |
|---|---|---|
| **Part 2a and 2b (cont.)** | **Pharmacodynamics (PD) (cont.)** | • In participants that are HBeAg positive at study entry, incidence of HBeAg loss and incidence of hepatitis B e antibody (anti-HBe) seroconversion.<br>• Participants will have a suppressed HBV DNA at study entry and will be monitored to ensure that HBV DNA suppression is maintained during the study. |

**OVERALL DESIGN**

The study will be conducted in two parts, of which Part 1 will be in healthy participants and Part 2 will be in CHB patients. Both parts of the study are randomized and Observer-blinded.

Part 1 will evaluate the safety, tolerability and PK of RO7239958 following SC administration of single ascending doses in healthy participants. Part 2 will evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of multiple SC doses of RO7239958 in CHB patients on stable NUC therapy, and comprises two subparts, Part 2a and Part 2b. Part 2 is a dose range finding study (DRF).

**Study Design**

**Part 1** – In Part 1, at least four cohorts will receive a single dose of RO7239958 or placebo. An optional cohort with participants receiving RO7239958 or placebo may be included, based on the need for further safety or PK data. Ten healthy participants, eight receiving RO7239958 and two receiving placebo, will be enrolled in each cohort using a 4:1 randomization scheme. [redacted] Each cohort will implement sentinel dosing to monitor acute reactions over 24 hours post-dosing: Two participants will be dosed on Day 1, and at least one of the two participants will have received RO7239958; the remaining eight participants shall be dosed the following day (i.e., after 24 hours) following satisfactory clinical safety review of the first two participants by the Investigator. For each cohort, safety will be monitored for 28 days (21 days for safety assessment plus 7 days of clinical safety observation, before escalating to the next cohort. A dose escalation meeting will take place prior to starting the next cohort. In all participants, safety will be monitored for a total of 12 weeks post-dosing.

**Part 2a** – In Part 2a, CHB patients will be enrolled into one of two arms (Arms 1 and 2), which will run in parallel. Each arm will enroll seven participants using a 6:1 randomization scheme. To ensure balance between arms, enrolment of HBeAg positive participants will be capped. The Sponsor will communicate to the investigators the capping level arm prior to respective start of enrollment. Participants of each arm will receive RO7239958 or placebo over 4 weeks. [redacted]

[redacted]. *Two* additional, parallel arms (Arms 3 *and 4*) will open after Arms 1 and 2 have enrolled and followed-up for at least 28 days a sufficient number of participants to provide the safety and PK/PD information required to further inform dose and regimen optimization. *An optional Arm 5 will open if further doses or regimens need to be explored based on data from Arms 3 and 4.* A data review meeting will also take place before opening Arms 3 *and 4 (and potentially optional Arm 5)*. Decision on dose levels and regimens for Arms 3 *and 4* will be based on the safety, PK, and PD data from Arms 1 and 2 and all available safety and PK data from Part 1. If efficacious dose levels cannot be reliably predicted from PK/PD modeling and Part 1 data, the doses administered in Part 2a will be within the range demonstrated to be safe and well tolerated in Part 1. [redacted] In all patients, safety will be monitored for a total of 12 weeks post-dosing.

**Part 2b (optional)** – The two additional arms (Arms 6 and 7) of Part 2b will open if further doses or regimens need to be explored based on the data from Part 2a, or a dose or regimen from Part 2a needs to be optimized and additional data evaluated. There may be inclusion of participants who are not treated with NUCs, or inclusion of a larger number of participants of a given HBeAg status. Each arm in Part 2b will comprise seven participants randomized to RO7239958 or placebo using a 6:1 randomization scheme. [redacted] In all patients, safety will be monitored for a total of 12 weeks post-dosing.

**Treatment Groups and Duration**

The IMPs are RO7239958 (active) and placebo. The dose given will be in milligrams per kilogram of body weight and administered SC.

Part 1: The total duration of the study for each participant will be up to 16 weeks, divided as follows:

- Screening: Up to 28 days
- In clinic period: Days -1 to 3.
- Treatment Period: Day 1
- Safety follow-up: up to at least 84 days after the dose of RO7239958 or placebo.

Part 2a: The total duration of the study for each participant will be up to 20 weeks divided as follows:

- Screening: Up to 28 days.
- In clinic period (optional): Days 1 to 3 and Days 29 to 30 (overnight stay optional).
- Treatment Period: Day 1 to 29.
- Safety follow-up: up to 84 days after the last dose of RO7239958 or placebo.

Part 2b: The total duration of the study for each participant will be up to 28 weeks divided as follows:

- Screening: Up to 28 days.
- In clinic period (optional): Days 1 to 3 and Days 29 to 30 (overnight stay optional).
- Treatment Period: Day 1 up to Day 85. Safety follow-up: up to 84 days after last dose of RO7239958 or placebo.

**End of Study**

The end of the study is defined as the date when the last participant last visit (LPLV) occurs (includes the safety and follow-up visit), or the date at which the last data point from the last participant required for statistical analysis is received, whichever is the later date, unless the participant was prematurely discontinued.

**Data Monitoring: No**

No Internal Data Monitoring Committee is planned for this study. A communication strategy will detail the data review and decision making prior to dose-escalation and initiation of study arms.

## PARTICIPANT POPULATION

Participants will be healthy female and male volunteers and patients diagnosed with chronic HBV infection who fulfill all of the given inclusion criteria.

## INCLUSION/ EXCLUSION CRITERIA

### Inclusion Criteria:

Participants are eligible to be included in the study only if all of the following criteria apply:

**ALL STUDY PARTS**

**Informed Consent:**

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.

**Age:**

2. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

**Weight:**

3. Body weight of at least 45 kg and maximally 150 kg, and BMI within the range of 18 to 32 $kg/m^2$ (inclusive).

**Sex:**

4. Male and female participants:

   The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence to meet enrolment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

a) Female participants: Should be women of non-childbearing potential (WONCBP).

b) Male participants: During the treatment period and for at least 105 days after the last dose of RO7239958 or placebo, agreement to:

i. With partners who are women of childbearing potential (WOCBP): Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year.

ii. With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.

iii. Refrain from donating sperm for at least 105 days after last dose of RO7239958 or placebo.

**PART 1 (SAD HV) ONLY**

**Type of participants:**

1. Healthy, as judged by the Investigator. Healthy status will be defined as the absence of evidence of any active or chronic disease following a detailed medical and surgical history, concomitant drug use (including hormonal supplements), a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology, and urinalysis.

**Others Inclusions:**

2. Non-smoker (nor tobacco containing products) for at least 90 days prior to dosing on Day 1, and agrees to remain non-smoker during the study.

**PART 2 (CHB) ONLY**

**Type of Participants and Disease Characteristics**

1. Positive serum HBsAg status for > 6 months prior to screening.
2. Serum HBsAg level ≥ 250 IU/mL at screening.
3. On stable entecavir or tenofovir (alone or in combination) treatment, and having received the same NUC in the 3 months prior to randomisation, and expected to remain on the same NUC for the duration of study participation.
4. HBV DNA below the lower limit of quantification (LLQ < *20 IU/mL*) for ≥ 6 months prior to screening by local testing, and confirmed at screening.
5. Screening laboratory values (including hematology, chemistry, urinalysis) within normal ranges, or judged to be not clinically significant by the Investigator and Medical Monitor, and:

a) Screening alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 × upper limit of normal (ULN), confirmed between Day -7 to Day -4.

b) Screening *gamma*-glutamyl transferase (GGT) *≤ ULN (Note: GGT ≤ 1.5 x ULN is acceptable if considered not clinically significant)* and alkaline phosphatase (ALP) ≤ ULN, and normal values of prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). *PT and/or aPTT > ULN is acceptable if considered not clinically significant and INR and other parameters of liver function are within normal limits and there are no current and historical concerns. Whenever the Screening tests are repeated, the mean of the repeat values will be considered.*

c) Screening total bilirubin of ≤ ULN (Note: isolated bilirubin ≤ 1.5 × ULN is acceptable for patients with Gilbert's syndrome.

d) Screening neutrophil count > 1500 cells/mm$^3$ (Note: > 1200 cells/mm$^3$ is acceptable in participants of black race).

e) Screening hemoglobin > 11 g/dL in females and > 12.5 g/dL in males.

f) Screening platelet count ≥ 150,000 cells/$\mu$L.

6. No past or current diagnosis of cirrhosis. Transient elastography at screening showing a kPa value consistent with a degree of liver fibrosis not higher than F3. By FibroScan, a cut-off of < 8.5 kPa in the fasted status (last meal ≥ 3 hours prior) is recommended.

**Exclusion Criteria**

Participants are excluded from the study if any of the following criteria apply:

**ALL STUDY PARTS**

**Medical Conditions**

1. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within three months prior to screening.

**PART 1 (SAD HV) ONLY:**

**Medical Conditions**

1. History or presence of significant (as judged by the investigator) cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological disorders, or diagnosed central or peripheral neurological disease, capable of significantly altering the absorption, metabolism, or elimination of drugs, or constituting a risk when taking the study treatment, or of interfering with the interpretation of the data.
2. Screening ECG showing clinically relevant abnormalities (including arrhythmias or marked QT abnormalities [QTcF < 300 msec or > 450 msec], or other cardiac abnormalities that are considered clinically significant by the Investigator. Known risk factors for Torsade de Pointes (e.g., hypokalemia, heart failure), or a personal or family history of congenital long QT syndrome.
3. Abnormal blood pressure: supine systolic blood pressure (SBP) <90 mmHg or >140mmHg or diastolic blood pressure (DBP) <45mmHg or >90mmHg at the time of screening and at Day -1, confirmed by two consecutive triplicate measurements, properly measured with well-maintained equipment.
4. History of lymphoma, leukaemia, or malignancy within the past five years, except for squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for three years.
5. History or presence of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
6. ALT ≥1.5 × ULN at screening and at Day −1.
7. Any clinically significant out of range findings in other laboratory test results or any other clinically significant (as judged by the Investigator) abnormalities in the physical examination at screening and on Day -1.

8. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.
9. Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration, or exposure to foods or environmental agents.
10. Any major illness within one month preceding the screening visit, or any febrile illness within the two weeks preceding the screening visit.
11. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.

**Prior/Concomitant Therapy**

12. Used or intend to use of over-the-counter (OTC) or prescription medication (including herbal and traditional remedies) before study start and during the study as described in list of prohibited medications.
13. Live vaccine(s) within 28 days of screening, or plans to receive live vaccines during the study or within 28 days of the last dose.
14. Likely to need concomitant medication during the study period.
15. Treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within three months or five half-lives (whichever is longer) prior to dosing.

**Prior/Concurrent Clinical Study Experience**

16. Currently enrolled in or have participated within the last 90 days or five times the half-life of the investigational drug (whichever is longer) from signing of consent in this or any other clinical study involving an investigational product or in any other type of medical research.
17. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

**Diagnostic Assessments**

18. Known positive for hepatitis B surface antigen (HBsAg), or hepatitis B core total antibody [anti-HBc]), or hepatitis C virus (HCV) antibody test result at screening.
19. Known positive for human immunodeficiency virus (HIV) infection and/or positive for HIV infection at screening.
20. Positive pre-study drugs and alcohol screen.

**Other Exclusions**

21. History or evidence of alcohol abuse (consumption of more than two standard drinks per day on average; one standard drink equals 10 grams of alcohol), and/or drug abuse within one year of screening.
22. Any suspicion or history of substance abuse or dependence.
23. Dietary restrictions that would prohibit the consumption of standardised meal.
24. Healthy participants under judicial supervision, guardianship or curatorship.

**PART 2 (CHB) ONLY**

**Medical Conditions**

1. History or presence of significant (as judged by the Investigator) cardiovascular (including poorly controlled blood hypertension), respiratory, hepatic, renal, gastrointestinal, endocrine, haematological disorders, or diagnosed central or peripheral neurological disease, capable of altering the absorption, metabolism, or elimination of drugs, or constituting a risk when taking the study treatment, or of interfering with the interpretation of the data.
2. History or presence of bridging fibrosis or cirrhosis or decompensated liver disease.

3. History or presence of a medical condition associated with liver disease other than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, non-alcoholic steatohepatitis). Other known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. History of or suspicion of hepatocellular carcinoma or alpha fetoprotein (AFP) ≥13 ng/mL at screening.
5. History of lymphoma, leukaemia, or malignancy within the past five years, except for squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for three years.
6. History of having received (in the last six months) or currently receiving any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic corticosteroids).
7. History of organ transplantation.
8. Any major illness within one month preceding the screening visit, or any febrile illness within the two weeks preceding randomisation.
9. Clinically significant (multiple or severe) drug allergies, or intolerance to topical corticosteroids, or history of severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
10. Estimated glomerular filtration rate (eGFR) < 70 mL/min/1.73m$^2$ (CKD-epi equation).
11. Confirmed QT interval corrected using Fridericia's formula (QTcF) >450 ms. Patients with correctable risk factors for prolonged QT (e.g., electrolyte abnormalities) can be re-assessed after correction of the risk factor(s).

**Prior/Concomitant Therapy**

12. Live vaccine(s) within 28 days of screening, or plans to receive live vaccines during the study or within 28 days of the last dose.
13. Expected to need any other systemic antiviral therapy at any time during participation in the study, with the exception of current NUC treatment and / or oral/ topical therapy for Herpes Simplex Virus (HSV).

**Prior/Concurrent Clinical Study Experience**

14. Currently enrolled in *(i.e., the end of study visit has not been performed)* or have *received investigational treatment* within the last 90 days or five times the half-life of the investigational drug (whichever is longer) from signing of consent in this or any other clinical study involving an investigational product or in any other type of medical research, *or the total volume of all blood samples provided during the follow-up visits of the former clinical trial exceeds 100 mL.*

**Diagnostic Assessments**

15. Positive hepatitis C antibody at screening.
16. Known positive for human immunodeficiency virus (HIV) infection and/or positive for HIV infection at screening.
17. Positive pre-study treatment/alcohol screen.

**Other Exclusions**

18. History or evidence of alcohol abuse (consumption of more than two standard drinks per day on average; one standard drink equals 10 grams of alcohol) and/or drug abuse within one year of screening; positive test result for drugs of abuse at screening.
19. Patients under judicial supervision, guardianship or curatorship.

20. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator contraindicates the participation in the study.

**NUMBER OF PARTICIPANTS**

In Part 1, approximately 40-50 participants will be enrolled in four to five cohorts of 10 participants each (eight to receive RO7239958 and two to receive placebo). In Part 2, approximately *28*-49 CHB patients will be enrolled in *four* to seven arms of seven participants each (six to receive RO7239958 and one to receive placebo). Part 2a will include approximately *28*-35 participants in *four to* five arms. Part 2b will include approximately 14 participants in two arms.

**CONCOMITANT MEDICATIONS**

All medications (prescription and over-the-counter [OTC]) taken within 30 days of study screening until the follow-up visit will be recorded in the electronic case report form (eCRF).

For all parts of the study, paracetamol/acetaminophen, at doses of up to 1 g/day, is permitted for use any time during the study. Hormone replacement therapy (HRT) is allowed during the study.

As a general rule, no prescribed concomitant medication will be prohibited for Part 2 of the study. All concomitant medications (except standard NUC therapy) need to be discussed with the Medical Monitor prior to enrolling study participants.

Participants must abstain from taking nonprescription drugs (including OTC medication, vitamins, dietary, herbal supplements, protein powders or fish oils) within 7 days before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and the Medical Monitor, the medication or the vitamins, dietary, herbal supplements, protein powders or fish oils are necessary and will not interfere with the study. Some supplements, herbal and traditional remedies, and OTC drugs may affect laboratory values. Abnormal values may lead to screening failures or withdrawal from the study. As such, participants should be carefully questioned regarding such substances at screening, and advised to refrain from them, if deemed possible. Pre-existing medications and medications that may be newly needed during participation in the study should be discussed with the Medical Monitor.

For all parts of the study, there are restrictions that should be maintained:

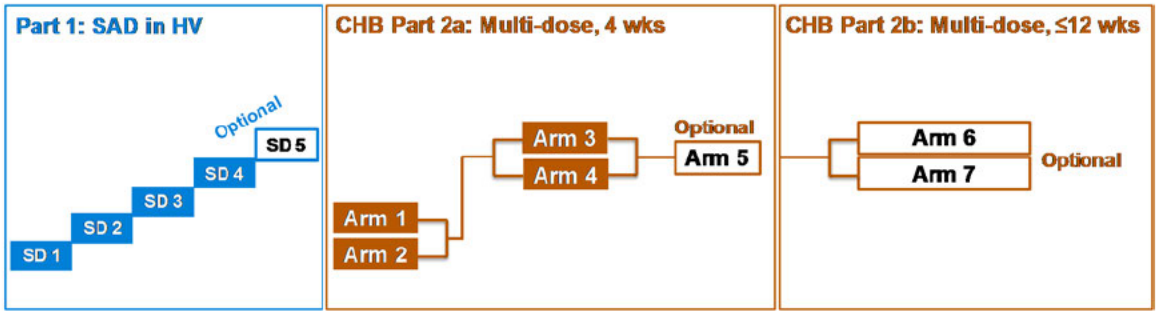
- Live vaccine(s) can be given provided this is done at least more than 28 days ahead of screening. The participant should not receive live vaccines during the study or within 28 days of the last dose.
- In the event that a participant requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor.

For CHB patients, NUC-related food restrictions may apply.

## 1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

**Figure 1 Overview of Study Design**




[redacted]

## 1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 to Table 6.

## Table 1 Schedule of Activities – Main Table, Part 1 (SAD in HV)

| Period | Screening | | | | Period 1 | | | | | Follow Up Visit | Follow Up Visit | Follow Up Visit | Follow Up Visit | Early Termination |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Day -28 to Day -2 | Day -1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 8 | Day 15 | Day 22 | Day 43 | Day 85[e)] | NA |
| Time relative (h) | *** | *** | 0 | 24 | 48 | 72 | 96 | 120 | 168 | 336 | 672 | 1008 | 2016 | |
| Visit Window (days) | | | | | | | | | | ±1 | ±2 | ±7 | ±7 | |
| In-clinic Period | | | | | | | | | | | | | | |
| Ambulatory Visit | X | | | | | X | X | X | X | X | X | X | X | X |
| Informed Consent | X | | | | | | | | | | | | | |
| Eligibility | X | X | | | | | | | | | | | | |
| Randomisation | | | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | |
| Anthropometric Measurements | X | | | | | | | | | | | | | |
| Physical Examination[a)] | X | X | | | | | | | X | X | X | X | X | X |
| ECG-12 lead[b)] | X | X | 5 | X | | | | | X | X | X | X | X | X |
| Vital Signs | X | X | 5 | X | X | X | X | X | X | X | X | X | X | X |
| Substance Use[f)] | X | X | | | | | | | | | | | | |
| Serology | X | | | | | | | | | | | | | |
| Blood Chemistry | X | X | | X | | | | | X | X | X | X | X | X |
| Hematology | X | X | | X | | | | | X | X | X | X | X | X |
| Urinalysis | X | X | | X | | | | | X | X | X | X | X | X |
| Coagulation | X | X | | X | | | | | X | X | X | X | X | X |
| Anti-Drug Antibody[c)] | | | X | | | | | | | | X | | X | |
| Pregnancy test | X | X | | | | | | | | | | X | X | X |
| | | | | | | | | | | | | | | |
| Blood PK Sample | | | 12 | 3 | X | X | X | X | X | | X | | | X[g] |
| Urine PK Sample | | | 4 | | | | | | | | | | | |
| Administration of Study Medication | | | X | | | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Previous and Concomitant Treatments | X | X | X | X | X | X | X | X | X | X | X | X | X | |

## Table 1 Schedule of Activities – Main Table, Part 1 (SAD in HV) (cont.)

a) A complete physical examination is required at screening. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator. Height and weight will be recorded at the Screening visit only. BMI will be calculated at Screening.

b) Twelve-lead ECGs will be obtained in triplicate (three consecutive interpretable 12-lead ECGs in less than 5 minutes) after the participant has been in a supine position for at least 10 minutes, and prior to dosing when applicable.

c) Anti-drug antibody (ADA) samples to be taken pre-dose.

[redacted]

e) If necessary, participants may be asked to return for additional follow-up visits.

f) Includes alcohol testing.

g) PK sample at early termination visit is optional.

## Table 2 Schedule of Assessments – Detailed Table, Part 1 (SAD in HV)

| Study Period | Day | Scheduled Time (h) | Vital Signs | ECG-12 lead | Blood PK Sample | Urine PK Sample[a] | ADA Sample |
|---|---|---|---|---|---|---|---|
| Screening | Day -28 to Day -2 | | X | X | | | |
| | Day -1 | | X | X | | | |
| | Day 1 | Pre-dose | X | X | X | | X |
| | | 0 | | | | X | |
| | | 0.25 | | | X | | |
| | | 0.5 | | | X | | |
| | | 1 | X | X | X | | |
| | | 1.5 | | | X | | |
| | | 2 | | | X | | |
| | | 3 | | | X | | |
| | | 4 | X | X | X | X | |
| Period 1 | | 6 | | | X | | |
| | | 8 | X | X | X | X | |
| | | 12 | X | X | X | X | |
| | | 18 | | | X | | |
| | | 24 | X | X | X | | |
| | Day 2 | 30 | | | X | | |
| | | 36 | | | X | | |
| | Day 3 | 48 | X | | X | | |
| | Day 4 | 72 | X | | X | | |
| | Day 5 | 96 | X | | X | | |
| | Day 6 | 120 | X | | X | | |
| | Day 8 | 168 | X | X | X | | |
| Follow Up Visit | Day 15 | | X | X | | | |
| | Day 22 | | X | X | X | | X |
| | Day 43 | | X | X | | | |
| | Day 85 | | X | X | | | X |
| Early termination | Anytime | | X | X | X | | |

a) Urine collection periods [0-4], [4-8], [8-12] and [12-24] hours post-dose. Subject should void bladder immediately before dosing. Within a given collection period, all urine voids should be collected and pooled; the sample should be taken from the pooled urine for the respective collection period.

## Table 3 Schedule of Assessments – Main Table, Part 2a and Part 2b (CHB [redacted], 5 weeks)

| Period | Screening | | | | | | | | | Discontinuation | Rebound[k)] | Follow Up Visit | Follow Up Visit | Follow Up Visit | Follow Up Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | Week 2 | Week 3 | Week 4 | Week 5 | | | | | | | |
| Day | Day -29 to Day 2 | Day -7 to -4 | Day 1 | Day 2 | Day 8 | Day 15 | Day 22 | Day 29 | Day 30 | | | 14 days after last dose | 28 days after last dose | 56 days after last dose | 84 days after last dose |
| Time Relative (h) | *** | *** | 0 | 24 | 168 | 336 | 504 | 672 | 696 | *** | | | | | |
| Visit Window (days)[a)] | | | | | | | | | | | | ±3 | ±3 | ±7 | ±7 |
| In-clinic Period[b)] | | | | | | | | | | | | | | | |
| Ambulatory Visit | X | X | | | X | X | X | | | X | | X | X | X | X |
| Informed Consent | X | | | | | | | | | | | | | | |
| Eligibility | X | X | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Elastography | X | | | | | | | | | | | | | | |
| Physical Examination | X[c)] | | X | | | X | | X[c)] | | | | X | X[c)] | X[c)] | X[c)] |
| ECG-12 lead[d, e)] | X | | 4 | | X | X | X | 4 | | X | | X | X | X | X |
| Vital Signs[e)] | X | | 4 | X | X | X | X | 4 | | X | | X | X | X | X |
| Substance Use[l)] | X | X | | | | | | | | | | | | | |
| Serology | X | | | | | | | | | | | | | | |
| Blood Chemistry[e)] | X | X | X | X | X | X | X | X | | X | | X | X | X | X |
| Hematology[e)] | X | | X | X | X | X | X | X | | X | | X | X | X | X |
| Urinalysis[e)] | X | X | | X | X | X | X | X | | X | | X | X | X | X |
| Coagulation[e)] | X | | X | X | X | X | X | X | | X | | X | X | X | X |
| Anti-Drug Antibody[f)] | | | X | | | | | X | | | | | X | | |
| Urine Injury Biomarkers[e)] | | | X | | X | | | X | | X | | X | X | X | X |
| Blood Liver Injury Biomarkers[e)] | | | X | | X | | | X | | X | | X | X | X | X |
| Pregnancy Test[e)] | X | | X | | | | | X | | X | | | X | X | X |
| Alpha Fetoprotein | X | | | | | | | | | | | | | | |

## Table 3 Schedule of Assessments – Main Table, Part 2a and Part 2b (CHB [redacted], 5 weeks) (cont.)

| Period | Screening | | | | | | | | | Discontinuation | Rebound[k)] | Follow Up Visit | Follow Up Visit | Follow Up Visit | Follow Up Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | Week 2 | Week 3 | Week 4 | Week 5 | | | | | | | |
| Day | Day -29 to Day -2 | Day -7 to -4 | Day 1 | Day 2 | Day 8 | Day 15 | Day 22 | Day 29 | Day 30 | | | 14 days after last dose | 28 days after last dose | 56 days after last dose | 84 days after last dose |
| Time Relative (h) | *** | *** | 0 | 24 | 168 | 336 | 504 | 672 | 696 | *** | | | | | |
| Visit Window (days)[a)] | | | | | | | | | | | | ±3 | ±3 | ±7 | ±7 |
| In-clinic Period[b)] | | | | | | | | | | | | | | | |
| Ambulatory Visit | X | X | | | X | X | X | | | X | | X | X | X | X |
| Blood PK Sample [redacted] | | | 7 | X | 2 | 2 | 2 | 7 | X | X | | X | X | X | X |
| Blood PK Sample [redacted] | | | 7 | X | X | 2 | X | 7 | X | X | | X | X | X | X |
| Blood PK Sample [redacted] | | | 7 | X | X | X | X | 7 | X | X | | X | X | X | X |
| Urine PK Sample | | | 2 | | | | | 2 | | | | | | | |
| NUC PK | | | | | | | | | | | X | | | | |
| HBV DNA quant[e)] | X | | X | | | X | | X | | X | X | X | X | X | X |
| HBV serology[e,i)] | X | | X | | X | X | X | X | | X | | X | X | X | X |
| HBV RNA quant[e)] | | | X | X | X | X | | X | | X | | X | X | X | X |
| HBV core-related antigen[e)] | | | X | | X | X | | X | | X | | X | X | X | X |
| [redacted] | | | | | | | | | | | | | | | |
| HBV DNA Genotyping (Rebound) | | | | | | | | | | | X | | | | |
| HBV genotyping | | | X | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | | X | X | X | X |
| Previous and Concomitant Treatments | X | X | X | X | X | X | X | X | X | X | | X | X | X | X |

**Table 3 Schedule of Assessments – Main Table, Part 2a and Part 2b (CHB [redacted], 5 weeks) (cont.)**

a) All visits can be done ±3 days, if applicable, with the exception of the safety and follow-up visits 56 and 84 days after last dose (±7 days). The safety and follow-up visits in Table 3 will only apply to Part 2a (for Part 2b, see Table 5).

At home nurse visits: vital signs, AEs and previous and concurrent treatments will be assessed; Blood for PK may be collected as specified, and other laboratory specimens may be collected as specified in the SoA table. ECG may be performed if appropriate. If site is not participating in home nurse visit, this will be an outpatient visit in clinic.

b) Optional overnight stay in the clinic: On Day 1 as well as on Day 29 participants can either stay overnight in the clinic or can be discharged after completion of the 8 hours post-dose assessments and return the next morning for the subsequent assessments, at the Investigator's discretion.

c) Complete physical examination is required. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator. Height and weight will be recorded at the Screening visit only. BMI will be calculated at Screening.

d) Twelve-lead ECGs will be obtained in triplicate (three consecutive interpretable 12-lead ECGs in less than 5 minutes) after the participant has been in a supine position for at least 10 minutes.

e) Pre-dose (on days of study treatment administration). For ECG and VS as given in the Detailed Table for Part 2a.

f) ADA samples to be taken pre-dose (when applicable)

[redacted]

i) HBV serology will include HBsAg (quantitative), anti-HBs (quantitative), HBeAg (qualitative) and anti-HBeAb (qualitative).

[redacted]

k) In case of HBV DNA rebound an unscheduled confirmatory HBV DNA quantification sample should be taken, a sample for HBV DNA genotyping and a sample for NUC PK.

l) Includes alcohol testing.

## Table 4 Schedule of Assessments – Detailed Table, Part 2a and Part 2b (CHB [redacted], 5 weeks)

| Visit | Day | Scheduled Time (h) | Vital signs | ECG | PK Blood [redacted] | PK Blood [redacted] | PK Blood [redacted] | PK Urine[a] | ADA |
|---|---|---|---|---|---|---|---|---|---|
| Screening | Day -29 to -2 | | X | X | | | | | |
| Week 1 | Day 1 | Predose | X | X | X | X | X | | X |
| | | 0 | | | | | | X | |
| | | 0.5 | | | X | X | X | | |
| | | 1 | X | X | X | X | X | | |
| | | 2 | | | X | X | X | | |
| | | 4 | X | X | X | X | X | X | |
| | | 6 | | | X | X | X | | |
| | | 8 | X | X | X | X | X | | |
| | Day 2 | 24 | X | | X | X | X | | |
| Week 2 | Day 8 | Predose | X | X | X | X | X | | |
| | | 2 | | | X | | | | |
| Week 3 | Day 15 | Predose | X | X | X | X | X | | |
| | | 2 | | | X | X | | | |
| Week 4 | Day 22 | Predose | X | X | X | X | X | | |
| | | 2 | | | X | | | | |
| Week 5 | Day 29 | Predose | X | X | X | X | X | | X |
| | | 0 | | | | | | X | |
| | | 0.5 | | | X | X | X | | |
| | | 1 | X | X | X | X | X | | |
| | | 2 | | | X | X | X | | |
| | | 4 | X | X | X | X | X | X | |
| | | 6 | | | X | X | X | | |
| | | 8 | X | X | X | X | X | | |
| | Day 30 | 24 | | | X | X | X | | |
| Discontinuation | | | X | X | X | X | X | | |
| Follow up Visits | 14 days after last dose | | X | X | X | X | X | | |
| | 28 days after last dose | | X | X | X | X | X | | X |
| | 56 days after last dose | | X | X | X | X | X | | |
| | 84 days after last dose | | X | X | X | X | X | | |

a) Urine collection periods [0-4] and [4-8] hours post-dose. Patient should void bladder immediately before dosing. Within a given collection period, all urine voids should be collected and pooled; the sample should be taken from the pooled urine for the respective collection period.

## Table 5 Schedule of Assessments – Main Table, Part 2b (CHB [redacted] 12 weeks – as of Week 6)

| Period | | | | | | | | Discontinuation | Rebound[i)] | Follow Up Visit | Follow Up Visit | Follow Up Visit | Follow Up Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 6 [a)] | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 | | | | | | |
| Day | Day 36 | Day 43 | Day 50 | Day 57 | Day 64 | Day 71 | Day 78 | | | 14 days after last dose | 28 days after last dose | 56 days after last dose | 84 days after last dose |
| Time Relative (h) | 840 | 1008 | 1176 | 1344 | 1512 | 1680 | 1848 | | | | | | |
| Visit Window (days) | | | | | | | | | | ±3 | ±3 | ±7 | ±7 |
| Ambulatory Visit | X | X | X | X | X | X | X | | | X | X | X | X |
| Physical Examination | | X | | X [b)] | | X | | | | | | X | X |
| ECG 12 lead [c, d)] | | X | | X | | X | | X | | X | X | X | X |
| Vital Signs [d)] | | X | | X | | X | | X | | X | X | X | X |
| Blood Chemistry [d)] | | X | | X | | X | | X | | X | X | X | X |
| Hematology [d)] | | X | | X | | X | | X | | X | X | X | X |
| Urinalysis [d)] | | X | | X | | X | | X | | X | X | X | X |
| Coagulation [d)] | | X | | X | | X | | X | | X | X | X | X |
| Anti Drug Antibody [e)] | | X | | | | X | | | | | X | | |
| Urine Injury Biomarkers [d)] | | X | | X | | X | | X | | X | X | X | X |
| Blood Injury Biomarkers [d)] | | X | | X | | X | | X | | X | X | X | X |
| Pregnancy Test | | | | | | | | X | | | X | X | X |
| Blood PK Sample[redacted] | 2 | 2 | 2 | 2 | 2 | 2 | 2 | X | | X | X | X | X |
| Blood PK Sample[redacted] | | 2 | | 2 | | 2 | | X | | X | X | X | X |
| Blood PK Sample[redacted] | | | | 2 | | | | X | | X | X | X | X |
| Urine PK Sample | | | | 2 | | | | | | | | | |
| NUC PK | | | | | | | | | X | | | | |
| HBV DNA quant [d)] | | X | | X | | X | | X | X | X | X | X | X |
| HBV serology [d,g)] | | X | | X | | X | | X | | X | X | X | X |
| HBV RNA quant [d)] | | X | | X | | X | | X | | X | X | X | X |
| HBV core related antigen [d)] | | X | | X | | X | | X | | X | X | X | X |
| [redacted] | | | | | | | | | | | | | |
| HBV DNA Genotyping (Rebound) | | | | | | | | | X | | | | |
| [redacted] | | | | | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | | X | X | X | X |
| Previous and Concomitant Treatments | X | X | X | X | X | X | X | X | | X | X | X | X |

**Table 5 Schedule of Assessments – Main Table, Part 2b (CHB [redacted] 12 weeks – as of Week 6) (cont.)**

a) For the assessments of Weeks 1 to 5, see the Part 2a/ Part 2b (CHB, 5 Week) Main SoA table. All visits can be done ±3 days with the exception of the safety and follow-up visits on D134 and 182 (±7 days).

   At home nurse visits: vital signs, AEs and previous and concurrent treatments will be assessed; Blood for PK and other laboratory specimen may be collected as specified in the SoA table. ECG may be performed if appropriate. If site is not participating in home nurse visits, this will be an outpatient visit in clinic.

b) Complete physical examination is required. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator.

c) Twelve-lead ECGs will be obtained in triplicate (three consecutive interpretable 12-lead ECGs in less than 5 minutes) after the participant has been in a supine position for at least 10 minutes.

d) Pre-dose (on days of study treatment administration).

e) ADA samples to be taken pre-dose (when applicable).

[redacted]

g) HBV serology will include HBsAg (quantitative), anti-HBs (quantitative), HBeAg (qualitative) and anti-HBeAb (qualitative).

[redacted]

i) In case of HBV DNA rebound an unscheduled confirmatory HBV DNA quantification sample should be taken, a sample for HBV DNA genotyping and a sample for NUC PK.

## Table 6 Schedule of Assessments – Detailed Table, (CHB [redacted] 12 weeks – as of Week 6)

| Visit | Day | Scheduled Time (h) | Vital signs | ECG | PK Blood [redacted] | PK Blood [redacted] | PK Blood [redacted] | PK Urine[a] | ADA |
|---|---|---|---|---|---|---|---|---|---|
| Week 6 | Day 36 | Predose | | | X | | | | |
| | | 2 | | | X | | | | |
| Week 7 | Day 43 | Predose | X | X | X | X | | | X |
| | | 2 | | | X | X | | | |
| Week 8 | Day 50 | Predose | | | X | | | | |
| | | 2 | | | X | | | | |
| Week 9 | Day 57 | Predose | X | X | X | X | X | | |
| | | 0 | | | | | | X | |
| | | 2 | | | X | X | X | | |
| | | 4 | | | | | | X | |
| Week 10 | Day 64 | Predose | | | X | | | | |
| | | 2 | | | X | | | | |
| Week 11 | Day 71 | Predose | X | X | X | X | | | X |
| | | 2 | | | X | X | | | |
| Week 12 | Day 78 | Predose | | | X | | | | |
| | | 2 | | | X | | | | |
| Discontinuation | | | X | X | X | X | X | | |
| Follow up Visits | 14 days after last dose | | X | X | X | X | X | | |
| | 28 days after last dose | | X | X | X | X | X | | X |
| | 56 days after last dose | | X | X | X | X | X | | |
| | 84 days after last dose | | X | X | X | X | X | | |

a) Urine collection periods [0-4] and [4-8] hours post-dose. Patient should void bladder immediately before dosing. Within a given collection period, all urine voids should be collected and pooled; the sample should be taken from the pooled urine for the respective collection period.

# 2. INTRODUCTION

## 2.1 STUDY RATIONALE

This is the first study with RO7239958 in humans, designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending doses in healthy participants and participants diagnosed with chronic hepatitis B (CHB). Data collected in this study will be critical to define optimal doses and dosing regimens to be studied in Phase II clinical trials in CHB patients.

[redacted]

[redacted] The ASGPR is expressed predominantly by hepatocytes with low to no expression in other cell types (Stockert 1995; Zelensky et al 2005). [redacted]

[redacted]

For further information, see the RO7239958 Investigator's Brochure.

## 2.2 BACKGROUND

### 2.2.1 Background on Disease

Chronic HBV infection is a major global cause of liver disease, and substantial morbidity and mortality result from its main complications – cirrhosis, liver failure, and hepatocellular carcinoma. An estimated 257 million people worldwide are chronic HBV carriers, defined by the persistent detection of hepatitis B surface antigen (HBsAg) in serum. Nearly 900,000 people die annually due to the complications of chronic hepatitis B (CHB), and mortality rates are predicted to continue to rise over the next five decades (Nayagam et al 2016; WHO 2018).

RO7239958 is being developed for the curative treatment of chronic HBV infection. In patients with CHB, the current goal of antiviral therapy is to prevent liver disease progression, induce remission of liver inflammation and improvement of liver fibrosis, and reduce the risk of morbidity and mortality. Currently, there are 2 main treatment options for CHB: subcutaneous interferon alpha preparations (IFNα; conventional or pegylated) and oral nucleoside/nucleotide analogues (NUCs), including tenofovir, entecavir, adefovir, telbivudine, and lamivudine (EASL 2017). IFNα is administered by subcutaneous injections and shows overall modest efficacy and poor tolerability (Terrault et al 2018). NUCs, the current mainstay of therapy, inhibit transcription of pre-genomic HBV RNA into HBV DNA. NUCs have a more favorable tolerability profile than IFNα, and treatment guidelines recommend use of tenofovir or entecavir due to their greater potency and very low risk of drug resistance relative to other NUCs. Treatment with tenofovir or entecavir results in suppression of HBV replication in most patients. Over time, this is typically accompanied by normalized indices of liver inflammation and improved indices of liver fibrosis. Whereas IFNα treatment has a finite duration of typically 48-52 weeks, NUCs are commonly administered long-term. Neither form of treatment commonly achieves a "functional cure", defined by the loss of detectable hepatitis B surface antigen (HBsAg) in serum. Loss of HBsAg signals virus control and indicates that NUC treatment may be stopped. However, loss of HBsAg occurs in 0-3%

of patients after 1 year of NUC treatment (vs. 3-7% with IFNα). Rates increase slowly over several years of NUC treatment among hepatitis B e antigen (HBeAg) positive subjects, while still remaining below 14% after 5 to 8 years in this group. Rates of HBsAg loss among HBeAg negative patients are approximately 0-1% despite years of therapy (EASL 2017; Terrault et al 2018). In the absence of HBsAg loss, virological relapse is common if NUC treatment is discontinued.

Even in subjects that achieve HBsAg loss, HBV persists as covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes, posing a challenge to the achievement of a “complete cure”, i.e., virus eradication. HBV sequences can also integrate in the host chromosome, a phenomenon that appears to be especially common in HBeAg negative patients. The integrated viral DNA does not encode a complete virus genome and cannot sustain production of virus particles; however, surface HBV sequences that encode HBsAg can be expressed from integrated HBV DNA, allowing persistent HBsAg production (Allweiss et al 2017; Woddell et al 2017; Pfefferkorn et al 2017). New treatments of finite duration that are well tolerated and can produce greater rates of durable HBsAg loss, and potentially contribute to virus eradication, are required.

## 2.3 BENEFIT/RISK ASSESSMENT

Within current standard of care HBV therapies, NUCs have a more favorable tolerability profile than IFNα, but commonly have to be administered long term, possibly lifelong, in order to maintain viral suppression. Neither form of treatment commonly achieves a “functional cure”, defined by the loss of detectable hepatitis B surface antigen (HBsAg) in serum. Study NP40520 will provide the key information necessary to support further clinical development of RO7239958, with the ultimate aim of providing patients with a curative combination treatment for chronic HBV infection.

Study NP40520 is designed to evaluate the safety, tolerability, PK and PD properties of RO7239958. The study will be conducted in two parts, of which Part 1 will be a single ascending dose (SAD) study in healthy participants, and Part 2 will be a dose range finding (DRF) study in CHB patients established on NUC therapy. Part 2 comprises two sub-parts (Part 2a and Part 2b). Patients will receive RO7239958 or placebo for 4 weeks in Part 2a, and for up to 12 weeks in Part 2b. The study is randomized to control for known and unknown factors between active treatment and placebo. The aims of the study are to obtain data on safety (primary end-point) and PK (secondary end-point). Although antiviral activity will be explored in CHB patients, there is no expected direct benefit for study participants. The benefit is to be intended for the overall CHB population. Results will be used to inform future trials of RO7239958 and guide further clinical development as a treatment against CHB.

No prior clinical experience with RO7239958 exists. In Study NP40520 healthy participants and CHB patients will be kept under medical observation and monitored closely for clinical and laboratory adverse events. CHB patients eligible to join study NP40520 will be established on effective NUC therapy, have preserved hepatic function, and have no current or past history of cirrhosis, thus reducing the risk of liver-related adverse events. The evaluation of the potential risks of treatment, and the specific tests, observations, and precautions required for clinical studies with RO7239958 are based on information obtained preclinically from 2-week and 4-week studies in rats and NHPs, and a 39-week exploratory study in NHPs. In addition, there is prior experience with other LNA SSOs, such as that derived from study BP39405 (a two-part randomized SAD/multiple ascending dose study to evaluate RO7062931 in healthy volunteers and CHB patients).

[redacted] A reduction of expression levels for a certain subset of host transcripts could not be detected (Lim et al 2018).

[redacted]

[redacted]

[redacted]

[redacted]

RO7239958 will be administered in a hospital or clinic environment under supervision of an experienced clinician. Detailed instructions on dosage and administration of RO7239958 are provided. SC administration of LNA SSOs carries a risk of injection-site reactions (ISRs). At higher doses, there is also a potential risk for LNA SSO-related liver and kidney toxicity (Chen et al 2015; van Poelgeest et al 2015). Furthermore, it is hypothesized that HBsAg suppression may potentially contribute to restoring HBV-specific immunity in CHB patients, which may result in a transaminase flare. Frequent monitoring of full blood count, clotting, serum biochemistry and urinalysis will be performed during the course of the study, and close monitoring of renal and hepatic safety parameters will be included, comprising testing for renal function, urine sediment, serum transaminases, and hepatic synthetic and secretory function. Defined stopping criteria are proposed for dosing of individual study participants, cohorts and arms. In addition to standard measures of renal and liver safety, exploratory markers of renal and liver injury will be analyzed in urine and blood samples, respectively. Safety monitoring will be extended post-dosing for 12 weeks in both healthy participants and CHB patients.

[redacted]

More detailed information about known and expected benefits in the context of potential risks and reasonably expected adverse events of RO7239958 is provided in the RO7239958 Investigator's Brochure.

## 3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 7.

### Table 7 Objectives and Endpoints

| | Objectives | Endpoints |
|---|---|---|
| **Primary** | | |
| **All parts** | **Safety** | |
| | • To assess the safety and tolerability of RO7239958 compared to placebo after single subcutaneous (SC) ascending doses in healthy participants and multiple SC ascending doses in CHB patients stable on NUC therapy. | • Incidence, severity, and causal relationship of adverse events (AEs).<br>• Changes in vital signs, physical findings and electrocardiogram (ECG) findings, and clinical laboratory results during and following RO7239958 administration.<br>• Incidence of injection site reactions (ISRs). |
| **Secondary** | | |
| **All Parts** | **Pharmacokinetics (PK)** | |
| | • To assess plasma and urine PK of RO7239958 after single ascending SC doses in healthy participants and after multiple SC doses in CHB patients on stable NUC therapy. | • Plasma and urine PK parameters determined using non-compartmental analysis (NCA).<br>• The following plasma PK parameters will be calculated:<br>o Time to maximum concentration ($T_{max}$).<br>o Maximum plasma concentration observed ($C_{max}$).<br>o Area under the curve (AUC) for various time intervals post-dose.<br>• Additional PK parameters may be calculated in plasma (e.g., apparent clearance [CL/F], terminal half-life [$t_{1/2}$], K [elimination rate constant]).<br>• Additional urine parameters may be calculated, e.g., cumulative amount of drug excreted in urine over defined time periods ($A_e$). |

**Table 7 Objectives and Endpoints (cont.)**

| | | |
|---|---|---|
| **Part 2a and 2b** | **Pharmacodynamics (PD)**<br>• To assess the antiviral activity of RO7239958 after multiple ascending SC doses in CHB patients on stable NUC therapy. | • Time course profile of HBsAg levels and maximum decline from baseline.<br>• Time course profile of hepatitis B surface antibody (anti-HBs) levels.<br>• In participants that are HBeAg positive at study entry, incidence of HBeAg loss and incidence of hepatitis B e antibody (anti-HBe) seroconversion.<br>• Participants will have a suppressed HBV DNA at study entry and will be monitored to ensure that HBV DNA suppression is maintained during the study. |
| **Exploratory** | | |
| **All parts** | **PK**<br>• To evaluate the PK-safety relationships.<br>• To screen for the presence of RO7239958-derived metabolites.<br>• To assess the relative abundance and PK parameters of any metabolite as appropriate. | • Relationship between dose and/or plasma exposure of RO7239958 and safety-related parameters.<br>• PK concentrations of RO7239958-derived metabolites, if appropriate.<br>• PK parameters of RO7239958-derived metabolites, if appropriate. |
| **Exploratory** | | |
| **All Parts (cont.)** | **PK (cont.)** | |
| | [redacted] | |

## Table 7 Objectives and Endpoints (cont.)

| | | |
|---|---|---|
| **All parts** | [redacted] | |
| **Parts 2a and 2b** | **Safety**<br>• To study the effect of multiple ascending SC doses of RO7239958 on exploratory markers of kidney and liver injury. | Time course profiles of:<br>• Renal injury markers in urine (e.g., clusterin [CLU], cystatin C [CYS-C], kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], N-acetyl-beta-D-glucosamin*i*dase [NAG], osteopontin [OPN]); plus creatinine, albumin, and total protein.<br>• Liver injury markers in peripheral blood (e.g., glutamate dehydrogenase [GLDH], MCSFR1, OPN, CK18, ccCK18, total HMGB1).<br>• Anti-drug antibodies (ADA). |
| **Parts 2a and 2b** | **PK/PD**<br>• To explore the relationship between PK and pharmacodynamics (PD) after multiple SC doses in CHB patients on stable NUC therapy. | • Relationship between dose and/or plasma exposure of RO7239958 and quantitative measures of antiviral activity. |

**Table 7 Objectives and Endpoints (cont.)**

| | | |
|---|---|---|
| **Parts 2a and 2b** | **PD**<br>• To explore the anti-viral activity of RO7239958 after multiple SC doses in CHB patients on stable NUC therapy. | The following parameters will be measured:<br>• Time course profile of HBV RNA levels.<br>• Time course profile of HBV core-related antigen (HBcrAg) levels<br>• Time course profile of HBeAg levels.<br>• Time course profile of HBeAg levels (in HBeAg positive patients). |
| [redacted] | | |

# 4. STUDY DESIGN

## 4.1 OVERALL DESIGN

An overview of the study design is provided in Section 1.2.

The study will be conducted in two parts, of which Part 1 will be in healthy participants and Part 2 will be in CHB patients (see Section 1.2). All parts of the study are Observer-blind (see Section 6.3.2). All members of the project and study team who are not in direct contact with the participants may be unblinded. Part 1 will evaluate the safety, tolerability and PK of RO7239958 following subcutaneous (SC) administration of single ascending doses in healthy participants. Part 2 will evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of multiple SC doses of RO7239958 in CHB patients established on NUC therapy, and comprises two subparts, Part 2a and Part 2b. Part 2 is a dose range finding study (DRF).

### Part 1 – Single-Ascending Dose (SAD) Study in Healthy Participants

In Part 1, at least four cohorts will receive a single dose of RO7239958 or placebo. An optional cohort with participants receiving RO7239958 or placebo may be included, based on the need for further safety or PK data. Ten healthy participants, eight receiving RO7239958 and two receiving placebo, will be enrolled in each cohort using a 4:1 randomisation scheme. [redacted] Each cohort will implement sentinel dosing to monitor acute reactions over 24 hours post-dosing. Two participants will be dosed on Day 1, and at least one of two participants will have received RO7239958; the remaining eight participants shall be dosed the following day (i.e., after 24 hours) following satisfactory clinical safety review of the first two participants by the Investigator. For each cohort, safety will be monitored for 28 days (21 days for safety assessment plus 7 days of clinical safety observation), before escalating to the next cohort. A dose escalation meeting will take place prior to starting the next cohort. In all participants, safety will be monitored for a total of 12 weeks post-dosing.

### Part 2 – Dose Range Finding (DRF) Study in CHB Patients

Part 2 is a placebo-controlled, adaptive, parallel multiple-dose study in participants with CHB on stable NUC therapy, with the aim to study the safety, tolerability, PK and PD of RO7239958, and the relationship between RO7239958 PK and PD parameters. Dosing will be initiated in CHB patients with a safe dose as determined in Part 1, which will fall within the human efficacious dose range predicted with PK/PD modeling. Part 2 is divided into two parts, Part 2a and Part 2b.

### Part 2a

In Part 2a, CHB patients will be enrolled into one of two arms (Arms 1 and 2), which will run in parallel. Each arm will enroll seven participants using a 6:1 randomization scheme. To ensure balance between arms, enrolment of HBeAg positive participants will be capped. Participants of each arm can receive up to five doses of RO7239958 or placebo over 4 weeks.

[redacted] *Two* additional, parallel arms (Arms 3 and *4*) will open after Arms 1 and 2 have enrolled and followed-up for at least 28 days a sufficient number of participants to provide the safety and PK/PD information required to further inform dose and regimen optimization. *An optional Arm 5 will open if further doses or regimens need to be explored based on data from Arms 3 and 4.* A data review meeting will also take place before opening Arms 3 and *4 (and potentially optional Arm 5)*. Decision on dose levels and regimens for Arms 3 and *4* will be based on the safety, PK, and PD data from Arms 1 and 2 and all available safety and PK data from Part 1. If efficacious dose levels cannot be reliably predicted from PK/PD modeling and Part 1 data, the doses administered in Part 2a will be within the range demonstrated to be safe and well tolerated in Part 1. [redacted] In all patients, safety will be monitored for a total of 12 weeks post-dosing.

### Part 2b (optional)

The two additional arms (Arms 6 and 7) of Part 2b will open if further doses or regimens need to be explored based on the data from Part 2a, or a dose or regimen from Part 2a needs to be optimized and additional data evaluated. There may be inclusion of participants who are not treated with NUCs, or inclusion of a larger number of participants of a given HBeAg status. Each arm in Part 2b will comprise seven participants randomized to RO7239958 or placebo using a 6:1 randomization scheme. [redacted] In all patients, safety will be monitored for a total of 12 weeks post-dosing.

### 4.1.1 Length of the Study

Part 1: The total duration of the study for each participant will be up to 16 weeks, divided as follows:

- Screening: Up to 28 days
- In clinic period: Days -1 to 3.
- Treatment Period: Day 1
- Safety follow-up: up to at least 84 days after the dose of RO7239958 or placebo.

Part 2a: The total duration of the study for each participant will be up to 20 weeks divided as follows:

- Screening: Up to 28 days.

- In clinic period (optional): Days 1 to 3 and Days 29 to 30 (overnight stay optional).
- Treatment Period: Day 1 to 29.
- Safety follow-up: up to 84 days after the last dose of RO7239958 or placebo.

Part 2b: The total duration of the study for each participant will be up to 28 weeks divided as follows:

- Screening: Up to 28 days.
- In clinic period (optional): Days 1 to 3 and Days 29 to 30 (overnight stay optional).
- Treatment Period: Day 1 up to Day 85. Safety follow-up: up to 84 days after the last dose of RO7239958 or placebo.

### 4.1.2 Dose Escalation Decision

The decision to escalate the dose in Part 1, and the decision to open Arms 3 and *4* in Part 2a (and potentially further arm(s) in *Part 2a and* Part 2b), will be made jointly by the Sponsor study team, the Investigator, and any other person the Investigator or the Sponsor consider necessary to assist with the decision (see Section 4.1.4). In Part 1, the decision will be made prior to each RO7239958 dose escalation following review of all relevant information, including applicable AEs, ECGs, vital signs, laboratory test results, and available PK data collected at the previous dose levels as applicable.

[redacted]

Dosing will be initiated in CHB patients in Part 2a with a safe dose as determined in Part 1, which will fall within the human efficacious dose range predicted with PK/PD modeling. The maximum dose in Part 2 will not exceed the maximum dose tested in Part 1 under any circumstances. Part 2a will only commence once all clinically relevant data are available from Cohort 4 of Part 1. Dose levels in Arms 3 and *4* of Part 2a will be based on all available PK and safety data from Part 1, and the safety, PK, and available PD data from Arms 1 and 2. Part 2a will employ real-time data analysis obtained during dosing and follow-up post-dosing. If data from Arms 1 and 2 are supportive, Arms 3 and *4* may start to enroll participants early, while follow-up post-dosing is ongoing in Arms 1 and 2. However, Arms 3 and *4* will only open once sufficient participants in Arms 1 and 2 have completed at least 28 days of post-dosing follow-up. *Arm 5 will be optional and will open if further doses or regimens need to be explored based on data from Arms 3 and 4.*

#### 4.1.2.1 Part 1 - Dose-Escalation Decision Criteria

Part 1 uses an adaptive dose-escalation process that may be modified if:

[redacted]

- Events emerge that the Sponsor and/or the Investigator consider indicators that the planned dose-escalation step would result in unacceptable risks for the safety of healthy participants.
- The Sponsor and the Investigator agree to do so, and neither considers that the proposed subsequent dose level poses an unacceptable risk to the study subjects.

Single doses will not be escalated if the dose-escalation stopping criteria are met (see Section 4.1.3).

### 4.1.3 Stopping Rules Criteria

**Liver-related**

Isolated elevations in liver transaminases (ALT or AST) in the absence of liver function abnormalities may occur after administration of RO7239958 as a recognized LNA SSO class effect. In addition to the LNA SSO class effect, CHB patients may also hypothetically experience transaminase flares if HBsAg suppression leads to immune-restoration. Stopping criteria have been developed to take these potential effects into account.

**Part 1:** If, at a given dose level, one or more of the criteria described below is fulfilled, dose-escalation to the next cohort will be paused in order to assess the possible underlying causes and relation to RO7239958. If a relation to study treatment cannot be excluded by the Investigator and the Sponsor's Medical Monitor, dose escalation will be halted.

Criteria:

- At least two of eight healthy participants receiving RO7239958 experience dose-limiting AEs (DLAEs) of an ALT or AST increase $>$ 5x the upper limit of normal (ULN; confirmed by retesting within 48 hours) with preserved measures of liver function (total bilirubin, and INR or prothrombin time [PT]),

or

- At least one of eight healthy participants receiving RO7239958 experiences one of the following DLAEs: confirmed (within 48 hours) increase in ALT or AST $>$ 3x ULN accompanied by confirmed total bilirubin $>$ 2x ULN, INR $>$ 1.5, or PT $\geq$ 1.5x ULN, or appearance of jaundice or symptoms suggestive of drug-induced liver injury (e.g., fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, and eosinophilia).

**Part 2:** If, at a given dose level and/or regimen, one or more of the criteria described below is fulfilled, dosing in a patient and in a given arm, and any dose escalation, will be paused in order to assess the possible underlying causes and relation to RO7239958. If a relation to study treatment cannot be excluded by the Investigator and Sponsor's Medical Monitor, dosing and any potential dose escalation will be halted.

Criteria:

- At least two of six patients receiving RO7239958 experience a DLAE of an ALT or AST increase of > 8-fold relative to the baseline value (defined as the average values of the two measurements taken within the screening period), confirmed by retesting within 48 hours, with preserved measures of liver function (total bilirubin and INR or PT),

  or

- At least one of six patients receiving RO7239958 experiences one of the following DLAEs: confirmed (within 48 hours) increase in ALT or AST > 3-fold the baseline value, accompanied by confirmed total bilirubin > 2x ULN, INR > 1.5, or PT ≥1.5x ULN, or appearance of jaundice or symptoms suggestive of drug-induced liver injury (e.g., fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, and eosinophilia).

Repeat dosing of a participant within an arm will be delayed if the participant receiving RO7239958 experiences an ALT or AST increase > 5-fold and ≤ 8-fold relative to the baseline value, confirmed by retesting within 48 hours, with preserved measures of liver function (total bilirubin and INR or PT). Dosing may resume when the ALT or AST levels return to ≤ 5-fold the baseline value.

### Other stopping criteria

[redacted]

**All Parts:** Dosing and dose-escalation in healthy participants in Part 1 and dosing for a patient and a treatment arm and any potential dose escalation in Part 2 will not be implemented as planned if one of the criteria described below is fulfilled, unless it is apparent to the Investigator and the Sponsor that the occurrence is not related to RO7239958.

Criteria: At least two of eight healthy participants or at least two of six CHB patients receiving RO7239958 experience one or more of the following DLAEs:

- Confirmed decline in eGFR < 60 ml/min
- Grade 3 or 4, or otherwise significant (as defined by the Investigator) RO7239958-related AEs of the same character, or Grade 3 or 4 laboratory abnormalities.
- Other findings (regardless of the incidence rates) that at the joint discretion of the Sponsor and the Investigator indicate that dosing and any dose escalation should be halted (see Section 7.1).

### General considerations

**Part 1:** In case dose-escalation is stopped, lower doses within the tolerated dose-range could be investigated or a previous dose could be repeated in subsequent cohorts, by mutual agreement between the Sponsor and Investigator, in order to increase the amount of data within the tolerated dose-range.

**Part 2:** In case an arm is stopped, alternative regimens within a previously tolerated dose/exposure range could be further investigated, or a previous regimen could be repeated in subsequent arms, by mutual agreement between the Sponsor and Investigator, in order to increase the amount of data within the tolerated dose/exposure range.

### 4.1.4 Communication Strategy

Information will be communicated, as follows:

- The Investigator must confirm to the Sponsor that a participant has been dosed and provide a brief summary of the status of the participant in terms of safety and tolerability to RO7239958 or placebo, communicated by email or telephone.
- In Part 1, the Investigator will provide a safety assessment feedback to the Sponsor of the first two sentinel-dosed healthy participants of each cohort before proceeding to dosing the remaining participants.
- For all parts of the study and in the event of a dose-limiting adverse event (DLAE), the Investigator will contact the Sponsor immediately to discuss participant status and action taken or to be taken.
- After completion of each cohort in Part 1 (i.e., after the last participant in the cohort has reached the last day of the evaluation period, comprising 21 days of monitoring plus a further 7 days of clinical observation, for a total of 28 days), the Sponsor will organize a teleconference with the Investigators to discuss the safety and tolerability of RO7239958 or placebo, and to discuss the dose for the next cohort.

During each teleconference:

- Safety and tolerability (see Appendix 2) will be discussed along with the results of available PK data, in addition to safety laboratory results and any other available data that may assist the decision process.
- Dose escalation will only proceed if the Investigator and the Sponsor are satisfied with the safety profile of the previous cohort and agree to escalate to the next dose level.
- The decision of these meetings will be documented in writing and both the Sponsor and Investigator will approve the minutes of these meetings to confirm agreement.

For Part 2, a teleconference will be organized to discuss accumulated data from Arms 1 and 2 in Part 2a prior to the start of Arms 3 and *4*; a teleconference will also be organized as above after completion of Arms 3 and *4 (and optional Arm 5)* and before the start of subsequent arms in Part 2b if applicable.

In addition to these communications, the Sponsor and investigators will be in regular contact throughout the study by email or telephone, as per normal interactions during the conduct of a clinical study, and the Sponsor will arrange regular teleconferences and meetings to discuss study status.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

In order to reduce safety risks, the effects of each dose level will be reviewed carefully before escalating to the next dose level. Dose escalation will take place after a review of safety, tolerability, and available PK data, as described in Section 4.1.2. Stopping rules are detailed in Section 4.1.3. The safety observation period has been set to 21 days for the safety laboratory assessments and to 28 days for adverse event monitoring, and this approach is supported by data from the BP39405 study (RO7062931) which has completed dosing in healthy participants (see the RO7062931 Investigator's Brochure).

The DRF part of the study, Part 2a, will evaluate the safety, tolerability, PK and PD effects of multiple doses of RO7239958 in CHB patients. Part 2b is an extension part of Part 2a to evaluate alternative regimens, additional safety, PK and PD data, if required. [redacted] The approach is based on the consideration that the PK profile of RO7239958 is anticipated to show minimal variation between healthy participants and patients, and that the doses in Part 2 will never exceed the maximum safe dose defined in healthy volunteers in Part 1. Opening Part 2a with two parallel dosing levels will increase the likelihood of detecting antiviral activity and identifying a dose for regimen optimization in subsequent arms, while remaining within acceptable safety margins, based upon non-clinical data and data from Part 1.

In this study RO7239958 will be given as an add-on to NUC treatment. It is envisaged that in future studies RO7239958 will contribute to combination regimens with one or more antiviral agents or immune-enhancers, with the aim of inducing a HBV cure.

### 4.2.1 Rationale for Study Population

Part 1 will be conducted in healthy males and female subjects of non-childbearing potential, 18 to 65 years of age. The absence of confounding diseases and co-medications in healthy volunteers allows for a more consistent and comprehensive assessment of the drug disposition and the safety profile.

Part 2 will be conducted in CHB patients established on effective NUC therapy that have no current or previous history of cirrhosis and have preserved liver function, thus reducing the risk of liver-related adverse events. The PD effects of RO7239958 in humans can only be tested in patients with CHB and will comprise both standard and exploratory markers of antiviral activity. The results will provide essential information for supporting future development, including dose-selection for a Phase II study in CHB patients.

### 4.2.2 Rationale for Control Group

This study is designed to be adequate and controlled. Participants will be randomized to RO7239958 or placebo in each cohort of Part 1 and each arm of Part 2. The randomization scheme to active and placebo groups is considered necessary to generate an adequate within-study comparator dataset and allow a proper initial evaluation of the magnitude of any treatment effects. The study is Investigator/participant-blind to eliminate potential bias.

### 4.2.3 Rationale for Biomarker Assessments

In Part 2 of Study NP40520 blood samples will be taken at defined time-points (as shown in the Schedule of Activities, see Section 1.3) to monitor viral parameters in correlation with administered doses and PK parameters of RO7239958.

RO7239958 inhibits the expression of HBV RNA transcripts in HBV-infected human hepatocytes and suppresses production of viral proteins, including HBsAg and HBeAg. Thus, it is proposed that in Part 2, RO7239958 may cause a reduction of serum HBsAg in CHB patients. HBsAg loss is the recognized endpoint of effective antiviral therapy in international guidelines (Terrault et al 2018; EASL 2017; APASL 2016). The main virological end-point in Study NP40520 is therefore the time-course of serum HBsAg levels (see Section 8.1). CHB patients will have a$n$ HBsAg level $>$ 250 IU/ml at screening and the kinetics of HBsAg decline during dosing will be monitored together with the kinetics of rebound post-dosing.

Additional parameters will include markers that are well established for the assessment of HBV treatment outcomes, including the time-course of anti-HBs levels, and evolution of HBeAg and anti-HBe status. [redacted]

Several exploratory virological end-points have recently emerged in the field that may provide an indication of improved virus control and achievement of a HBV cure. Among these, pregenomic HBV RNA that bypasses reverse transcription and is released in plasma is proposed to provide a direct measure of the transcriptional activity of cccDNA. Consistent with this view, in NUC-treated patients with suppressed HBV DNA, presence of detectable circulating HBV RNA signals an increased probability of HBV DNA rebound upon NUC cessation (Wang J et al 2016). [redacted]

Circulating HBcrAg levels provide one additional exploratory biomarker that will be monitored in patients pre-dosing, during dosing and post-dosing. HBcrAg is a composite circulating biomarker made of HBcAg (core antigen, which is part of HBV virions), HBeAg (which arises from the same open reading frame as HBcAg and is secreted), and p22cr (precore protein). Emerging data correlate HBcrAg measurements with treatment outcomes (Mak et al 2018; Chen et al 2017). [redacted]

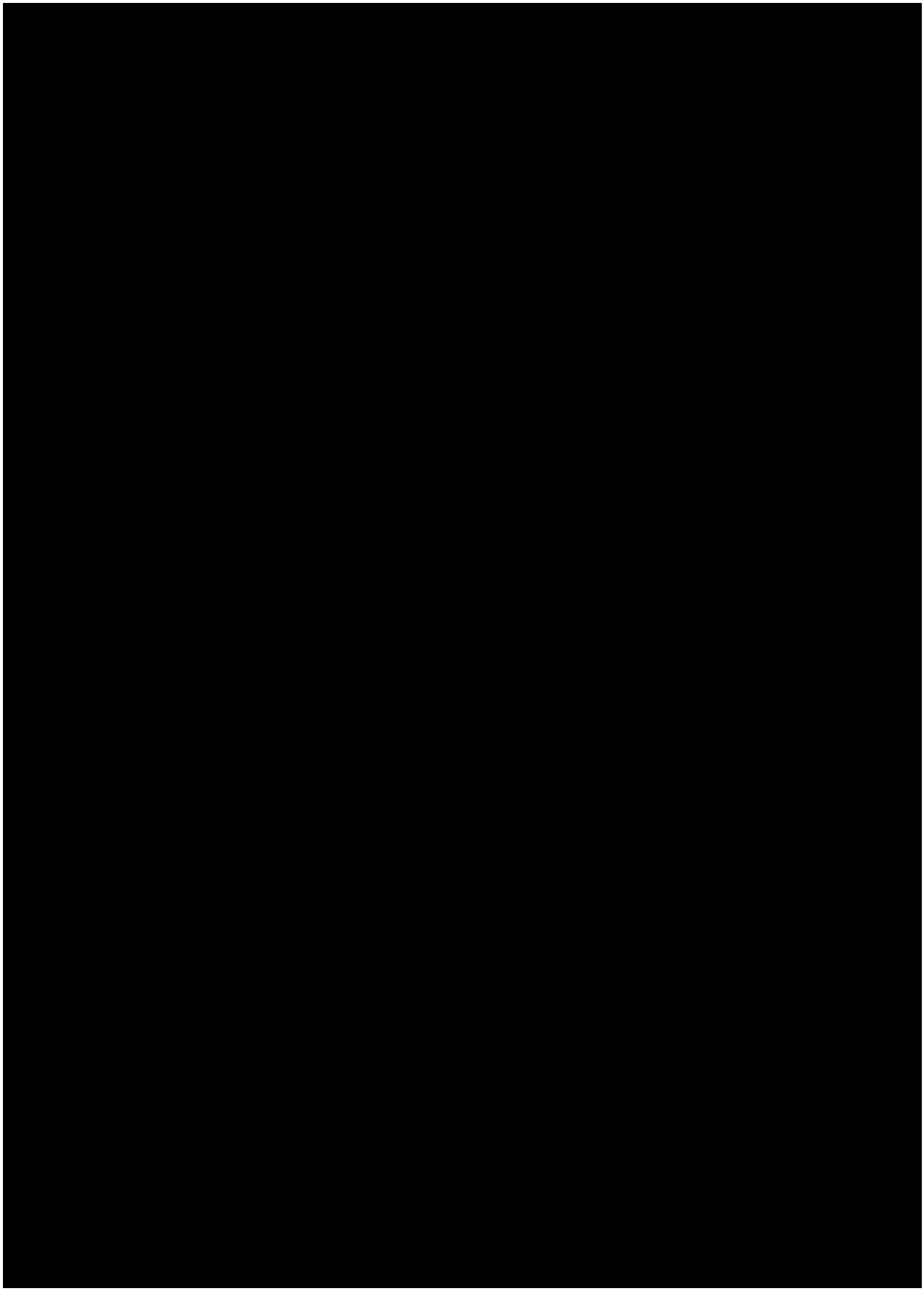
Patients in Part 2 will be established on effective NUC therapy at study entry and will have shown a circulating HBV DNA level below the assay lower limit of quantification for at least 6 months, and confirmed at screening. During Study NP40520, patients will be monitored to ensure that HBV DNA suppression is maintained. Patients who experience HBV DNA rebound during the study will be recalled for repeat testing. If the HBV DNA level is confirmed > 100 IU/ml, the patients will be assessed for evidence of NUC resistance using sequencing and potentially phenotyping, and the viral genotype will be determined by sequencing. In patients with no detectable HBV DNA, any sample with detectable HBV RNA will be used in an attempt to determine the HBV genotype by RNA sequencing.

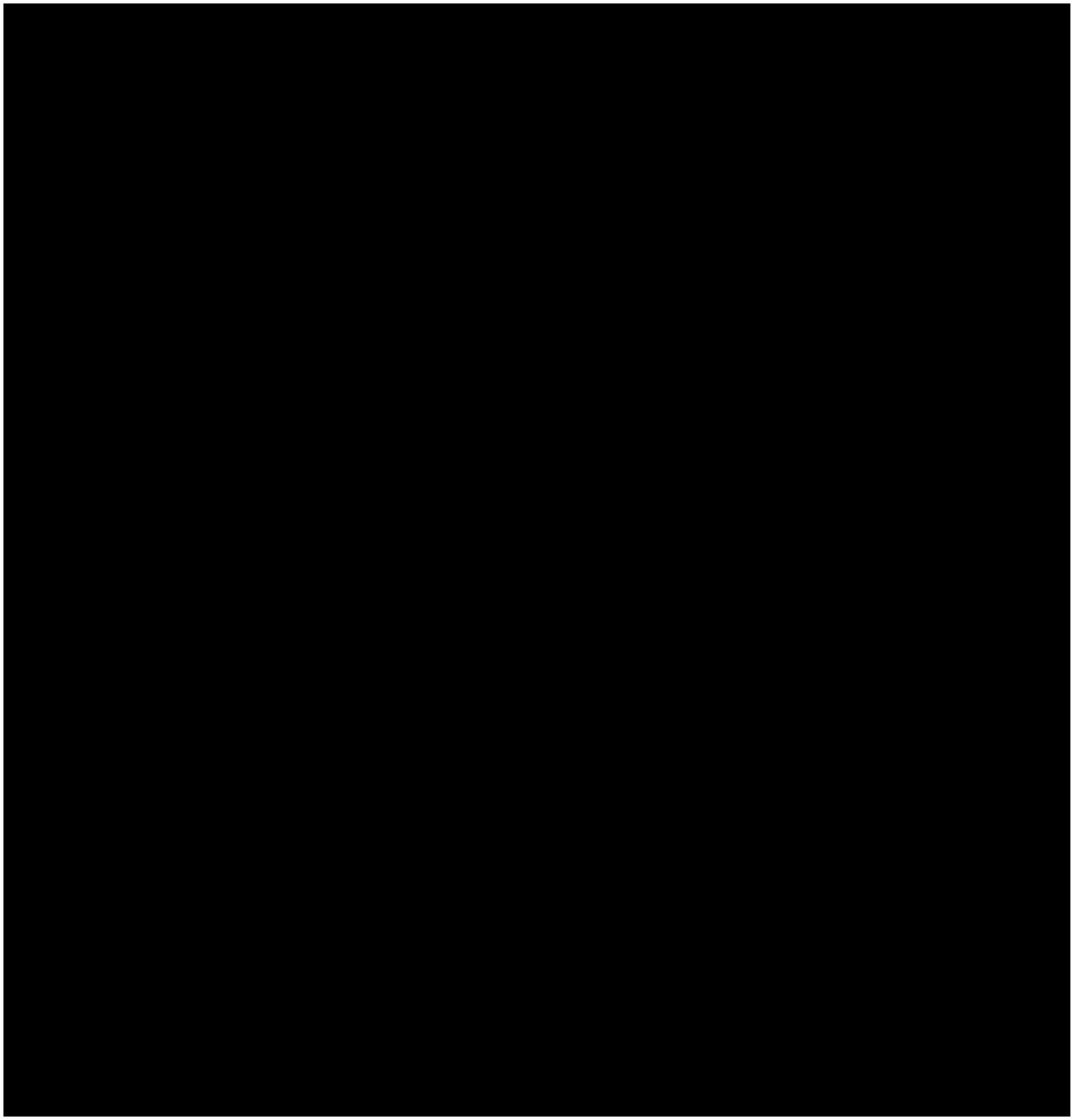
In Part 2, blood and urine samples will be collected during the course of the study for the analysis of exploratory safety biomarkers (see Section 1.3). Renal tubular injury is a known potential class effect of LNA SSOs and a potential safety risk of RO7239958 based on data obtained preclinically. The FDA recently approved six urinary markers (clusterin, cystatin C, KIM-1, NAG, NGAL, and osteopontin) as an integrated composite measure (CM) of a kidney tubular injury response (FNIH and PSTC Collaboration Briefing Book). By measuring the fold change from baseline of these urine markers (normalized to urine creatinine), the CM panel is intended to: i) evaluate the likelihood of a renal injury response in an arm or dose group, and ii) complement the standard measures used for kidney safety monitoring such as serum creatinine, blood urea nitrogen (BUN), urinary albumin/creatine ratio, and urinary total protein/creatinine ratio. The CM panel is not yet intended for individual patient safety monitoring. Due to the exploratory nature of the tests, the results will only be analyzed retrospectively and will not be used for decision making.

When measuring the above, the creatinine- and cystatin C-based estimated glomerular filtration rate (eGFR) will be also calculated by the CKD-epi equation as a standard measure of renal function (see Appendix 4 and Appendix 6).

Another potential safety risk of RO7239958 is hepatic injury, based on preclinical findings in NHPs and reflecting the intrinsic potential class effect of liver-targeted LNA SSOs. The standard liver injury markers (ALT and AST) have several limitations in terms of specificity (e.g., AST is not liver-specific), sensitivity (the rise in ALT and AST indicates that liver injury has already occurred), and prognostic value (the magnitude of the ALT elevation does not predict the patient's subsequent course). Study NP40520 will evaluate several emerging liver injury biomarkers (e.g., GLDH, MCSFR1, OPN, CK-18, ccK-18, and total HMGB1) that may complement ALT and AST and standard measures of liver function for the early detection of liver injury. Due to the exploratory nature of the tests, the results will only be analyzed retrospectively and will not be used for decision making.

[redacted]





## 4.4 END OF STUDY DEFINITION

The end of the study is defined as the date when the last participant last visit (LPLV) occurs (includes the safety and follow-up visit), or the date at which the last data point from the last participant required for statistical analysis is received, whichever is the later date, unless the participant was prematurely discontinued.

# 5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be healthy female and male volunteers and patients diagnosed with chronic HBV infection, between 18 and 65 years of age, inclusive, who fulfill all of the given inclusion criteria.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

**ALL STUDY PARTS**

**Informed Consent:**

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.

**Age:**

2. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

**Weight:**

3. Body weight of at least 45 kg and maximally 150 kg, and BMI within the range 18 to 32 kg/m2 (inclusive).

**Sex:**

4. Male and female participants:

   The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence to meet enrolment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

   a) Female participants: Should be women of non-childbearing potential (WONCBP; see Appendix 5).

b) Male participants: During the treatment period and for at least 105 days after the last dose of RO7239958 or placebo, agreement to:

i. With partners who are women of childbearing potential (WOCBP): Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year.

ii. With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.

iii. Refrain from donating sperm for at least 105 days after last dose of RO7239958 or placebo.

**PART 1 (SAD HV) ONLY**

**Type of participants:**

1. Healthy, as judged by the Investigator. Healthy status will be defined as the absence of evidence of any active or chronic disease following a detailed medical and surgical history, concomitant drug use (including hormonal supplements), a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology, and urinalysis.

**Others Inclusions:**

2. Non-smoker (nor tobacco containing products) for at least 90 days prior to dosing on Day 1, and agrees to remain non-smoker during the study.

**PART 2 (CHB) ONLY**

**Type of Participants and Disease Characteristics**

1. Positive serum HBsAg status for > 6 months prior to screening.
2. Serum HBsAg level ≥ 250 IU/mL at screening.
3. On stable entecavir or tenofovir (alone or in combination) treatment, and having received the same NUC in the 3 months prior to randomisation, and expected to remain on the same NUC for the duration of study participation.
4. HBV DNA below the lower limit of quantification (LLQ < $20\ IU/mL$) for ≥ 6 months prior to screening by local testing, and confirmed at screening.
5. Screening laboratory values (including hematology, chemistry, urinalysis) within normal ranges, or judged to be not clinically significant by the Investigator and Medical Monitor, and:

a) Screening alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 × upper limit of normal (ULN), confirmed between Day -7 to Day -4.

b) Screening *gamma*-glutamyl transferase (GGT) *≤ ULN (Note: GGT ≤ 1.5 x ULN is acceptable if considered not clinically significant)* and alkaline phosphatase (ALP) ≤ ULN, and normal values of prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). *PT and/or aPTT > ULN is acceptable if considered not clinically significant and INR and other parameters of liver function are within normal limits and there are no current and historical concerns. Whenever the Screening tests are repeated, the mean of the repeat values will be considered.*

c) Screening total bilirubin of ≤ ULN (Note: isolated bilirubin ≤1.5 × ULN is acceptable for patients with Gilbert's syndrome).

d) Screening neutrophil count > 1500 cells/$mm^3$ (Note: > 1200 cells/$mm^3$ is acceptable in participants of black race).

e) Screening hemoglobin > 11 g/dL in females and > 12.5 g/dL in males.

f) Screening platelet count ≥ 150,000 cells/$\mu$L.

6. No past or current diagnosis of cirrhosis. Transient elastography at screening showing a value consistent with a degree of liver fibrosis not higher than F3. By FibroScan, a cut-off of <8.5 kPa in the fasted status (last meal ≥ 3 hours prior) is recommended.

## 5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

**ALL STUDY PARTS**

**Medical Conditions**

1. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within three months prior to screening.

**PART 1 (SAD HV) ONLY:**

**Medical Conditions**

1. History or presence of significant (as judged by the investigator) cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological disorders, or diagnosed central or peripheral neurological disease, capable of significantly altering the absorption, metabolism, or elimination of drugs, of constituting a risk when taking the study treatment, or of interfering with the interpretation of the data.
2. Screening ECG showing clinically relevant abnormalities (including arrhythmias or marked QT abnormalities [QTcF < 300 msec or > 450 msec], or other cardiac abnormalities that are considered clinically significant by the Investigator. Known risk factors for Torsade de Pointes (e.g., hypokalemia, heart failure), or a personal or family history of congenital long QT syndrome.

3. Abnormal blood pressure: supine systolic blood pressure (SBP) <90 mmHg or >140mmHg or diastolic blood pressure (DBP) <45mmHg or >90mmHg at the time of screening and at Day -1, confirmed by two consecutive triplicate measurements, properly measured with well-maintained equipment.
4. History of lymphoma, leukaemia, or malignancy within the past five years, except for squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for three years.
5. History or presence of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
6. ALT ≥ 1.5 × ULN at screening and at Day −1.
7. Any clinically significant out of range findings in other laboratory test results or any other clinically significant (as judged by the Investigator) abnormalities in the physical examination at screening and on Day -1.
8. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.
9. Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration, or exposure to foods or environmental agents.
10. Any major illness within one month preceding the screening visit, or any febrile illness within the two weeks preceding the screening visit.
11. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.

**Prior/Concomitant Therapy**

12. Used or intend to use of over-the-counter (OCT) or prescription medication (including herbal and traditional remedies) before study start and during the study as described in list of prohibited medications.
13. Live vaccine(s) within 28 days of screening, or plans to receive live vaccines during the study or within 28 days of the last dose.
14. Likely to need concomitant medication during the study period (including dental conditions).
15. Treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within three months or five half-lives (whichever is longer) prior to dosing.

**Prior/Concurrent Clinical Study Experience**

16. Currently enrolled in or have participated within the last 90 days or five times the half-life of the investigational drug (whichever is longer) from signing of consent in this or any other clinical study involving an investigational product or in any other type of medical research.
17. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

**Diagnostic Assessments**

18. Known positive for hepatitis B surface antigen (HBsAg or hepatitis B core total antibody [anti-HBc]) and/or hepatitis C, or positive HBsAg or hepatitis C virus (HCV) antibody test result at screening.
19. Known positive for human immunodeficiency virus (HIV) infection and/or positive for HIV infection at screening.
20. Positive pre-study drugs and alcohol screen.

**Other Exclusions**

21. History or evidence of alcohol abuse (consumption of more than two standard drinks per day on average; one standard drink equals 10 grams of alcohol), and/or drug abuse within one year of screening.
22. Any suspicion or history of substance abuse or dependence.
23. Dietary restrictions that would prohibit the consumption of standardised meal.
24. Healthy participants under judicial supervision, guardianship or curatorship.

**PART 2 (CHB) ONLY**

**Medical Conditions**

1. History or presence of significant (as judged by the Investigator) cardiovascular (including poorly controlled blood hypertension), respiratory, hepatic, renal, gastrointestinal, endocrine, haematological disorders, or diagnosed central or peripheral neurological disease, capable of altering the absorption, metabolism, or elimination of drugs, of constituting a risk when taking the study treatment, or of interfering with the interpretation of the data.
2. History or presence of bridging fibrosis or cirrhosis or decompensated liver disease.
3. History or presence of a medical condition associated with liver disease other than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, non-alcoholic steatohepatitis). Other known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. History of or suspicion of hepatocellular carcinoma or alpha fetoprotein (AFP) $\geq$13 ng/mL at screening.
5. History of lymphoma, leukaemia, or malignancy within the past five years, except for squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for three years.
6. History of having received (in the last six months) or currently receiving any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic corticosteroids).
7. History of organ transplantation.
8. Any major illness within one month preceding the screening visit, or any febrile illness within the two weeks preceding randomisation.

9. Clinically significant (multiple or severe) drug allergies, or intolerance to topical corticosteroids, or history of severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
10. Estimated glomerular filtration rate (eGFR) < 70 mL/min/1.73m$^2$ (CKD-epi equation).
11. Confirmed QT interval corrected using Fridericia's formula (QTcF) >450 ms. Patients with correctable risk factors for prolonged QT (e.g., electrolyte abnormalities) can be re-assessed after correction of the risk factor(s).

**Prior/Concomitant Therapy**

12. Live vaccine(s) within 28 days of screening, or plans to receive live vaccines during the study or within 28 days of the last dose.
13. Expected to need any other systemic antiviral therapy at any time during participation in the study, with the exception of current NUC treatment and / or oral/ topical therapy for Herpes Simplex Virus (HSV).

**Prior/Concurrent Clinical Study Experience**

14. Currently enrolled in *(i.e., the end of study visit has not been performed)* or have *received investigational treatment* within the last 90 days or five times the half-life of the investigational drug (whichever is longer) from signing of consent in this or any other clinical study involving an investigational product or in any other type of medical research*, or the total volume of all blood samples provided during the follow-up visits of the former clinical trial exceeds 100 mL.*

**Diagnostic Assessments**

15. Positive hepatitis C antibody at screening.
16. Known positive for human immunodeficiency virus (HIV) infection and/or positive for HIV infection at screening.
17. Positive pre-study treatment/alcohol screen.

**Other Exclusions**

18. History or evidence of alcohol abuse (consumption of more than two standard drinks per day on average; one standard drink equals 10 grams of alcohol) and/or drug abuse within one year of screening; positive test result for drugs of abuse at screening.
19. Patients under judicial supervision, guardianship or curatorship.
20. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator contraindicates the participation in the study.

## 5.3 LIFESTYLE CONSIDERATIONS

### 5.3.1 Meals and Dietary Restrictions

It is unlikely that food will have an impact on the PK of RO7239958; however RO7239958 doses will be administered in the fasted state (either two hours before or two hours after a meal). Taking RO7239958 in a fasted state will apply to healthy participants and CHB patients.

In CHB patients, any food restrictions applicable to NUCs should continue to be observed throughout the study.

In Part 1, participants must abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and PD sample. In Part 2, participants must abstain from alcohol abuse.

For Part 1, the use of tobacco products will not be allowed for at least 90 days prior to dosing on Day1 until after the final follow-up visit.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure. Individuals of Parts 1 and 2 who do not initially meet the criteria for participation in this study can be re-screened if deemed appropriate by the Investigator. Participants with borderline laboratory assessments can be re-tested within the assigned screening period or rescreened for the next cohort or arm.

## 5.5 RECRUITMENT PROCEDURES

Participants in Part 1 of the study might be identified for potential recruitment using pre-screening enrollment logs, clinical database and IEC/IRB approved newspaper/radio/social-media advertisements prior to consenting to participate in this study. *In Part 2, more participants than the minimum numbers may prove eligible throughout the screening process and to respect and recognize the participants' commitment, over-enrollment by a maximum of two patients per Arm will be accepted.*

# 6. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMP) required for completion of this study are RO7239958 and placebo. RO7239958 will be provided by the Sponsor. Placebo will be provided by the site. All RO7239958 doses and placebo will be administered by investigational staff (i.e., the Investigator or study nurse) at the study clinic in the morning and in the fasted state (either two hours before or two hours after a meal). After SC administration of study drug, Part 2 participants should remain at the site at least until the post-dose assessments are completed.

## 6.1 TREATMENTS ADMINISTERED

Table 10 summarizes the treatments administered.

**Table 10 Summary of Treatments Administered**

| **Study Treatment Name:** | RO7239958 | Placebo |
|---|---|---|
| **Dosage Formulation:** | Yellow, brownish yellow or greenish yellow sterile liquid. | Sodium chloride |
| **Unit Dose Strength:** | 100 mg/mL | NA |
| [redacted] | | |
| **Route of Administration:** | SC | SC |
| **Dosing Instructions:** | The dose given will be in milligrams per kilogram of body weight. | – |
| [redacted] | | |
| **Manufacturer** | Hoffmann-La Roche Ltd. | (provided by the site) |

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the RO7239958 Investigator's Brochures and Pharmacy Manual for more details.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging for RO7239958 will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication (active IMP) will be in accordance with Roche standard and local regulations.

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the Pharmacy Manual.

The Investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

### 6.3.1 Method of Treatment Assignment

Participants will be randomized to placebo or, active treatment in each dose cohort or arm. Randomization numbers for healthy participants will be generated by independent representatives of the Sponsor, or its designee, for Part 1 of the study. The randomized treatment assignment will be allocated from the list sequentially to participants in the order in which they are enrolled.

The patient randomization numbers for Part 2 will be generated by the Interactive voice/web response system (IxRS), according to specifications provided by the Sponsor to the external randomization vendor. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Study treatment will be dispensed at the study visits summarized in SoA (see Section 1.3). Returned study treatment should not be re-dispensed to the participants.

The Investigator or designee will enter the corresponding participant number for allocation to the dosing groups/cohorts in the appropriate place on each participant's eCRF.

### 6.3.2 Blinding

The study is Observer-blind. This means that the participant, the Investigator and all individuals in direct contact with the participant at the site will be blinded to the individual treatment assignment except the pharmacist handling the study drug. All members of the project and study team who are not in direct contact with the participants may be unblinded.

To allow informed recommendations or decisions regarding dosing in this study, an integrated assessment of the safety and tolerability data and available PK data will be made prior to each dose-escalation decision. The Clinical Pharmacologist and the Clinical Pharmacology Scientist who perform this assessment, together with the Statistician, Data Acquisition Specialist and Clinical/Statistical Programmer will be unblinded with regard to the treatment allocation of participants. PK/PD data can be received and cleaned on an ongoing basis. The data will be handled and cleaned in a secure area which is not accessible by any blinded member. Likewise, the Bioanalyst and the Pharmacometrician will be unblinded. Other members of the Sponsor's project and study teams who do not have direct contact with the participant may be unblinded, at the *Clinical Science Lead's* discretion. The Clinical Pharmacologist or Clinical Pharmacology Scientist may share aggregated reports (e.g., tabular summaries or mean graphs by treatment group) with other individuals (e.g., Drug Safety Physician, Principal Investigator) who are involved in the dose decision process, but should not disclose individual treatment assignment.

In order to maintain the blind in Part 1, the unblinded pharmacist at the site will be responsible for the dispensation of all study-treatment. The randomization list will be made available to the Pharmacist preparing the study treatment. A sealed envelope that contains the treatment assignment for each participant will be provided to the Investigator. The sealed envelope will be retained by the Investigator (or representative) in a secured area. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the Sponsor.

In order to maintain the blind in Part 2, the unblinded pharmacist at the site will be responsible for the dispensation of all study treatment (i.e., RO7239958 [active IMP] and placebo). For Part 2, the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations when necessary for medical management of the patient. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly before the code is broken, if possible. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event [SAE]).

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAEs (see Appendix 2) that are considered by the Investigator to be related to study treatment.

The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for medical emergency in which the knowledge of the specific blinded treatment will affect the immediate management of the participant's conditions (e.g., antidote is available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded and the name of all the person(s) who had to be unblinded in the source documentation and eCRF, as applicable.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding from the Investigator side will be documented in the study report with date, reason for identifying the drug and the name(s) and role(s) in the study of the person(s) unblinded.

## 6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and participant number on the study treatment vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

## 6.5 CONCOMITANT THERAPY

All medications (prescription and OTC) taken within 30 days of study screening until the follow-up visit will be recorded in electronic case report form (eCRF).

Any prescription or OTC medicine (including nutritional supplements and herbal and traditional remedies) or vaccine used by a participant from 4 weeks prior to screening until the last follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates), and regimen information (including dose and frequency).

Participants of Part 2 should take the standard NUC treatment as normally prescribed.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All therapy or medication administered to manage AEs should be recorded on the Adverse Event eCRF.

### 6.5.1 Permitted Therapy

Concomitant medication includes any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements used by a patient from 30 days prior to screening until the follow-up visit.

For all parts of the study, paracetamol/acetaminophen, at doses of up to 1 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.

Hormone replacement therapy (HRT) is allowed during the study.

Standard NUC therapy will be expected to be continued throughout study participation, and recorded on the NUC Concomitant Medications eCRF.

All medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

### 6.5.2 Prohibited Therapy

As a general rule, no prescribed medication will be prohibited for Part 2 of the study. All concomitant prescribed medications (except standard NUC therapy) need to be discussed with the Medical Monitor prior to enrolling study participants.

Participants must abstain from taking nonprescription drugs (including OTC medication, vitamins, dietary, herbal supplements, protein powders or fish oils) within 7 days before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and Medical Monitor, the medication is necessary and will not interfere with the study.

Some supplements, herbal and traditional remedies, and OTC drugs may affect laboratory values. Abnormal values may lead to screening failures or withdrawal from the study. As such, participants should be carefully questioned regarding such substances at screening, and advised to refrain from them, if deemed necessary.

For all parts of the study, there are restrictions that should be maintained:

- Live vaccine(s) are not to be given within 28 days prior to screening. The participant should not receive live vaccines during the study or within 28 days after the last dose.
- In the event that a participant requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Medical Monitor.

For CHB patients, NUC-related food restrictions may apply (see Section 5.3.1).

## 6.6 DOSAGE MODIFICATION

[redacted]

The decision to proceed to the next dose level of RO7239958 (either an increase or a decrease), will be made by the Study Team (and the Investigator) based on safety, tolerability and available PK and/or PD data obtained described as in Section 4.1.2.

If unacceptable adverse events, or pharmacological effects, reasonably attributable to RO7239958 in the opinion of the Investigator are observed in the participants in a cohort or an arm, dosing and any dose-escalation will be temporarily halted for maximally 3 weeks (see Section 4.1.2) and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant site personnel (i.e., Investigator), and the IRB/IEC will take place before resumption of dosing.

## 6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO7239958 or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

# 7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate patients to comply with all the study specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1 Study Governance Considerations Study.

## 7.1 DISCONTINUATION OF STUDY TREATMENT

See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Participant must discontinue study treatment if they experience any of the following:

- Participant withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the participant.
- Pregnancy
- If stopping criteria are met (see Section 4.1.3)
- If non-compliance with study requirements as judged by the Investigator and consultation with the Sponsor.

Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 1.3) and may undergo follow-up assessments (see Section 1.3). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely can be replaced in both Parts 1 and 2.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Section 6 of Appendix 3 or if the Investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG taken at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

### 7.1.1 Temporary Interruption

Temporary interruption will not be allowed for the study (e.g., because of holidays, weekends, inclement weather, or other justifiable events).

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of specimens donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons can be replaced.

See SoA (Section 1.3) for data to be collected at the time of study discontinuation and at safety and follow-up visits, and for any further evaluations that need to be completed.

### 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

## 8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the Schedules of Activities (SoA; Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time-frame defined in the SoA.

## 8.1 EFFICACY ASSESSMENTS

Efficacy assessment endpoints are measured through markers of antiviral activity in Part 2 of the study. The short duration of treatment with RO7239958 is not anticipated to provide CHB patients with therapeutic benefit, but rather to provide evidence on the effect of multiple doses of RO7239958 on HBsAg and the other viral parameters under evaluation (see SoA, Section 1.3). Blood samples will be taken at defined time-points in Part 2 (as shown in the Schedule of Activities, see Section 1.3) to monitor viral markers, and study their correlation with administered doses and PK data. The main virological end-point is the time-course of serum HBsAg levels, measured as actual values pre-dosing, during dosing and post-dosing, and as changes from baseline over time (see Section 8.1). As this is the first study of RO7239958 in CHB patients and eligible patients are established on effective NUC with suppressed circulating HBV DNA, HBsAg levels are being explored as part of the secondary endpoints in this study. Additional parameters include incidence of HBsAg loss and anti-HBs seroconversion, the time-course of anti-HBs levels, and changes in HBeAg and anti-HBe status in the course of the study. Exploratory viral parameters include serum HBeAg levels, and circulating HBcrAg and HBV RNA levels.

The efficacy assessments will include all patients in the efficacy analysis population analyzed according to the treatment group (dose-level/regimen/extension) to which they are randomized (see Section 9.3).

## 8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3).

### 8.2.1 Physical Examinations

A complete physical examination should be performed at the time-points specified in the SoA tables (see Section 1.3) and include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Height and weight will be collected at the screening visit only. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities will be recorded in the medical file of the healthy volunteer or patients. New or worsened, clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 8.2.2 Vital Signs

Vital signs will be obtained after the subject has been resting in a supine position for at least 5 minutes.

Blood pressure (BP; systolic and diastolic), pulse rate and body temperature (tympanic) will be recorded at the time-points specified in the SoA tables (see Section 1.3). Blood pressure and pulse rate will be performed in triplicate (can be as short as 20 seconds to 1-minute interval between measurements). The mean of three consecutive replicates will be used as the value for the defined time-point. Vital signs should be measured prior to blood draw. When possible, the same arm should be used for all blood pressure measurements.

Blood pressure and heart rate should be obtained in a quiet room at a comfortable temperature, with the subject's arm unconstrained by clothing or other material. Where possible all measurements will be obtained from the same arm and, with the same cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study (the “ideal” cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). The study subject should be asked to remove all clothing that covers the location of cuff placement. The individual should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum).

### 8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QTc intervals. ECGs will be collected after the participant has been in a supine position for at least 10 minutes prior to each ECG evaluation. At the specified time-points, 12-lead ECGs will be obtained in triplicate, i.e., three consecutive interpretable 12-lead ECGs within a 3-5-minute period, and recorded in the case report form (CRF). Triplicate recordings should be taken for any unscheduled ECG.

At each time-point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, and the full set of triplicates should be completed in less than 5 minutes.

All ECG recordings must be performed using a standard digital high-quality, high-fidelity ECG machine equipped with computer-based interval measurements. Automated ECG intervals (PR [PQ], QRS, QT, QTcF [Fridericia's correction; to be derived in eCRF]) and heart rate (HR) will be captured or calculated, and the changes in T-wave and U-wave morphology will be documented. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

The following are requirements for ECG assessments:

1. Digital ECG recordings, storage and analysis.
2. Three useful recordings must be collected without artefacts, per time-point.
3. Body position should also be consistently maintained for each ECG performed. In particular, changes in HR should be avoided. The absence of any environmental distractions (television, radio, conversation) during the pre-ECG rest and the ECG recording in the clinic must be emphasized.
4. Avoid ECG recordings within 3 hours after meals (it is accepted that this is not possible after the light breakfast which is administered prior to dosing in the fed period for the relevant cohort).
5. Strictly match timing and conditions of ECG recording to baseline. Conditions to be standardized include food intake, activity level, stressors, and room temperature.
6. If possible, the same machine, brand and model, should be used for the same study subject throughout the study.
7. ECGs should be 12-lead, recorded at 25 mm/sec for at least 10 seconds.
8. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.
9. ECG machines should have periodic calibration and service records (minimum once a year).
10. If any QT/QTc values $>$ 500 msec or increases from pre-dose on Day 1 QTc $>$ 60 msec (as provided by the machine and read by the cardiologist), the site should repeat the ECG (triplicate) within the next 5 minutes and notify the Sponsor. If confirmed, ECG recordings should be repeated at least hourly until two successive ECGs show QTc values below the threshold value that triggered the repeated measurement.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

### 8.2.4 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) the results must be recorded in the CRF.

Results of clinical laboratory testing will be recorded in the eCRF or be received as electronically produced laboratory reports submitted directly from the central laboratory.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility.

If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

### 8.2.5 Medical History and Demographic Data

Medical history includes clinically significant diseases, i.e., surgeries, cancer history, reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the study subject within 30 days prior to the Screening visit.

For CHB patients, the detailed HBV history will be documented, which will include date of HBV diagnosis, any previous assessment of liver fibrosis (including date and outcome of any liver biopsy), HBV genotype (if documented), all previous HBV treatments and outcomes of treatments, occurrence of any NUC resistance.

Demographic data will include age, sex, and self‑reported race/ethnicity.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious adverse events of special interest and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Section 8.3.6 and 8.3.7.

The Investigator and any qualified designees are responsible for ensuring that all adverse events (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording adverse events are provided in Appendix 3:

- Diagnosis versus signs and symptoms:
  - ISR
  - Other AEs
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
- Preexisting medical conditions
- Worsening of CHB
- Hospitalization or prolonged hospitalization

### 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on adverse events at each participant's contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

**After informed consent** has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.

**After initiation of study treatment**, all adverse events, regardless of relationship to study treatment, will be reported until 105 days after the last dose of study treatment.

**Post-study adverse events and serious adverse events:** The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period (105 days after the last dose of study treatment).

However, if the Investigator learns of any SAE (including a death) or other adverse events of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

### 8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation time−points.

### 8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

#### 8.3.3.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better until, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

#### 8.3.3.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

### 8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB and EC, see Appendix 2.

#### 8.3.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical monitors is available. 24 hours a day 7 days a week. Medical monitors contact details will be available on a separate list generated by the study management team.

### 8.3.5 Pregnancy

Male participants will be instructed through the Informed Consent Form (ICF) to immediately inform the Investigator if their partner becomes pregnant during the study or within 105 days after the last dose of study drug.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

### 8.3.6 Non-Serious Adverse Events of Special Interest

Non-serious adverse events of special interest (NSAESI) are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

NSAESI for this study include the following:

- Dose-dependent gastrointestinal disorders (including nausea, vomiting and diarrhea).
- Confirmed ALT or AST > 5x ULN (in healthy participants) or > 8x baseline (in CHB patients).
- Confirmed ALT or AST > 3x ULN (in healthy participants) or > 3x baseline (in CHB patients) accompanied with increased total bilirubin > 2x ULN (or clinical jaundice).
- Confirmed ALT or AST > 3x baseline (in CHB patients) accompanied with INR > 1.5 (or PT ≥ 1.5 ULN).
- Confirmed ALT or AST >3x baseline (in CHB patients) with the appearance of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness. fever, rash, and eosinophilia

- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

### 8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events can be observed in CHB patients:

- ALT or AST increase < 5-fold the baseline value with preserved hepatic function

Because these events may be associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs. These events will be recorded on the corresponding CRF page in the participant's CRF within the appropriate time-frame.

## 8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Document the quantity of the excess dose, as well as the reason and circumstances, and duration of the overdose, in the CRF.

## 8.5 PHARMACOKINETICS

Blood samples to evaluate concentrations of RO7239958 and its metabolite(s) if applicable, and urine samples to evaluate concentrations of RO7239958 will be collected as outlined in the SoA tables (see Section 1.3). During the course of the study, PK sampling time-points may be modified on the basis of emerging data to ensure the PK of RO7239958 can be adequately characterized. Additional PK samples will be taken at the time of treatment discontinuation, if the participant experiences an injection-related AE (such as an ISR), or if the participant experiences an adverse event leading to dose-reduction or delayed RO7239958 administration (see Section 6.6 Dosage Modifications). The date and time of each RO7239958 administration and of each sample collection will be recorded in the eCRF.

RO7239958 levels will be analyzed by using validated assays.

- Metabolites may be measured by a specific validated LC-MS/MS assay, or other fit for purpose methods as appropriate.
- Placebo-treated participants may not be analyzed in the first instance, but retained for subsequent analysis if appropriate.
- Any volume of blood samples remaining after the specified analyses may also be used for additional validation experiments (e.g., anti-drug antibodies).

The blood samples for PK analyses will be destroyed within 2 years after the date of final CSR. Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

*For participants who consent to RBR, leftover samples will be transferred to RBR.* Genetic analyses will not be performed on these samples unless consent for this was included in the RBR informed consent. Participant confidentiality will be maintained.

Drug concentration information that would unblind the study, will not be reported to investigative sites or blinded personnel until the study has been unblinded.

### 8.5.1 Immunogenicity Assessments

As RO7239958 is an oligonucleotide, there is a risk that anti-drug antibody (ADA) against RO7239958 could develop, potentially reducing its efficacy or potentially resulting in hypersensitivity reactions, in particular immune-complex reactions.

Antibodies to RO7239958 may be evaluated in blood samples collected from all participants according to the SoA (Section 1.3). Additional ADA samples may also be collected at the time of treatment discontinuation or at safety follow-up visits in participants who experience a Grade $\geq$ 3 ISR or have clinical signs of a hypersensitivity reaction. For each collected ADA sample, a paired PK sample will be collected at the same time-point for the determination of RO7239958 concentrations. The date and time of each sample will be recorded in the eCRF.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against RO7239958. Samples from placebo-treated participants may not be analyzed in the first instance, but retained for subsequent analysis if appropriate.

If required, remaining ADA samples may also be used for assay development/validation experiments.

Leftover blood samples will be destroyed within 2 years after the date of final CSR. *For participants who consent to RBR, leftover samples will be transferred to RBR.*

Details on sampling procedures, sample storage and shipment are described in the sample documentation.

## 8.6 PHARMACODYNAMICS AND BIOMARKERS

For assessment time points please see the SoA (Section 1.3).

### 8.6.1 Viral Dynamic Biomarkers

Standard viral dynamics biomarkers include:

- Quantitative HBsAg
- Quantitative anti-HBs
- Qualitative HBeAg and anti-HBe

Exploratory viral dynamics biomarkers include:

- Quantitative HBcrAg
- Quantitative HBV RNA
- Semi-quantitative HBeAg

[redacted]

### 8.6.2 Viral Genetic Analyses

The samples for HBV RNA extraction will be collected for quantitative purposes as outlined in the SoA (see Section 1.3). If RNA can be quantified, viral genotyping will be performed by sequencing. In addition, should HBV DNA rebound occur during the study, the HBV DNA will be tested to determine genotype and NUC resistance by sequencing and potentially NUC resistance by phenotyping.

### 8.6.3 Exploratory Safety Biomarkers

A number of exploratory safety liver and kidney biomarkers will be analyzed from blood and urine samples in Part 2, including but not limited to:

- Urinary renal injury biomarkers: CLU, cystatin C, KIM-1, NAG, NGAL, and OPN.
- Liver blood injury biomarkers: HMGB, GLDH, MCSFR1, OPN, CK18, and ccCK18

## 8.7 PHARMACODYNAMICS AND BIOMARKER SAMPLES

Samples should be collected as specified in the SoA (see Section 1.3).

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

Details on processes for collection and shipment of these samples can be found in Sample Handling Manual.

Unless otherwise specified below, samples (including plasma/serum, slides, extracts, etc.) will be destroyed no later than 5 years after the date of final CSR. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.8).

### 8.7.1 Mandatory samples

The following samples for pharmacodynamics and biomarker research are required and will be collected from all participants in this study.

#### Blood Sampling

Blood samples will be collected for extraction of HBsAg, HBsAb, HBeAg, HBeAb, viral RNA and HBcrAg and exploratory liver biomarkers. For time points see the SoA (Section 1.3).

[redacted]

#### Urine Sampling

Urine samples will be collected for exploratory renal (urine) injury biomarkers.

[redacted]

## 8.8 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

### 8.8.1 Overview of the Research Biosample Repository

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins). The collection, storage and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens will be collected from participants who give specific consent to participate in this optional RBR. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease.
- To increase knowledge and understanding of disease biology.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

#### 8.8.1.1 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7239958 or diseases:

- Leftover serum, plasma, *urine* and liver tissue samples [redacted] for development of biomarkers and associated assays.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate Sample Handling Manual.

RBR specimens will be stored and used until no longer needed or until they are exhausted. The Research Biosample Repository storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

## 8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

## 8.10 TIMING OF STUDY ASSESSMENTS

### 8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed within 28 days prior to Day 1, unless otherwise specified. Results of standard-of-care elastography examinations performed prior to obtaining informed consent and within 3 months prior to screening may be used (and do not need to be repeated for screening).

Re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized within 28 days after the start of screening period because of an administrative reason. In order to re-screen such a patient, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated if done more than 28 days before randomization. For re-screening, there is no need to repeat the fibroscan (elastography) if done for this study within 6 months if reliably documented.

[redacted]

Re-screened participants should be assigned the same participant number as for the initial screening.

### 8.10.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified, be permitted to re-enroll in the study.

All assessments must be performed as per SoA (see Section 1.3). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

### 8.10.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study (see Section 4.1.1) or discontinue from the study early will be asked to return to the clinic for a total of four safety and follow up visits after the last dose of study drug.

### 8.10.4 Follow-Up Assessments

After the study completion/early termination visit, adverse events should be followed as outlined in Section 8.3.1 and 8.3.3

### 8.10.5 Section Assessments at Unscheduled Visits

For activities that are required to be performed in case of an unscheduled visit, assessments and samples may be taken at the discretion of the Investigator as specified in Section 1.3

# 9. STATISTICAL CONSIDERATIONS

Statistical summaries will be descriptive in nature and will be reported separately for each part of the study within the clinical study report (CSR). All study participants who are randomized to receive placebo in Part 1 will be pooled as a respective placebo control group for Part 1. Placebo from Part 2a and Part 2b will be pooled separately.

## 9.1 STATISTICAL HYPOTHESES

No statistical hypothesis testing is planned for this study.

## 9.2 SAMPLE SIZE DETERMINATION

The sample size was determined by practical considerations and not based on statistical power calculations. In Part 1, approximately 40-50 participants will be enrolled in four to five cohorts of 10 participants each (eight to receive RO7239958 and two to receive placebo). In Part 2, approximately *28*-49 CHB patients will be enrolled in *four* to seven arms of seven participants each (six to receive RO7239958 and one to receive placebo). Part 2a will include approximately *28*-35 participants in *four to* five arms. Part 2b will include approximately 14 participants in two arms.

## 9.3 POPULATIONS FOR ANALYSES

For the purpose of analysis, the following populations are defined in Table 11.

### Table 11 Analysis Populations

| Population | Description |
|---|---|
| Safety | All study subjects who have received at least one dose of the study medication, whether prematurely withdrawn from the study or not, will be included in the safety analysis. |
| Pharmacokinetic | Study subjects will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol, or if data are unavailable or insufficiently complete to allow the analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure. |
| Efficacy | The analyses of viral dynamic response in Part 2a (and potentially Part 2b) of the study will include all patients who were randomized and received at least one dose of study drug (RO7239958 or placebo) and with at least one post-treatment assessment. Participants will be analyzed according to the treatment group to which they are randomized. |

## 9.4 STATISTICAL ANALYSES

### 9.4.1 Demographics and Baseline Characteristics

Descriptive statistics will be used for demographic and baseline disease characteristics as applicable for each part of the study. These will include for Part 1 and Part 2 age, gender, race, ethnicity, country of origin, weight, height, body mass index; and for Part 2 only, HBV baseline characteristics (e.g., HBsAg levels) and HBV history (e.g., duration of HBV diagnosis HBV treatment history, fibrosis status), and where measurable (participants with detectable HBV RNA), the viral genotype. All study participants who are randomized to receive placebo will be pooled as respective placebo control groups, according to each part of the study.

For continuous variables, mean, standard deviation, median, and minimum and maximum values will be presented. For categorical data, the proportion of study participants in each category will be summarized.

### 9.4.2 Safety Analyses

All safety analyses will be based on the entire safety analysis population (see Table 11).

The objectives of the safety analyses are to assess the safety and tolerability of RO7239958 compared to placebo after single SC ascending doses in healthy participants and multiple SC ascending doses in CHB patients.

Participants randomized to receive RO7239958 will be analyzed by cohort or arm. All study subjects who are randomized to receive placebo will be pooled as respective placebo control groups, according to each part of the study (See Section 9).

The safety data, including AEs, ISRs, reason for withdrawal from study, laboratory data, ECG, concomitant medications, vital signs, and physical examination results will be listed and summarized descriptively. Marked abnormalities of laboratory data will be flagged. As appropriate, listings, summary tables and graphs (participant plot and/or mean plots) will be provided to describe safety and tolerability assessments.

**Table 12 Safety Statistical Analysis Methods**

| Endpoint | Statistical Analysis Methods |
|---|---|
| Adverse events | The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor.<br>Adverse events will be summarized by mapped term and appropriate thesaurus level. |
| Clinical laboratory tests | All clinical laboratory data will be stored on the database in the units in which these were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results.<br>Summary tables of change from baseline over time will be displayed. Shifts in NCI CTCAE grades v5.0 from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. See Appendix 4 for details on standard reference ranges and data transformation and the definition of laboratory abnormalities. |
| Vital signs | Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate. |
| ECG data analysis | For the analyses of ECG data, see Section 8.2.3. |
| Concomitant medications | The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.<br>Concomitant medications will be presented in summary tables and listings. |

#### 9.4.2.1 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. Summary descriptive statistics for the actual values and changes from baseline will be tabulated by nominal time for HR, QRS duration, PR and QTcF. For multiple measurements taken at a nominal time-point, the average of these measurements will be used as the value at that nominal time-point in all summaries. In addition, QTcF will be categorized at each time-point as ≤ 450 msec, > 450-480 msec, > 480-500 msec and > 500 msec and summarized. Similarly, a summary will be provided of the QTcF changes from baseline at each time-point categorized as < 30 msec, 30-60 msec, and > 60 msec. Changes of the overall ECG interpretation, T-wave and U-wave morphology will be summarized. QTcF will be assessed by a central group.

#### 9.4.2.2 Exploratory Safety Biomarkers Analysis

The exploratory safety parameters (see Section 8.6.3), will be analyzed graphically. Plots will include longitudinal plots for both actual result and change from baseline. Longitudinal plots will include means/medians by arm as well as individual subject responses by dose. Box and whisker plots may also be used to detect outliers.

### 9.4.3 Pharmacokinetic Analyses

Non-compartmental analysis will be used to calculate PK parameters where appropriate. Summary descriptive statistics of plasma PK parameters including $C_{max}$, $T_{max}$, AUC, and $t_{1/2}$ for RO7239958 may be presented by cohort/arm including means, geometric means, standard deviation (SD), coefficient of variation (CV), medians and ranges. Other parameters may be calculated, e.g. $C_{168hr}$, CL and $V_{ss}$.

Listing summary tables and graphs (individual plots and/or mean plots) by treatment group will be provided.

Descriptive statistics of urine PK parameters, e.g. $A_e$, $F_e$, for RO7239958 and any metabolites, if applicable, will be presented, where available.

A population PK modeling approach may also be used to describe plasma and urine PK. PK data from this study may be pooled with data from other studies to develop the population PK model.

### 9.4.4 Pharmacodynamic Analyses

The viral dynamic response analysis is only applicable to Part 2 of the study and is based on the Efficacy Population (Table 10). Blood samples for measuring standard (e.g., HBsAg, anti-HBs) and exploratory (e.g., HBV RNA) viral dynamic parameters will be collected as detailed in the SoA (see Section 1.3).

Descriptive statistics will be utilized to summarize the main viral dynamic response outcome measure of serum HBsAg levels (in $\log_{10}$ IU/mL) as actual and change from baseline, at each time-point and by arm. Plots of HBsAg levels (in $\log_{10}$ IU/ml) including actual and change from baseline over time will be utilized to compare the longitudinal profiles across doses and frequencies of dosing. Further exploration may include plots of quantitative HBsAg over time, grouped by HBeAg status or baseline characteristics of interest as appropriate.

**Table 13 Viral Dynamic Response Statistical Analysis Methods**

| Endpoints | Statistical Analysis Methods |
|---|---|
| HBsAg and anti-HBs | Time course profile: summary descriptive statistics of values (in $log_{10}$ IU/mL), including actual and change from baseline (including mean, standard deviation, median, minimum and maximum) at each time-point. |
| HBsAg loss | Proportion of HBsAg loss (below lower limit of sensitivity) at each time-point. |
| HBeAg | In participants that are HBeAg positive at study entry, proportion of serum HBeAg loss (below lower limit of sensitivity) and proportion of serum anti-HBe seroconversion. |
| Maintenance of suppressed HBV DNA levels | Proportion of patients with HBV DNA below the assay lower limit of quantification at each time-point. In case of rebound, this will be confirmed by repeat testing, further evaluated and eventually correlated with NUC resistance and NUC plasma levels. |

**Table 14 Exploratory Viral Dynamic Response Statistical Analysis methods**

| Endpoint | Statistical Analysis Methods |
|---|---|
| HBV RNA, HBcrAg, HBeAg | Summary descriptive statistics to summarize values (in $log_{10}$), including actual and change from baseline (including mean, standard deviation, median, minimum and maximum) at each time-point. |
| [redacted] | |

The population PK analysis and PD analyses may be presented separately from the main CSR.

#### 9.4.4.1 PK/Safety and PK/PD Relationships Analysis

Relationship between dose and plasma exposure of RO7239958 and any PD parameters and/or outcome (e.g., safety-related marker, adverse events, exploratory safety biomarkers, viral dynamic markers, viral response) may be done by graphical analysis and further development of a model.

#### 9.4.4.2 Immunogenicity Analyses

The immunogenicity analyses will include participants with at least one pre-dose and one post-dose ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative participants during both the treatment and follow-up periods will be summarized.

- Participants are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response).
- Patients are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported descriptively.

## 9.5 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study drug administration and concomitant medication will be listed. The number of participants who were randomized, discontinued and completed the study will be summarized and listed.

## 10. REFERENCES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## 11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as:

Appendix 1 (for regulatory, ethical and study oversight considerations)

Appendix 2 (for AE definitions, reporting)

Appendix 3 (procedures of recording)

Appendix 4 (clinical laboratory tests)

Appendix 5 (contraceptive guidance and collection of pregnancy information)

Appendix 6 (CKD-EPI GFR)

Appendix 7 (Grading of ISRs)

# Appendix 1
# Regulatory, Ethical, and Study Oversight Considerations

## 1. REGULATORY AND ETHICAL CONSIDERATIONS

### 1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

### 1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant (e.g. advertisements, diaries etc.), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all adverse events to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 1.3. INFORMED CONSENT

The Sponsor's Master ICF (and ancillary sample ICFs such as a RBR ICF and pregnant partner ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

A participant who is re-screened is required to sign another Consent Form, only if significant new information/findings led to a more recent version of the Consent Form (or addendum in accordance with applicable laws and IRB/EC policy).

### Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a subject who is participating in the Research, the participant's specimens and data will continue to be used as part of the RBR.

### Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

### Withdrawal from the Research Biosample Repository

Participants who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from study NP40520 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from study NP40520. Data already generated before time of withdrawal of consent to RBR will still be used.

## 1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### Confidentiality for Research Biosample Repository

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR specimen analysis on individual participants will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR specimen data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

### Monitoring and Oversight Research Biosample Repository

Specimens collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

## 1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV).

# 2. DATA HANDLING AND RECORD

## 2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

### 2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 2.1.2. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial‑related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

### 2.1.3. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## 2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## 2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

### 2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

### 2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

### 2.3.3. Dissemination of Clinical Study Data

A description of this clinical trial will be available at http://www.ClinicalTrials.gov.

### 2.3.4. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

## 4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

# Appendix 2
# Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

## 1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Events Meeting the AE Definition:**

- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

**Events NOT Meeting the AE Definition (for Part 1):**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, unless judged by the Investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**Events NOT Meeting the AE Definition (for Part 2):**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease being studied or expected progression, signs, or symptoms of the disease being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## 2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

## 3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by Sponsor's Medical Monitor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor's Medical Monitor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

## 3.1. ASSESSMENT OF SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the categories provided in Table 1 (as a guidance for assessing adverse event severity).

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 1 Adverse Event Severity Grading Scale**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated[d] |
| 5 | Death related to adverse event[d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v5.0), which can be found at:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 6 of this Appendix for reporting instructions), per the definition of serious adverse event in Section 2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2.

## 3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

## 4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

## 5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

## 5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

**Events that Occur prior to Study Treatment Initiation**

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

**Events that Occur after Study Treatment Initiation**

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

**Reporting of Post-Study Adverse Events and Serious Adverse Events**

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event is believed to be related to prior study treatment the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

## 5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7239958 or placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with RO7239958 or placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose*:* Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

## 6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and NSAESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document{s}:

- RO7239958 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study treatment exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Isolated ALT/AST elevation $<$ 5x ULN (with normal liver function tests) in healthy participants
- Isolated ALT/AST elevation $<$ 8x baseline (with normal liver function tests) in CHB patients

# Appendix 3
# Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

## 1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

### 1.1. INJECTION-SITE REACTIONS

Adverse events that occur during or after study drug administration and are judged to be related to study treatment injection should be captured as a diagnosis (e.g., " ISR", "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction”. Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

### 1.2. OTHER ADVERSE EVENTS

For adverse events other than injection reactions (see Section 1.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

## 2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

## 3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

## 4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 5. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 6. ABNORMAL LIVER TRANSAMINASES AND FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN in healthy participants or $>$ 3x baseline in CHB patients) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN (or $>$ 3x baseline) in combination with total bilirubin $>2\times$ULN.
- Treatment-emergent ALT or AST $>3\times$ULN (or $>$ 3x baseline) in combination with clinical jaundice.
- Treatment-emergent ALT or AST $>3\times$ULN (or $>$ 3x baseline) in combination with INR/PT $>$ 1.5
- Treatment-emergent ALT or AST >3x ULN (or $>$ 3x baseline) with the appearance of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash and/or eosinophilia.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 8.3.6).

## 7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to progression of CHB.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

## 8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

## 9. WORSENING OF CHB

Lack of RO7239958 efficacy in terms of changes in HBsAg does not qualify for adverse event in Part 2 of this study.

Medical occurrences or symptoms of deterioration in a course of chronic HBV infection should be recorded as adverse events if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study.

Virological breakthrough (HBV DNA rebound) and abnormal liver function tests (total bilirubin > 2x ULN, INR/PT > 1.5) should be reported as adverse events.

Medical occurrences or symptoms of deterioration that are anticipated as part of chronic HBV infection should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of CHB on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “worsening of CHB”).

## 10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The participant has not suffered an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

# Appendix 4
# Clinical Laboratory Tests

The tests detailed in Table 1 will be performed locally for Part 1 of the study and by the central laboratory for Part 2 (with the exception of urinalysis specific gravity, urine dipstick, and alcohol testing which will be performed locally).

In Part 2, local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be captured in source documentation and entered as a comment into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

## Table 1 Protocol-Required Safety Laboratory Assessments

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | • Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). |
| Clinical Chemistry | • Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, cystatin C (and estimated creatinine- and cystatin C-based eGFR by CKD-epi equation [see Appendix 6]) total protein, albumin, phosphate, calcium, total and direct bilirubin, gamma-glutamyl transferase (GGT), alkaline phosphatase, ALT, AST, urate. *In Part 2, Creatinine Kinase (CK) will be performed as reflex testing on any AST value ≥ 2 x ULN.*<br>For additional assessments relating to exploratory safety BMs, please see Section 8.6.1. |
| Coagulation | • INR, aPTT/ PT. |
| Viral Serology (Part 1) | • HIV (HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), Hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc), hepatitis C virus (HCV) antibody. |
| Viral Serology (Part 2) | • HIV (HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis C virus (HCV) antibody. |
| Pregnancy Test | • All women will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. |
| Urinalysis | • Specific gravity<br>Dipstick: pH, glucose, protein, blood, ketones leukocytes, nitrites.<br>If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.<br>• Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if there is a clinically significant positive result. |
| Other Screening Tests | • Alcohol and drug screen as per local procedure (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)}. |

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study, will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

## Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

# Appendix 5
# Contraceptive Guidance and Collection of Pregnancy Information

## 1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

– Documented hysterectomy.

– Documented bilateral salpingectomy.

– Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

– A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause.

– Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

## 2. CONTRACEPTION GUIDANCE

- **Female Participants**

Only female participants of non-childbearing potential are eligible to participate. Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly as described in Table 1 below.

### Table 1 Highly Effective Contraceptive Methods

| **Highly Effective Contraceptive Methods That Are User-Dependent[a]**<br>(Failure rate of < 1% per year when used consistently and correctly) |
|---|
| Combined (estrogen- and progestogen-containing ) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal<br>• Transdermal<br>Progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Injectable |
| **Highly Effective Methods That Are User-Independent[a]** |
| Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• Bilateral tubal occlusion<br>**Vasectomized partner**<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*<br>**Sexual abstinence**<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* |

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

## 3. PREGNANCY TESTING

For WO*N*CBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to SoA tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

## 4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive RO7239958.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **Female participants who become pregnant**

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

## 5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective abortion not associated with toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

## 6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female  partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 8.3.5).

# Appendix 6
# CKD-EPI GFR

References:

Levey AS, Lesley AS, Schmid CH et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Medicine. 2009; 150(9):604-612.

Stevens LA, Coresh, J, Schmid CH et al. Estimating GFR using Serum Cystatin C Alone and in Combination with Serum Creatinine: A pooled Analysis of 3418 Individuals with CKD. Am J Kidney Dis. 2008; 51(3):395-406.

Zhu Y, Ye X, Zhu B, et al. Comparisons between the 2012 New CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations and other four approved equations. PLoS One. 2014;9(1):1-9.

# Appendix 7

## Grading of Injection Site Reactions (ISRs)

| Parameter | Grade 1 (Mild) | Grade 2 (Moderate) | Grade 3 (Severe) |
|---|---|---|---|
| **Pain** | Mild tenderness at injection site | Moderate pain without limitation of usual activities | Severe pain requiring prescription non topical analgesics, and/or limiting usual activities |
| **Erythema** average diameter (mm) of skin redness at the site of injection | Present but < 25mm | ≥ 25 mm but < 50 mm | ≥ 50 mm |
| **Swelling** average diameter (mm) of swelling at the site of injection | Present but < 25mm | ≥ 25 mm but < 50 mm | ≥ 50 mm |
| **Pruritus** | Mild, not requiring any treatment | Requiring topical treatment | Refractory to topical treatment, or requiring oral or parenteral treatment |

For more detailed information, please use the following link to access the full DAIDS table : https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.