Official Title: A Phase I Study to Investigate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO7565020 in Healthy Participants and in Participants with Chronic Hepatitis B Virus Infection

NCT Number: NCT05763576

Document Date: Protocol Version 3: 15-May-2023

PROTOCOL

TITLE:	**A PHASE I STUDY TO INVESTIGATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7565020 IN HEALTHY PARTICIPANTS AND IN PARTICIPANTS WITH CHRONIC HEPATITIS B VIRUS INFECTION**
PROTOCOL NUMBER:	BP44118
VERSION:	3
REGULATORY AGENCY IDENTIFIER NUMBERS:	**IND Number**: 163100 **EU Trial Number**: 2022-502579-46-00
TEST PRODUCT:	RO7565020
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 21 December 2022
DATE AMENDED	Version 2: 24 March 2023 Version 3: See electronic signature and date stamp on the final page of this document

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE I STUDY TO INVESTIGATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7565020 IN HEALTHY PARTICIPANTS AND IN PARTICIPANTS WITH CHRONIC HEPATITIS B VIRUS INFECTION**
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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 Site Monitor.

PROTOCOL AMENDMENT, VERSION 3
RATIONALE

Protocol BP44118 Version 2 has been amended with the following changes, along with a rationale for each change, are summarized below.

- Table 1 (Part 1a SoA) and Table 2 (Part 1b SoA) have been updated to remove hepatitis D virus (HDV) and hepatitis E virus (HEV) tests at screening. As a defective virus, HDV is always co-infected with hepatitis B virus (HBV), and subjects with HBV infection will be excluded from the healthy volunteer parts of this study (Parts 1a and 1b) by serology. In addition, Part 1 will only be conducted in New Zealand and Hong Kong, which are non-endemic areas for HEV. Section 5.1.2 exclusion criterion #2 has been updated according.
- Section 5.4 (Screen Failures) has been updated to allow re-screening for participants who failed screening due to a transient illness (e.g., influenza or COVID-19 infection).
- Nucleos(t)ide analogues (NUCs) designation has been updated to authorized auxiliary medicinal products (AxMPs)/non-investigational medicinal products (NIMPs) in Section 6 (Treatments) and Appendix 6 (Investigational Medicinal Product and Non-Investigational Medicinal Product Designations), including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and entecavir (ETV). TDF, TAF, and ETV have been approved globally for the treatment of chronic hepatitis B (CHB) and are the current standard of care. In this study, NUCs will be used as background treatment for all virologically suppressed participants with CHB (i.e., all participants in Parts 2 and 3) and administered per local prescribing information.
- Appendix 4 (Clinical Laboratory Tests) has been updated to allow, in some cases, determination of study eligibility based on local laboratory results.

Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

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1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE I STUDY TO INVESTIGATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7565020 IN HEALTHY PARTICIPANTS AND IN PARTICIPANTS WITH CHRONIC HEPATITIS B VIRUS INFECTION**
SHORT TITLE	**RO7565020 Phase I Study in healthy participants and participants with chronic hepatitis B**
PROTOCOL NUMBER:	BP44118
VERSION:	3
REGULATORY AGENCY IDENTIFIER NUMBERS:	**IND Number**: 163100 **EU Trial Number**: 2022-502579-46-00
TEST PRODUCT:	RO7565020
PHASE:	I

RATIONALE

Chronic hepatitis B (CHB) virus infection is a major global healthcare problem, with an estimated prevalence of 296 million people. The current standard of care is either a possibly lifelong treatment with nucleos(t)ide analogues (NUCs) or interferon (IFN)-α preparations that, despite their poor safety and tolerability, provide in rare cases (~3%) a functional cure for patients (defined as the sustained loss of serum hepatitis B surface antigen [HBsAg] and hepatitis B virus [HBV] DNA).

RO7565020 is a human origin monoclonal antibody (mAb) being developed for the treatment of CHB. RO7565020 binds the antigenic loop present in all forms of HBsAg and, as a potent HBsAg depleting agent, offers a potential to increase the functional cure rate or shorten the duration of treatment when given in combination with a direct acting antiviral and/or an immunomodulator for patients with CHB.

This first-in-human (FIH), multi-center, dose-escalation Phase I clinical study of RO7565020 is aiming to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antiviral responses following single and/or multiple doses of RO7565020 via SC injection and/or IV infusion in healthy participants and in virologically suppressed participants with CHB.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the safety and tolerability o following a single dose of RO7565020 administered subcutaneously (SC) or intravenously (IV) to healthy participants (**Part 1a**) and SC to virologically suppressed participants with chronic hepatitis B (CHB) (**Part 2**) o following multiple doses of RO7565020 administered SC to healthy participants (**Part 1b**) and virologically suppressed participants with CHB (**Part 3**)	• Frequency and severity of adverse events (AEs), including adverse events of special interest (AESI), serious adverse events (SAE), and treatment discontinuations due to AEs • Frequency of abnormal laboratory findings based on hematology, blood chemistry (including liver function tests), coagulation and urinalysis test results • Frequency of clinically significant abnormalities in ECGs and vital signs • Mean changes from baseline in vital signs (temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate) over time
Secondary	
• To investigate the serum PK of RO7565020 o following single-ascending doses of RO7565020 administered SC or IV to healthy participants (**Part 1a**) and SC to virologically suppressed participants with CHB (**Part 2**) o following multiple doses of RO7565020 administered SC to healthy participants (**Part 1b**) and virologically suppressed participants with CHB (**Part 3**)	• PK parameters of RO7565020 o Time to maximum concentration (t_{max}) o Maximum serum concentration observed (C_{max}) o AUC from Time 0 to time of last sampling point or last quantifiable sample, whichever comes first ($AUC_{0\text{-last}}$) o AUC from Time 0 to infinity (AUC_{inf}) o Terminal half-life ($t_{1/2}$) o Volume of distribution (Vss) and clearance (CL) (*IV only*) o Apparent clearance (CL/F), apparent volume of distribution at terminal phase (Vz/F) (*SC only*)

Objectives	Endpoints
Secondary (cont.)	
• To characterize the antiviral response after a single dose or multiple doses of RO7565020 in virologically suppressed participants with CHB (**Parts 2 and 3, respectively**)	• Change from baseline in serum quantitative HBsAg • Maximum reduction from baseline of serum HBsAg across all timepoints • Proportion of participants with HBsAg loss (on quantitative and qualitative HBsAg assays) • Proportion of participants with HBsAg seroconversion (sustained loss of HBsAg and detection of anti-HBs antibody) • Proportion of participants with hepatitis B e antigen (HBeAg) loss among HBeAg-positive participants at baseline • Proportion of participants with HBeAg seroconversion (sustained loss of HBeAg and detection of anti-HBe antibody) among HBeAg-positive participants at baseline
• To assess the immunogenicity (induction of anti-drug antibodies [ADA]) of RO7565020 in healthy participants and virologically suppressed participants with CHB	• ADA prevalence at baseline • Incidence and titer of ADA over time

OVERALL DESIGN AND STUDY POPULATION

This FIH study of RO7565020 will be conducted in three parts: Part 1a is a Sponsor-open, Investigator-blinded, single-ascending dose (SAD) study in healthy participants with at least 8 participants per cohort. Part 1b is an optional, Sponsor-open, Investigator-blinded multiple-dose study with 8 healthy participants in 1 cohort. Part 2 is a SAD study in virologically suppressed participants with CHB with 6 participants in each cohort. Participants will be enrolled into Parts 2a and 2b on the basis of the screening HBsAg level (cutoff: 3000 IU/mL). Part 3 is an optional, multiple-dose study with 6 virologically suppressed participants with CHB per cohort.

RO7565020 will be administered via SC injection in healthy participants and participants with CHB, and via IV infusion over 2 hours to healthy participants only. In Parts 1a and 1b, participants will be randomized 6:2 to receive RO7565020 or placebo. In Parts 2 and 3, all participants will receive RO7565020 and all participants will continue to receive NUC therapy throughout the study. Sentinel dosing will be applied to each cohort. The sentinel participants will be monitored for at least 72 hours to confirm safety.

A Dose Decision Team (DDT) consisting of Sponsor members (collectively having expertise in clinical science, clinical pharmacology, pharmacodynamics, statistics, and clinical safety) and Investigators will review emerging study data and make recommendations regarding dose escalation and overall study conduct. The dose escalation may be stopped if stopping criteria are met. Additional dose cohorts that assess lower or repeat doses may be investigated, however, dose modifications of the RO7565020 doses of individual participants are not permitted during the study.

Several key aspects of the study design and study population are summarized below.

Parts 1a and 1b

Phase:	I	**Population Type:**	Heathy participants
Control Method:	Placebo	**Population Diagnosis or Condition:**	Not applicable
Interventional Model:	Sequential	**Population Age:**	18–65 years
Test Compound:	RO7565020	**Site Distribution:**	Multi-center
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Permuted block randomization
Number of Arms:	Up to 7	**Number of Participants to Be Enrolled:**	48–56

Parts 2 and 3

Phase:	I	**Population Type:**	Adult patient
Control Method:	Not applicable	**Population Diagnosis or Condition:**	virologically suppressed participants with chronic hepatitis B
Interventional Model:	Sequential	**Population Age:**	18–65 years
Test Compound:	RO7565020	**Site Distribution:**	Multi-center
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Centralized assignment
Number of Arms:	Up to 9	**Number of Participants to Be Enrolled:**	30–54

STUDY TREATMENT

The investigational medicinal product (IMP) for this study is RO7565020, *an* HBsAg mAb *and it* will be *administered* at the study center under supervision of site staff. *NUCs are background treatment and are classified as authorized auxiliary medicinal products (AxMPs)/non-investigational medicinal products (NIMPs).*

In Part 1a, four provisional escalating RO7565020 dose levels are planned to be administered sequentially to 6 different cohorts of participants. The anticipated ascending-dose scheme is 70 mg SC, 230 mg SC, 360 mg SC, 360 mg IV, and 900–1500 mg IV or matching placebo. Cohort 6 (ethnicity bridging cohort: 360 mg SC or matching placebo) may be conducted in parallel with Cohort 4 after the preliminary safety evaluation in Cohort 3 is completed and considered safe.

In Part 1b (optional), one dose cohort (SC injection; RO7565020 or matching placebo) is planned and the dose level and dosing frequency will be determined by using emerging safety and PK data from Part 1a.

In Part 2a, a single dose of 70 mg SC, 230 mg SC, and 360 mg SC will be administered and in Part 2b, a single dose of 70 mg SC (optional), 230 mg SC, 360 mg SC, and 720 mg SC (optional) may be administered.

In Part 3 (optional), multiple doses will be administered and dose level and dosing frequency will be determined using Part 1 and Part 2 data.

In Parts 2 and 3, all participants will continue to receive NUC therapy throughout the study.

DURATION OF PARTICIPATION

Duration of participation for each part of this study as follows:

Study part	Screening	Treatment period	In-clinic period	End-of-study visit***
Part 1a	Up to 28 days	Day 1	Day −1 to Day 4	36 weeks after study treatment administration
Part 1b	Up to 28 days	Up to 169 days	Day −1 to Day 4, and 1 day after each administration for the following doses, including optional overnight stay*	36 weeks after the last study treatment administration
Parts 2a and 2b	Up to 56 days *(Pregnancy testing and liver function up to 14 days)*	Day 1	Day 1** to Day 4, including optional overnight stay*	24 weeks after study treatment administration (If HBsAg does not return to baseline level at follow-up Week 24, will have additional follow-up visits until returns to < 0.1 log below baseline for two consecutive visits, or up to 56 weeks postdose, whichever comes first.)
Part 3	Up to 56 days *(Pregnancy testing and liver function up to 14 days)*	Up to 337 days	Day 1** to Day 4, and 1 day after each administration for the following doses, including optional overnight stay*	24 weeks after last study treatment administration (If HBsAg does not return to baseline level at follow-up Week 24, will have additional follow-up visits until return to < 0.1 log below baseline for two consecutive visits, or up to 56 weeks post the final dose, whichever comes first.)

Abbreviation: ADA = anti-drug antibody; HBsAg = hepatitis B surface antigen; PK = pharmacokinetic.

* For Part 1b, all participants will stay at the clinic overnight on Day 1 after each dose. Optional overnight stay at the clinic on Day 2 and Day 3 after the first dose, i.e., on Day 2 and Day 3, participants can either stay at the clinic overnight or can be discharged after completion of the assessments and return the next morning for the subsequent assessments, at the Investigator's discretion.
For all cohorts in Part 2a and Cohorts 1 and 2 in Part 2b, all participants will stay at the clinic for at least 8 hours postdose for safety observation and sample collection. The overnight stay from Day 1 to Day 4 for sample collection and assessment is optional, at the Investigator's discretion.
For Cohorts 3 and 4 in Part 2b, all participants will stay at the clinic overnight on Day 1. The overnight stay on Day 2 and Day 3 for sample collection and assessment is optional, at the Investigator's discretion.
For Part 3, all participants will stay at the clinic for at least 8 hours post each dose for safety observation and sample collection. Optional overnight stay at the clinic on Day 1 after each dose, and Day 2 and Day 3 after the first dose.

** Participants can stay at clinic the night before Day 1 (i.e., Day −1) if site prefers due to logistic reasons.

*** After completing the scheduled visits, an additional ADA and PK sample collection may be needed, depending on the emerging ADA data.

CONCOMITANT MEDICATIONS

Permitted Therapy

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Paracetamol/Acetaminophen at doses of ≤ 2 g/day is permitted for use any time during the study.

Prohibited Therapy

Participants should avoid taking non-prescription drugs (including vitamins and dietary or herbal supplements) within 2 weeks or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Vaccination is prohibited between 2 weeks before and 1 week after a dose of RO7565020.

For Part 1, as a general rule, no other concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

For Parts 2 and 3, use of the following therapies is prohibited (with the exception of medications to treat AEs), unless otherwise specified below, or the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

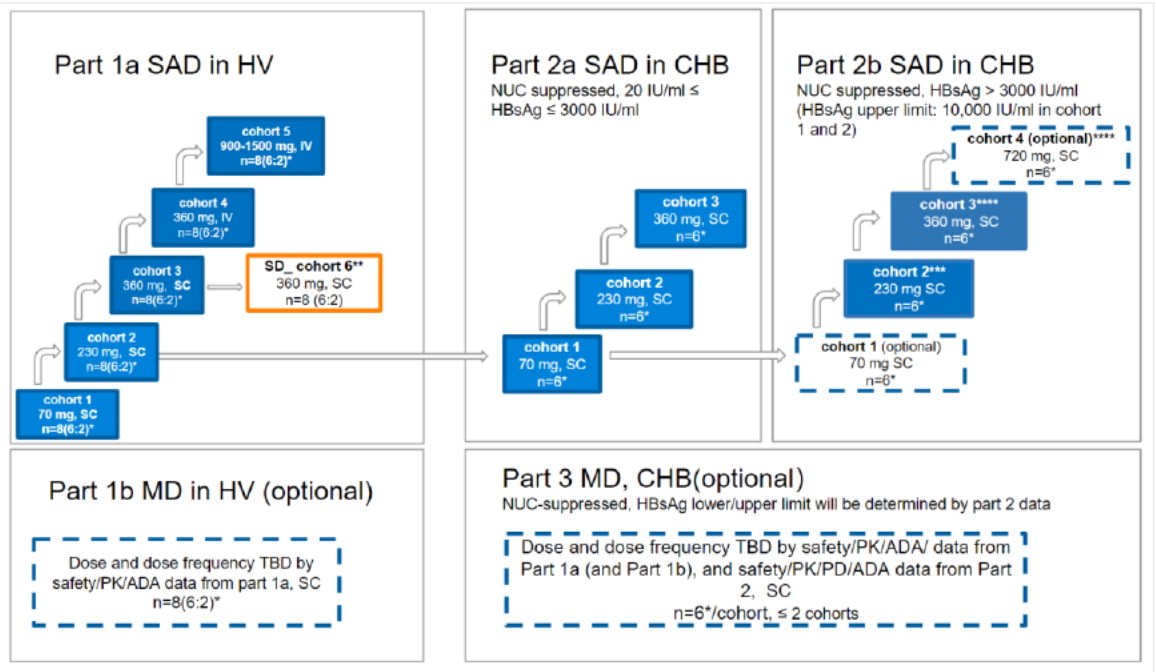
- Any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids, IFN or pegylated [PEG]-IFN) is prohibited at any time during the study and for at least 8 weeks prior to the first dose of study treatment. Eye drop-containing, topical, and infrequent inhaled corticosteroids are permissible up to 4 weeks.
- Any systemic antiviral therapy other than NUC (with the exception of oral therapy for herpes simplex virus [HSV] I or HSV II) is prohibited at any time during the study.

Participants should follow the NUC prescribing information with respect to concomitant medication use while taking the NUC.

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design



Abbreviations: ADA = anti-drug antibody; CHB = chronic hepatitis B; HBsAg = hepatitis B surface antigen; HV = healthy volunteer; IV = intravenous; MD = multiple doses; NUC = nucleos(t)ide analogue; PD = pharmacodynamic; PK = pharmacokinetic; SAD = single-ascending dose; SC = subcutaneous; SD = single dose; TBD = to be determined.

Note: Provisional dose levels are listed in the figure and the decision to escalate to the next dose level and/or cohort will be made by the Dose Decision Team, based on 28-day postdose data from at least 6 participants (5 on active treatment and 1 on placebo) in Part 1, or a minimum of 5 participants on active treatment in Part 2.

* In Parts 1a and 1b, participants will be randomized 6:2 to receive RO7565020 or placebo. In Parts 2 and 3, all participants will receive RO7565020 and all participants will continue to receive NUC therapy throughout the study.

** PK ethnicity bridging cohort, only in Chinese population.

*** If Part 2b Cohort 1 is not conducted, Part 2b Cohort 2 will start after Part 2a Cohort 2 has completed at least 28 days of follow-up in at least 5 participants, i.e., RO7565020 at 230 mg is considered to be safe in participants with HBsAg ≤ 3000 IU/mL.

**** The HBsAg upper limit of the first 2 participants in Part 2b Cohort 3 and Part 2b Cohort 4 is 10,000 IU/mL. If HBsAg at screening is > 10,000 IU/mL, dosing of this participant will be on hold until at least 2 participants with 3000 IU/mL < HBsAg ≤ 10,000 IU/mL have been dosed and considered to be safe after 28 days of follow-up.

1.3 SCHEDULE OF ACTIVITIES

The schedule of activities (SoA) provided in Table 1 for Part 1a (single-ascending dose [SAD] in healthy participants), in Table 2 for part 1b (multiple doses in healthy participants), in Table 3 for Part 2 (SAD in participants with chronic hepatitis B [CHB]), and in Table 4 for Part 3 (multiple doses in participants with CHB).

Table 1 Schedule of Activities – Part 1a

Protocol Section	Cycle/Visit/Week	Screening	Visits														ET
	Day	D-28 to D-2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	Day 21	Day 29	Day 57	Day 85	Day 141	Day 197	Day 253	
	Time Relative (h)	***	NA	0	24	48	72	168	336	480	672	1344	2016	3360	4704	6048	
	Visit Window		0	0	0	0	0	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days	± 7 days	
	Assessments																
Appendix 1	Informed Consent	x															
8.2.5	Demography	x										`					
5.1	Eligibility	X	x														
8.2.5	Medical History	x															
8.2.1	Complete Physical Examination	x [a]															
8.2.1	Symptom-Directed Physical Examination		x [a]	x [a]	x	x	x	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]
Appendix 4	Immunology (ANA, AMA, ASMA, a-TPO)	x											x			x	x
Appendix 4	Blood Chemistry (includes lipids, Cystatin C)	x	x [b]		x			x	x	x	x	x	x	x	x	x	x
Appendix 4	Hematology	x	x [b]		x			x	x	x	x	x	x	x	x	x	x
Appendix 4	Urinalysis	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Appendix 4	Coagulation	x	x [b]		x			x	x	x	x	x	x	x	x	x	x
Appendix 4	C3, C4, and total hemolytic complements (CH50), CRP		x														
8.2.2	Vital Signs - SC cohorts	x	x	3 [c]	x	x	x	x	x	x	x	x	x	x	x	x	x
8.2.2	Vital Signs - IV cohorts	x	x	4 [c]	x	x	x	x	x	x	x	x	x	x	x	x	x
8.2.3	ECG-12 lead	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Appendix 4	Thyroid function tests	x											x			x	x
Appendix 4	Pregnancy Test [d]	x	x								x		x	x	x	x	x
Appendix 4	HAV, HCV, HIV, HBV	x															
5.1.2	Alcohol Use History	x															
5.1.2, Appendix 4	Alcohol, cotinine, and drugs abuse testing	x	x														
4.3	Admission to Unit		x														
4.3	Discharge from Unit						x										
4.3	Ambulatory Visit							x	x	x	x	x	x	x	x	x	x
4.1	Administration of Study Treatment			x													
8.5	RO7565020 PK Sample(Serum) - SC cohorts [e,f]			4 [g]	x	x	x	x	x	x	x	x	x	x	x	x	x
8.5	RO7565020 PK Sample(Serum) - IV cohorts [e,f]			5 [h]	x	x	x	x	x	x	x	x	x	x	x	x	x
8.6	Anti-Drug Antibody (ADA) [f]			x [i]					x	x	x	x	x	x	x	x	x
8.7.4	Cytokine/Chemokine profile and complement activation (SC5b-9) (serum)			3 [j]	x	x	x	x	x	x	x	x	x	x			
8.3	Adverse Events	x															
6.5	Previous and Concomitant Treatments	x															

Table 1 Schedule of Activities – Part 1a (cont.)

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; a-TPO = anti-thyroid peroxidase; CRP = C-reactive protein; ECG = electrocardiogram; ET = early termination; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IV = intravenous; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous.

a. Weight and height will be collected during screening period and Day 1. Weight will be collected in the following visits except Day 2, Day 3, and Day 4.
b. These assessments do not need to be repeated on Day −1, if screening tests sample collection performed within 7 days before dosing.
c. For the SC Cohorts (i.e., Cohorts 1, 2, 3, and 6), vital sign assessments will be performed at predose, 1 hour postdose, and 4 hours postdose on Day 1. For the IV Cohorts (i.e., Cohorts 4 and 5), vital sign assessments will be performed at predose, at the end of infusion, 1 hour after infusion completion, and 4 hours after infusion completion on Day 1. In addition, vital signs will be assessed every 30 minutes during infusion in the IV cohorts to support the evaluation of infusion-related reaction and these vital signs during infusion are not required to be captured in the electronic data capture (EDC) system unless abnormalities are observed.
d. For all women enrolled in the study, blood sample for determining β-human chorionic gonadotropin (HCG) 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. Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.
e. Unscheduled PK sample may be collected according to Section 8.2.3 and Section 8.5, e.g., at the time of treatment discontinuation if an infusion-related AE (such as an infusion- or injection-related reaction [IRR]) is reported, or when clinical significant abnormal ECG, an SAE, a severe AE, an AE leading to dose interruption or delay of RO7565020 administration, or an accidental overdose is reported.
f. After participants complete the scheduled visits, an additional ADA and PK sample may be collected depending on the emerging ADA data.
g. PK samples will be collected at predose (within 2 hours prior to drug administration), and 1 hour (± 5 minutes), 4 hours (± 15 minutes), and 8 hours (± 30 minutes) postdose on Day 1.
h. PK samples will be collected at predose (within 2 hours prior to drug administration), 5 minutes (± 1 minute) after the start of infusion, end of infusion (+5 minutes), and 4 hours (± 15 minutes) and 8 hours (± 30 minutes) after infusion completes on Day 1. PK samples at 5 minutes after the start of infusion and at the end of infusion on the day of IV administration of RO7565020 MUST NOT be taken from the same arm as that used for study treatment administration. In the case of a participant being unable to provide venous access on the opposite arm to that used for study treatment administration, the leg may be used for PK blood sampling.
i. Samples will be collected at predose.
j. Samples will be collected at predose, and 4 hours and 8 hours postdose.

Table 2 Schedule of Activities – Part 1b

Protocol Section	Period/Visit/Week [a]	Screening	1st treatment period										Intermediate treatment periods (up to 4 cycles)						
	Day [b]	D-28 to D-2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 8 [c]	Day 15 [c]	Day 21 [c]	Day 29 [c]	Day 57 [c]	Day 1	Day 2	Day 4	Day 8 [c]	Day 15 [c]	Day 29 [c]	Day 57 [c]
	Time Relative (h)	***	NA	0	24	48	72	168	336	480	672	1344	0	24	72	168	336	672	1344
	Visit Window [b]		0	0	0	0	0	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	0	0	0	± 1 days	± 1 days	± 3 days	± 3 days
	Assessments																		
Appendix 1	Informed Consent	x																	
8.2.5	Demography	x																	
5.1	Eligibility	x	x																
8.2.5	Medical History	x																	
8.2.1	Complete Physical Examination	x [d]																	
8.2.1	Symptom-Directed Physical Examination		x [d]	x [d]	x	x	x	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]
Appendix 4	Blood Chemistry (includes lipids, Cystatin C)	x	x [e]		x			x	x		x	x	x [f]	x		x	x	x	x
Appendix 4	Hematology	x	x [e]		x			x	x		x	x	x [f]	x		x	x	x	x
Appendix 4	Urinalysis	x	x		x	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
Appendix 4	Coagulation	x	x [e]		x			x	x		x	x	x [f]	x		x	x	x	x
Appendix 4	C3, C4, and total hemolytic complements (CH50), CRP		x																
8.2.2	Vital Signs	x	x	3 [g]	x	x	x	x	x	x	x	x	3 [g]	x	x	x	x	x	x
8.2.3	ECG-12 lead	x	x		x	x	x	x	x	x	x	x	x [f]		x	x	x	x	x
Appendix 4	Immunology (ANA, AMA, ASMA, a-TPO)	x											x [f,h]						
Appendix 4	Thyroid function tests	x											x [f,h]						
Appendix 4	Pregnancy Test [i]	x	x									x	x [f,j]						x
Appendix 4	HAV, HCV, HIV, HBV	x																	
5.1.2	Alcohol Use History	x																	
5.1.2, Appendix 4	Alcohol, cotinine, and drugs abuse testing	x	x																
4.3	Admission to Unit [k]		x										x						
4.3	Discharge from Unit [k]						x							x					
4.3	Ambulatory Visit [k]							x	x	x	x	x			x	x	x	x	x
4.1	Administration of Study Treatment			x									x						
8.5	RO7565020 PK Sample(Serum) [l,m]			4 [n]	x	x	x	x	x	x	x	x	x [f]		x	x	x	x	x
8.6	Anti-Drug Antibody (ADA) [m]			x [f]					x	x	x	x	x [f]				x	x	x
8.7.4	Cytokine/Chemokine profile and complement activation (SC5b-9) (serum)			3 [o]	x	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
8.3	Adverse Events	x											x						
6.5	Previous and Concomitant Treatments	x											x						

Table 2 Schedule of Activities – Part 1b (cont.)

Protocol Section	Period/Visit/Week [a]	Last treatment period													ET
	Day [b]	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	Day 21	Day 29	Day 57	Day 85	Day 141	Day 197	Day 253	
	Time Relative (h)	0	24	48	72	168	336	480	672	1344	2016	3360	4704	6048	
	Visit Window [b]	0	0	0	0	± 1 days	± 1 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days	± 7 days	
	Assessments														
Appendix 1	Informed Consent														
8.2.5	Demography														
5.1	Eligibility														
8.2.5	Medical History														
8.2.1	Complete Physical Examination														
8.2.1	Symptom-Directed Physical Examination	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]	x [d]
Appendix 4	Blood Chemistry (includes lipids, Cystatin C)	x [f]	x		x	x	x	x	x	x	x	x	x	x	x
Appendix 4	Hematology	x [f]	x		x	x	x	x	x	x	x	x	x	x	x
Appendix 4	Urinalysis	x [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Appendix 4	Coagulation	x [f]	x		x	x	x	x	x	x	x	x	x	x	x
Appendix 4	C3, C4, and total hemolytic complements (CH50), CRP														
8.2.2	Vital Signs	3 [g]	x	x	x	x	x	x	x	x	x	x	x	x	x
8.2.3	ECG-12 lead	x [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Appendix 4	Immunology (ANA, AMA, ASMA, a-TPO)	x [f]									x			x	x
Appendix 4	Thyroid function tests	x [f]									x			x	x
Appendix 4	Pregnancy Test [i]	x [f]							x		x	x	x	x	x
Appendix 4	HAV, HCV, HIV, HBV														
5.1.2	Alcohol Use History														
5.1.2, Appendix 4	Alcohol, cotinine, and drugs abuse testing														
4.3	Admission to Unit [k]	x													
4.3	Discharge from Unit [k]		x												
4.3	Ambulatory Visit [k]			x	x	x	x	x	x	x	x	x	x	x	x
4.1	Administration of Study Treatment	x													
8.5	RO7565020 PK Sample(Serum) [l,m]	4 [n]	x	x	x	x	x	x	x	x	x	x	x	x	x
8.6	Anti-Drug Antibody (ADA) [m]	x [f]					x	x	x	x	x	x	x	x	x
8.7.4	Cytokine/Chemokine profile and complement activation (SC5b-9) (serum)	3 [o]	x	x	x	x	x	x	x	x	x	x			x
8.3	Adverse Events	x													x
6.5	Previous and Concomitant Treatments	x													x

Table 2 Schedule of Activities – Part 1b (cont.)

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; a-TPO = anti-thyroid peroxidase; CRP = C-reactive protein; ECG = electrocardiogram; ET = early termination; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event.

a. A period refers to the time between one dose of treatment and the start of the next. Up to 6 periods in total.
b. Day 1 refers to the first day of each treatment period. Study day will be calculated on the basis of dosing frequency, e.g., if the dosing frequency is every 28 days, Day 1 of the 2nd treatment period will be Day 29 of the study; If the dosing frequency is every 56 days, Day 1 of the 2nd treatment period will be Day 57 of the study; If the dosing frequency is every 84 days, Day 1 of the 2nd period will be Day 85 of the study. From the second treatment period, for sentinel participants, the whole period can be advanced or delayed by 1 day (i.e., an additional $\pm$1 day visit window); for non-sentinel participants, the whole period can be advanced by 1 day or delayed by 3 days (i.e., an additional -1/+3 days visit window).
c. Dose frequency will be determined by emerging Part 1a data. Some of these visits will not be needed depending on dose frequency, e.g., if the dose frequency is every 28 days, Day 29 and Day 57 visits will not be needed; if the dose frequency is every 56 days, Day 57 visit will not be needed.
d. Weight and height will be collected during screening period and Day 1. Weight will be collected in the following visits except Day 2, Day 3, and Day 4.
e. These assessments do not need to be repeated on Day $-$1, if screening tests sample collection performed within 7 days before dosing.
f. Assessment and sample collection will be performed at predose.
g. Vital signs assessments on dosing days: predose, 1 hour postdose, and 4 hours postdose.
h. This assessment will be needed for Day 1 of some intermediate treatment periods only, depending on dose frequency. The minimum testing frequency of this assessment during treatment period is every 12 weeks. Thus, e.g., if the dose frequency is every 28 days, this assessment will be needed for Day 1 of the 4th treatment period only; if the dose frequency is every 56 days or every 84 days, this assessment will be needed for Day 1 of every intermediate treatment period.
i. For all women enrolled in the study, blood sample for determining β-human chorionic gonadotropin (HCG) 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. Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.
j. This assessment will be needed for Day 1 of some intermediate treatment periods only, depending on dose frequency. The minimum testing frequency of this assessment during treatment period is every 8 weeks. Thus, e.g., if the dose frequency is every 28 days, this assessment will be needed for Day 1 of the 3rd and the 5th treatment period; if the dose frequency is every 56 days or every 84 days, this assessment will be needed for Day 1 of every intermediate treatment period.

Table 2 Schedule of Activities – Part 1b (cont.)

k. All participants will stay at the clinic overnight on Day 1 after each dose. Optional overnight stay at the clinic on Day 2 and Day 3 in the first treatment period: participants can either stay at the clinic overnight or can be discharged after completion of the postdose assessments and return the next morning for the subsequent assessments, at the Investigator's discretion.

l. Unscheduled PK sample may be collected according to Section 8.2.3 and Section 8.5, e.g., at the time of treatment discontinuation if an infusion-related AE (such as an injection-related reaction) is reported, or when clinical significant abnormal ECG, an SAE, a severe AE, an AE leading to dose interruption or delay of RO7565020 administration, or an accidental overdose is reported.

m. After participants complete the scheduled visits, an additional ADA and PK sample may be collected depending on the emerging ADA data.

n. PK samples will be collected at predose (within 2 hours prior to drug administration), then 1 hour (± 5 minutes), 4 hours (± 15 minutes), and 8 hours (± 30 minutes) postdose on Day 1 of the first and the last treatment periods.

o. Samples will be collected at predose, then 4 hours and 8 hours postdose on Day 1 of the first and the last treatment periods.

Table 3 Schedule of Activities – Part 2

Protocol Section	Cycle/Visit/Week	Screening		Visits													Additional visits [a]	ET	Virological breakthrough
	Day	D-56 to D-1	D-14 to D-1	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	every 56 days		
	Time Relative (h)			0	24	48	72	168	336	504	672	1344	2016	2688	3360	4032			
	Visit Window			0	0	0	0	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days		
	Assessments																		
Appendix 1	Informed Consent	x																	
8.2.5	Demography	x																	
5.2	Eligibility	x	x																
8.2.5	Medical History	x																	
8.2.1	Complete physical Examination	x [b]																	
8.2.1	Symptom directed physical examination			x [b, c]	x	x	x	x [b]	x [b]	x [b]	x [b]	x [b]	x [b]	x [b]	x [b]	x [b]	x [b]	x [b]	x
5.2, Appendix 4	Blood Chemistry (includes lipids and Cystatin C)	x	x	x [c]	x			x	x		x	x	x	x	x	x	x	x	x
5.2, Appendix 4	GLDH (exploratory)			x [c]	x			x	x		x	x	x	x	x	x	x	x	x
5.2, Appendix 4	Hematology	x		x [c]	x			x	x		x	x	x	x	x	x	x	x	x
5.2, Appendix 4	Urinalysis	x		x [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
5.2, Appendix 4	Coagulation	x		x [c]	x			x	x		x	x	x	x	x	x	x	x	x
Appendix 4	C3, C4, and total hemolytic complements (CH50), CRP [d]			x [c]															
8.2.2	Vital Signs	x		3 [e]	x	x	x	x	x		x	x	x	x	x	x	x	x	x
8.2.3	ECG-12 lead	x		x [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
5.2.2, Appendix 4	Immunology (ANA, AMA, ASMA, a-TPO)	x											x			x	x	x	
5.2.2, Appendix 4	Thyroid function tests	x														x	x [f]	x	
5.2.2, Appendix 4	Pregnancy Test [g]	x	x									x		x		x	x	x	
5.2.2, Appendix 4	AFP	x														x	x [f]	x	
5.2.2, Appendix 4	Abdominal ultrasound	x														x	x [f]	x	
5.2.1, 8.7.1	HBV DNA quantitative	x		x [c]									x			x	x	x	x
8.7.1	HBsAg	x		3 [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.7.1	HBV Serology (HBeAg, anti-HBs, anti-Hbe)	x		x [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.7.1	HBV RNA			x [c]				x	x		x	x		x		x	x	x	x
8.7.1	HBcrAg			x [c]				x	x		x	x		x		x	x	x	x
8.7.1	Total anti-HBc			x [c]				x	x		x	x		x		x	x	x	x
8.7.1	Total HBsAg (post-dissociation of HBsAg:HBsAb complexes)			3 [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.7.1	HbsAg isoforms			x [c]				x	x		x	x		x		x	x	x	x
8.7.2	HBV genotype			x [c]															
8.7.3	Viral Resistance			x [c]												x	x [i]	x	x
5.2.2	Transient elastography (e.g., Fibroscan)/ARFI/MRI [j]	x																	
5.2.2, Appendix 4	HAV, HCV, HDV, HEV, HIV	x																	
5.2.2	Alcohol Use History	x																	
5.2.2, Appendix 4	Alcohol and drugs abuse testing	x		x [c]															
4.3	Admission to Unit [k]			x															
4.3	Discharge from Unit [k]						x												
4.3	Ambulatory Visit [k]	x	x					x	x	x	x	x	x	x	x	x	x	x	x
4.1	Administration of Study Treatment			x															
6.1	NUC									x									
8.5	RO7565020 PK [l,m]			4 [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.6	Anti-Drug Antibody (ADA) [m]			x [c]					x	x	x	x	x	x	x	x	x	x	x
8.3.7	NUC PK																		x
8.7.4	Cytokine/Chemokine profile and complement activation (SC5b-9) [d]			3 [h]	x	x	x	x	x	x	x	x	x	x	x	x		x [o]	
8.7.4	PBMC HBV-specific cellular immune response [p]			x [c]							x		x			x		x [o]	
8.7.5	Clinical Genotyping				x														
8.7.4	scRNAseq			x [c]							x		x			x		x [o]	
8.9	Research Biosample Repository (RBR) [q]			x [c]							x		x			x			x
8.3	Adverse Events									x								x	x
6.5	Previous and Concomitant Treatments									x								x	x

Table 3 Schedule of Activities – Part 2 (cont.)

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AFP = α-fetoprotein; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ARFI = elastography/acoustic radiation force impulse; ASMA = anti-smooth muscle antibody; a-TPO = anti-thyroid peroxidase; CRP = C-reactive protein; ECG = electrocardiogram; ET = early termination; HAV = hepatitis A virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; NUC = nucleos(t)ide analogue; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RBR = research biosample repository; SAE = serious adverse event; scRNAseq = single-cell RNA sequencing.

a. If HBsAg value does not return to baseline level on Day 169, participants will come to the clinic for additional follow-up visits every 56 days until HBsAg value returns to < 0.1 log below baseline for two consecutive visits, or up to Day 393, whichever comes first.
b. Weight and height will be collected during screening period. Weight will be collected in the following visits except Day 2, Day 3, and Day 4 visits.
c. Assessments or sample collection will be performed at predose.
d. Unscheduled sample for complement activation and CRP will be collected for suspected immune complex mediated adverse events and other events following Section 8.3.7.
e. Vital sign assessments on Days 1: predose, 1 hour postdose, and 4 hours postdose.
f. Required for Day 337 visit only.
g. For all women enrolled in the study, blood sample for determining β-human chorionic gonadotropin (HCG) 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. Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.
h. Samples will be collected at predose, then at 4 hours and 8 hours postdose.
i. In the additional visits, viral resistance sample needs to be collected in the last visit only, i.e., if HBsAg value returns to < 0.1 log below baseline, viral resistance sample needs to be collected in the next confirmation visit.
j. Liver biopsy or transient elastography/ARFI/MRI results obtained within 6 months prior to study Day 1 are also acceptable.
k. For all cohorts in Part 2a and Cohorts 1 and 2 in Part 2b, all participants will stay at the clinic for at least 8 hours postdose for safety observation and sample collection. The overnight stay until Day 4 for sample collection and assessment is optional, at the Investigator's discretion. For Cohorts 3 and 4 of Part 2b, all participants will stay at the clinic overnight on Day 1. The overnight stay on Days 2 and 3 for sample collection and assessment is optional, at the Investigator's discretion.
l. Unscheduled PK sample may be collected according to Section 8.2.3 and Section 8.5, e.g., at the time of treatment discontinuation if an infusion-related AE (such as an injection-related reaction) is reported, or when clinical significant abnormal ECG, an SAE, a severe AE, an AE leading to dose interruption or delay of RO7565020 administration, or an accidental overdose is reported.

Table 3 Schedule of Activities – Part 2 (cont.)

m. After participants complete the scheduled visits, an additional ADA and PK sample may be collected depending on the emerging ADA data.
n. PK samples will be collected at predose (2 hours prior to drug administration), then 1 hour (± 5 minutes), 4 hours (± 15 minutes), and 8 hours (± 30 minutes) postdose.
o. Samples for these tests do not need to be collected if the participant has completed 169 days of follow-up.
p. Only for participants from selected sites that decide to participate in PBMC collection.
q. RBR samples will be collected only from participants who consent to RBR.

Table 4 Schedule of Activities – Part 3

Protocol Section	Period/Visit/Week [a]	Screening		1st treatment period								Intermediate treatment periods (up to 4 cycles)						
	Day [c]	D-56 to D-1	D-14 to D-1	Day 1	Day 2	Day 4	Day 8	Day 15	Day 22	Day 29 [d]	Day 57 [d]	Day 1	Day 2	Day 4	Day 8	Day 15	Day 29 [d]	Day 57 [d]
	Time Relative (h)			0	24	72	168	336	504	672	1344	0	24	72	168	336	672	1344
	Visit Window [c]			0	0	0	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	0	0	0	± 1 day	± 1 day	± 3 days	± 3 days
	Assessments																	
Appendix 1	Informed Consent	x																
8.2.5	Demography	x																
5.2	Eligibility	x	x															
8.2.5	Medical History	x																
8.2.1	Complete physical Examination	x [e]																
8.2.1	Symptom directed physical examination			x [e,f]	x	x	x [e]	x [e]	x [e]	x [e]	x [e]	x [e,f]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]
5.2, Appendix 4	Blood Chemistry (includs lipids and Cystatin C)	x	x	x [f]			x	x		x	x	x [f]			x	x	x	x
5.2, Appendix 4	GLDH (exploratory)			x [f]			x	x		x	x	x [f]			x	x	x	x
5.2, Appendix 4	Hematology	x		x [f]			x	x		x	x	x [f]			x	x	x	x
5.2, Appendix 4	Urinalysis	x		x [f]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
5.2, Appendix 4	Coagulation	x		x [f]			x	x		x	x	x [f]			x	x	x	x
Appendix 4	C3, C4, and total hemolytic complements (CH50), CRP [g]			x [f]														
8.2.2	Vital Signs	x		3 [h]	x	x	x	x		x	x	3 [h]	x	x	x	x	x	x
8.2.3	ECG-12 lead	x		x [f]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
5.2.2, Appendix 4	Immunology (ANA, AMA, ASMA, a-TPO)	x										x [i]						
5.2.2, Appendix 4	Thyroid function tests	x										x [i]						
5.2.2, Appendix 4	Pregnancy Test [k]	x	x								x	x [l]						x
5.2.2, Appendix 4	AFP	x										x [m]						
5.2.2, Appendix 4	Abdominal ultrasound	x										x [m]						
5.2.1, 8.7.1	HBV DNA quantitative	x		x								x [i]						
8.7.1	HBsAg	x		3 [n]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
8.7.1	HBV Serology (HBeAg, anti-HBs, anti-Hbe) [o]	x		x [f]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
8.7.1	HBV RNA [o]			x [f]			x	x		x	x	x [f]			x	x	x	x
8.7.1	HBcrAg [o]			x [f]			x	x		x	x	x [f]			x	x	x	x
8.7.1	Total anti-HBc [o]			x [f]			x	x		x	x	x [f]			x	x	x	x
8.7.1	Total HBsAg (post-dissociation of HBsAg:HBsAb complexes) [o]			3 [n]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
8.7.1	HBsAg isoforms [o]			x [f]			x	x		x	x	x [f]			x	x	x	x
8.7.2	HBV genotype			x [f]														
8.7.3	Viral Resistance			x [f]														
5.2.2	**Transient elastography(e.g., Fibroscan)/ARFI/MRI** [q]	x																
5.2.2, Appendix 4	HAV, HCV, HDV, HEV, HIV	x																
5.2.2	Alcohol Use History	x																
5.2.2, Appendix 4	Alcohol and drugs abuse testing	x		x [f]														
4.3	Admission to Unit [r,s]			x								x						
4.3	Discharge from Unit [r]					x							x					
4.3	Ambulatory Visit [r]	x	x				x	x	x	x	x			x	x	x	x	x
4.1	Administration of Study Treatment			x								x						
6.1	NUC	x		x														
8.5	RO7565020 PK Sample [t,u]			4 [v]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
8.6	Anti-Drug Antibody (ADA) [u]			x [f]				x	x	x	x	x [f]				x	x	x
8.3.7	NUC PK																	
8.7.4	Cytokine/Chemokine profile and complement activation (SC5b-9) (serum) [p]			3 [n]	x	x	x	x	x	x	x	x [f]	x	x	x	x	x	x
8.7.4	PBMC HBV-specific cellular immune response (blood) [x]			x [f]						x		x [f]					x	
8.7.5	Clinical Genotyping				x													
8.7.4	scRNAseq (blood)			x [f]						x		x [f]					x	
8.9	Research Biosample Repository (RBR) [y]			x [f]						x		x [f]					x	
8.3	Adverse Events	x										x						
6.5	Previous and Concomitant Treatments	x										x						

Table 4 Schedule of Activities – Part 3 (cont.)

Protocol Section	Period/Visit/Week [a]	Last treatment period												Additional visits [b]	ET	Virological breakthrough
	Day [c]	Day 1	Day 2	Day 4	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Every 56 days		
	Time Relative (h)	0	24	72	168	336	504	672	1344	2016	2688	3360	4032			
	Visit Window [c]	0	0	0	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days		
	Assessments															
Appendix 1	Informed Consent															
8.2.5	Demography															
5.2	Eligibility															
8.2.5	Medical History															
8.2.1	Complete physical Examination															
8.2.1	Symptom directed physical examination	x [e,f]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]	x
5.2, Appendix 4	Blood Chemistry (includs lipids and Cystatin C)	x [f]			x	x		x	x	x	x	x	x	x	x	x
5.2, Appendix 4	GLDH (exploratory)	x [f]			x	x		x	x	x	x	x	x	x	x	x
5.2, Appendix 4	Hematology	x [f]			x	x		x	x	x	x	x	x	x	x	x
5.2, Appendix 4	Urinalysis	x [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
5.2, Appendix 4	Coagulation	x [f]			x	x		x	x	x	x	x	x	x	x	x
Appendix 4	C3, C4, and total hemolytic complements (CH50), CRP [g]															
8.2.2	Vital Signs	3 [h]	x	x	x	x		x	x	x	x	x	x	x	x	x
8.2.3	ECG-12 lead	x [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	
5.2.2, Appendix 4	Immunology (ANA, AMA, ASMA, a-TPO)	x								x			x	x	x	x
5.2.2, Appendix 4	Thyroid function tests	x											x	x [j]	x	
5.2.2, Appendix 4	Pregnancy Test [k]	x							x		x		x	x	x	
5.2.2, Appendix 4	AFP	x											x	x [j]	x	
5.2.2, Appendix 4	Abdominal ultrasound	x											x	x [j]	x	
5.2.1, 8.7.1	HBV DNA quantitative	x								x			x	x	x	x
8.7.1	HBsAg	3 [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.7.1	HBV Serology (HBeAg, anti-HBs, anti-Hbe) [o]	x [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.7.1	HBV RNA [o]	x [f]			x	x		x	x	x	x	x	x	x	x	x
8.7.1	HBcrAg [o]	x [f]			x	x		x	x	x	x	x	x	x	x	x
8.7.1	Total anti-HBc [o]	x [f]			x	x		x	x	x	x	x	x	x	x	x
8.7.1	Total HBsAg (post-dissociation of HBsAg:HBsAb complexes) [o]	3 [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.7.1	HBsAg isoforms [o]	x [f]			x	x		x	x	x	x	x	x	x	x	x
8.7.2	HBV genotype															
8.7.3	Viral Resistance												x	x [p]	x	x
5.2.2	Transient elastography(e.g., Fibroscan)/ARFI/MRI [q]															
5.2.2, Appendix 4	HAV, HCV, HDV, HEV, HIV															
5.2.2	Alcohol Use History															
5.2.2, Appendix 4	Alcohol and drugs abuse testing															
4.3	Admission to Unit [r,s]	x														
4.3	Discharge from Unit [r]		x													
4.3	Ambulatory Visit [r]			x	x	x	x	x	x	x	x	x	x	x	x	x
4.1	Administration of Study Treatment	x														
6.1	NUC								x						x	
8.5	RO7565020 PK Sample [t,u]	4 [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8.6	Anti-Drug Antibody (ADA) [u]	x [f]				x	x	x	x	x	x	x	x	x	x	x
8.3.7	NUC PK															x
8.7.4	Cytokine/Chemokine profile and complement activation (SC5b-9) (serum) [p]	3 [n]	x	x	x	x	x	x	x	x	x	x	x		x [w]	
8.7.4	PBMC HBV-specific cellular immune response (blood) [x]	x [f]						x		x			x		x [w]	
8.7.5	Clinical Genotyping															
8.7.4	scRNAseq (blood)	x [f]						x		x			x		x [w]	
8.9	Research Biosample Repository (RBR) [y]	x [f]						x		x			x			x
8.3	Adverse Events								x						x	x
6.5	Previous and Concomitant Treatments								x						x	x

Table 4 Schedule of Activities – Part 3 (cont.)

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AFP = α-fetoprotein; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ARFI = elastography/acoustic radiation force impulse; ASMA = anti-smooth muscle antibody; a-TPO = anti-thyroid peroxidase; CRP = C-reactive protein; ECG = electrocardiogram; ET = early termination; FU = follow-up; HAV = hepatitis A virus; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; NUC = nucleos(t)ide analogue; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RBR = research biosample repository; SAE = serious adverse event; scRNAseq = single-cell RNA sequencing.

a. A period refers to the time between one dose of treatment and the start of the next. Up to 6 periods in total.
b. If HBsAg value does not return to baseline level on Day 169 of the last treatment period, participant needs to come to the clinic for additional follow-up visits every 56 days until HBsAg value returns to < 0.1 log below baseline for two consecutive visits, or up to 56 weeks after final dose, whichever comes first.
c. Day 1 refers to the first day of each treatment period. Study day will be calculated on the basis of dosing frequency, e.g., if the dosing frequency is every 28 days, Day 1 of the 2nd treatment period will be Day 29 of study; if the dosing frequency is every 56 days, Day 1 of the 2nd treatment period will be Day 57 of study; if the dosing frequency is every 84 days, Day 1 of the 2nd period will be Day 85 of study. From the second period, for sentinel participants, the whole period can be advanced or delayed by 1 day (i.e., an additional $\pm$ 1 day visit window); for non-sentinel participants, the whole period can be advanced by 1 day or delayed by 3 days, (i.e., an additional -1/+3 days visit window).
d. Dose frequency will be determined by emerging Parts 1 and 2 data. Some of these visits will not be needed depending on dose frequency, e.g., if the dose frequency is every 28 days, Day 29 and Day 57 visits will not be needed; if dose frequency is every 56 days, Day 57 visit will not be needed; if dose frequency is every 84 days, Day 29 and Day 57 visits will be needed.
e. Weight and height will be collected during screening period. Weight will be collected in the following visits except Day 2, Day 3, and Day 4 visits.
f. Assessments and sample collection will be performed at predose.
g. Unscheduled sample for complement activation and CRP will be collected for suspected immune complex mediated AEs and other events following Section 8.3.7.
h. Vital sign assessments on dosing days: predose, 1 hour postdose, and 4 hours postdose.
i. This assessment will be needed for Day 1 of some intermediate treatment periods only, depending on dose frequency. The minimum testing frequency of this assessment during treatment period is every 12 weeks. Thus, e.g., if the dose frequency is every 28 days, this assessment will be needed for Day 1 of the 4th treatment period; if the dose frequency is every 56 days or every 84 days, this assessment will be needed for Day 1 of every intermediate treatment period.
j. Required for Day 337 of the last treatment period only.

Table 4 Schedule of Activities – Part 3 (cont.)

k. For all women enrolled in the study, blood sample for determining β-human chorionic gonadotropin (HCG) 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. Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

l. This assessment will be needed for Day 1 of some intermediate treatment periods only, depending on dose frequency. The minimum testing frequency of this assessment during treatment period is every 8 weeks. Thus, e.g., if the dose frequency is every 28 days, this assessment is needed for Day 1 of the 3rd and the 5th treatment periods; if the dose frequency is every 56 days or every 84 days, this assessment is needed for Day 1 of every intermediate treatment period.

m. This assessment will be needed for Day 1 of some intermediate treatment periods only, depending on dose frequency. The minimum testing frequency of this assessment during treatment period is every 24 weeks. Thus, e.g., if the dose frequency is every 28 days, this assessment will not be needed during the intermediate treatment periods; if the dose frequency is every 56 days, this assessment will be needed for Day 1 of the 4th treatment period; if the dose frequency is every 84 days, this assessment will be needed for Day 1 of the 3rd treatment period.

n. Samples will be collected at predose, then at 4 hours and 8 hours postdose on Day 1 of the first and the last treatment periods.

o. The frequency of sample collection of these PD markers may be reduced depending on emerging data and dose frequency.

p. In the additional visits, viral resistance sample needs to be collected in the last visit only, i.e., if the HBsAg value returns to < 0.1 log below the baseline value, viral resistance sample needs to be collected in the next confirmation visit.

q. Liver biopsy or transient elastography/ARFI/MRI results obtained within 6 months prior to study Day 1 are also acceptable.

r. All participants will stay at the clinic for at least 8 hours post each dose for safety observation and sample collection. Overnight stay at the clinic on Day 1 after each dose, and on Days 2 and 3 after the first dose is optional.

s. Participants can stay at site on the night before dosing if site prefers.

t. Unscheduled PK sample may be collected according to Section 8.2.3 and Section 8.5, e.g., at the time of treatment discontinuation if an infusion-related AE (such as an injection-related reaction) is reported, or when clinical significant abnormal ECG, an SAE, a severe AE, an AE leading to dose interruption or delay of RO7565020 administration, or an accidental overdose is reported.

u. After participants complete the scheduled visits, an additional ADA and PK sample may be collected depending on the emerging ADA data.

v. PK samples will be collected at predose (2 hours prior to drug administration), then at 1 hour (± 5 minutes), 4 hours (± 15 minutes), and 8 hours (± 30 minutes) postdose on Day 1 of the first and the last treatment periods.

w. Samples for these tests do not need to be collected if the participant has completed 169 days of follow-up after the final dose.

x. Only for participants from selected sites that decide to participate in PBMC collection.

y. RBR samples will be collected only from participants who consent to RBR.

2. INTRODUCTION

2.1 STUDY RATIONALE

Chronic hepatitis B (CHB) virus infection is a major global healthcare problem, with an estimated prevalence of 296 million people (WHO 2022). The current standard of care is either a possibly lifelong treatment with nucleos(t)ide analogues (NUCs) or interferon (IFN)- α preparations that, despite their poor safety and tolerability, provide in rare cases (~3%) a functional cure for patients (defined as the sustained loss of serum hepatitis B surface antigen [HBsAg] and hepatitis B virus [HBV] DNA; Lok et al. 2017).

RO7565020 is a human origin monoclonal antibody (mAb) being developed for the treatment of CHB. RO7565020 binds the "a-determinant" of the antigenic loop present in all forms of HBsAg and, as a potent HBsAg depleting agent, offers a potential to increase the functional cure rate or shorten the duration of treatment when given in combination with a direct acting antiviral and/or an immunomodulator for patients with CHB.

This first-in-human (FIH), multi-center, dose-escalation Phase I clinical study of RO7565020 is aiming to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antiviral responses following single and/or multiple doses of RO7565020 via SC injection and/or IV infusion in healthy participants and in virologically suppressed participants with CHB.

The scientific rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

2.2.1 Background on Chronic Hepatitis B

HBV infection is a major cause of both acute hepatitis and chronic liver disease including cirrhosis and hepatocellular carcinoma (HCC). WHO estimates that 296 million people were living with CHB infection in 2019, with 1.5 million new infections each year. In 2019, HBV infection resulted in an estimated 820,000 deaths, mostly from complications including cirrhosis and HCC (WHO 2022).

Persistence of HBV infection is a consequence of the presence of covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes. Despite the advancement in the understanding of HBV disease biology, eradication of cccDNA (defined as disease cure) is not likely in the near future. Nevertheless, the sustained clearance of HBsAg has been shown to be protective against disease progression and development of HBV complications including cirrhosis, liver failure, and HCC. Accordingly, current drug development efforts aim to achieve functional cure of CHB (i.e., sustained loss of HBsAg and HBV DNA) with finite treatment regimens (Lok et al. 2017).

2.2.2 Currently Available Therapies

Currently, there are two therapeutic classes available for the treatment of CHB: subcutaneously (SC) administered IFN preparations (conventional or pegylated [PEG]-IFN-α) and orally administered NUCs (tenofovir, entecavir, adefovir, telbivudine, and lamivudine). After 1 year of treatment, both types of treatment can suppress circulating HBV DNA levels (virologic response 7%–94%), normalize serum liver transaminase enzymes (biochemical response 32%–83%), and induce hepatitis B e antigen (HBeAg) seroconversion in HBeAg-positive patients (serological response 10%–32%). Although these treatments reduce the risk of CHB sequelae, they are associated with very low rates of functional cure (HBsAg loss rates generally not exceeding 3% after 1 year of therapy) (European Association for the Study of the Liver [EASL] 2017).

Furthermore, the existing standard-of-care therapies have important limitations. For example, virologic relapse after treatment discontinuation is a major limitation of currently approved therapies, which rarely result in functional cure. IFN-based therapies have common adverse events (AEs) of flu-like symptoms and can be associated with treatment-limiting adverse effects (e.g., neutropenia, thrombocytopenia), while NUCs require long-term and possibly lifelong therapy in the majority of treated patients. Given these limitations, there is an unmet need for novel treatments of a finite duration that yield higher functional cure rates (Liu et al. 2017; Durantel and Zoulim 2016; Lok et al. 2017; Wang and Chen 2014).

2.2.3 Background on RO7565020

RO7565020 is a human IgG1 mAb (anti-HBs neutralizing antibody Bc1.187) with a well characterized neonatal Fc receptor (FcRn) affinity-enhancing Fc mutation (M252Y/S254T/T256E; YTE) introduced to increase the half-life and enhance the pharmacokinetic (PK) properties. RO7565020 binds to the antigenic loop present in all forms of HBsAg (L-HBsAg, M-HBsAg, and S-HBsAg) and showed potent and cross-reactive neutralization against genotypes A, B, C, and D in vitro.

Sequential to a single dose of small interfering RNA (siRNA) surrogate, single dose RO7565020 treatment further reduced HBsAg level in the adeno-associated virus (AAV)-HBV mouse model from 3 log10 IU/mL to close to undetectable levels ($<$0.2 log10 IU/mL).

In addition, RO7565020 can mediate phagocytic cell uptake of HBsAg particles, suggesting that antibody-coated viral particles and/or infected hepatocytes could be eliminated in vivo by phagocytes such as Kupffer cells. The Fc receptor-dependent function of antibody-dependent cellular phagocytosis (ADCP) may also facilitate antigen presentation to antigen-specific T cells, which could stimulate host humoral and cellular immune responses, a phenomenon known as the vaccine-like effect.

A detailed description of the chemistry, pharmacology, nonclinical efficacy and safety of RO7565020 is provided in the RO7565020 IB.

2.3 BENEFIT–RISK ASSESSMENT

As this is the first-in-human study with RO7565020, no therapeutic benefit is anticipated for participants in Part 1 of this study (as for all early clinical studies in healthy participants) and no long-term benefit to participants with CHB is anticipated in Parts 2 and 3 of this study. However, this study may benefit future patients, as it is essential for the development of new treatments for CHB, and for identifying the appropriate RO7565020 dose for study within a combination therapy setting.

Given no prior clinical experience with RO7565020 exists, the evaluation of the potential risks of treatment and the specific tests, observations, and precautions required for clinical studies with RO7565020 is based primarily on available data from nonclinical toxicology and safety pharmacology studies, as well as information from clinical studies with other anti-HBsAg mAbs. Overall, the level of risk for the individual participants due to treatment with RO7565020 is considered to be minimal and will be managed in a stepwise manner.

The main risk in healthy volunteers is related to the potential development of anti-drug antibody (ADA), while in participants with CHB there is an additional risk associated with target binding and the formation of HBsAg:HBsAb complexes. Risks will be mitigated by conservative selection of the starting dose, careful safety monitoring, staggered dose escalation, sentinel dosing, pre-specified stopping criteria, and well-defined participant characteristics and stopping criteria.

No effect is anticipated from the coronavirus disease 2019 (COVID-19) pandemic on the study benefit–risk assessment or the existing study safety monitoring and risk mitigation measures. Patients with symptomatic disease (including COVID-19) at screening will be excluded and enrolled participants will be closely monitored for new/emerging infections.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7565020 is provided in the IB.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 5.

Table 5 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability: o following a single dose of RO7565020 administered subcutaneously (SC) or intravenously (IV) to healthy participants (**Part 1a**) and SC to virologically suppressed participants with chronic hepatitis B (CHB) (**Part 2**) o following multiple doses of RO7565020 administered SC to healthy participants (**Part 1b**) and virologically suppressed participants with CHB (**Part 3**)	• Frequency and severity of adverse events (AEs), including adverse events of special interest (AESI), serious adverse events (SAE), and treatment discontinuations due to AEs • Frequency of abnormal laboratory findings based on hematology, blood chemistry (including liver function tests), coagulation and urinalysis test results • Frequency of clinically significant abnormalities in ECGs and vital signs • Mean changes from baseline in vital signs (temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate) over time
Secondary	
• To investigate the serum pharmacokinetics of RO7565020: o following single-ascending doses of RO7565020 administered SC or IV to healthy participants (**Part 1a**) and SC to virologically suppressed participants with CHB (**Part 2**) o following multiple doses of RO7565020 administered SC to healthy participants (**Part 1b**) and virologically suppressed participants with CHB (**Part 3**)	• PK parameters of RO7565020: o Time to maximum concentration (t_{max}) o Maximum serum concentration observed (C_{max}) o AUC from Time 0 to time of last sampling point or last quantifiable sample, whichever comes first ($AUC_{0\text{-last}}$) o AUC from Time 0 to infinity (AUC_{inf}) o Terminal half-life ($t_{1/2}$) o Volume of distribution (Vss) and clearance (CL) (*IV only*) o Apparent clearance (CL/F), apparent volume of distribution at terminal phase (Vz/F) (*SC only*)

Table 5 Objectives and Endpoints (cont.)

Objectives	Endpoints
Secondary (cont.)	
• To characterize the antiviral response after a single dose or multiple doses of RO7565020 in virologically suppressed participants with CHB (**Parts 2 and 3, respectively**)	• Change from baseline in serum quantitative hepatitis B surface antigen (HBsAg) • Maximum reduction from baseline of serum HBsAg across all timepoints • Proportion of participants with HBsAg loss (on quantitative and qualitative HBsAg assays) • Proportion of participants with HBsAg seroconversion (sustained loss of HBsAg and detection of anti-HBs antibody) • Proportion of participants with hepatitis B e antigen (HBeAg) loss among HBeAg-positive participants at baseline • Proportion of participants with HBeAg seroconversion (sustained loss of HBeAg and detection of anti-HBe antibody) among HBeAg-positive participants at baseline
• To assess the immunogenicity (induction of anti-drug antibodies [ADAs]) of RO7565020 in healthy participants and virologically suppressed participants with CHB	• ADA prevalence at baseline • Incidence and titer of ADA over time
Exploratory	
• To characterize the relationship between HBsAg at baseline, the serum concentration of RO7565020 and the maximum reduction of HBsAg (**Parts 2 and 3**)	• Model parameters describing relationships between ratio of RO7565020/HBsAg at baseline and maximum HBsAg reduction
• To explore the potential impact of ADA on safety and PK/PD after single dose or multiple doses of RO7565020 in healthy participants (**Part 1**) and virologically suppressed participants with CHB (**Parts 2 and 3**)	• Relationship between ADA, safety, and PK/PD
• To explore the effect of RO7565020 on other viral biomarkers, such as HBeAg (calculated), HBV RNA, hepatitis B core-related antigen (HBcrAg), total HBsAg after HBsAg:HBsAb complex dissociation, and HBsAg isoforms (**Parts 2 and 3**)	• Baseline and change from baseline in HBeAg (calculated), HBV RNA levels, HBcrAg levels, total HBsAg (after HBsAg:HBsAb complex dissociation), and distribution of HBsAg isoforms
• To explore the relationship between baseline disease characteristics and efficacy/safety responses (**Parts 2 and 3**)	• Association of the primary and secondary endpoints with the HBV genotype, baseline HBeAg status, and baseline exploratory parameters (such as HBV RNA, HBcrAg, total anti-HBc, HBsAg isoforms)

Table 5 Objectives and Endpoints (cont.)

Objectives	Endpoints
Exploratory (cont.)	
• To explore the relationship between HBsAg decrease, HBsAg-HBsAb immune complex formation, and the recovery of the immune response (**Parts 2 and 3**)	• Baseline and change from baseline of cytokines and other soluble markers of immune activation and inflammation • Changes in immune cell subsets and activation status (flow cytometry/ICS) and antigen-specific immune response (ELISpot/FluoroSpot) at baseline and post-treatment (PBMC samples) • Baseline and changes from baseline in the transcriptional profile of immune cells subsets in peripheral blood (host gene sc-RNAseq)
• To explore the relationship between potential AEs and inflammatory cytokines released in healthy participants (**Part 1**) and participants with CHB (**Parts 2 and 3**)	• Association between cytokines and other soluble markers of immune activation and inflammation with AEs
• To monitor the potential emergence of RO7565020-resistant variants and their impact on efficacy/safety outcomes (**Parts 2 and 3**)	• Baseline and changes in free and total HBsAg over time in relationship to RO7565020 PK • Baseline and changes from baseline in binding affinity of RO7565020 to HBsAg • Baseline and changes from baseline in the clonality of the S gene sequences

4. STUDY DESIGN

4.1 OVERALL DESIGN

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

This is a FIH, multi-center, dose-finding, and dose-escalation Phase I clinical study of RO7565020 to investigate the safety and tolerability and to characterize the pharmacokinetics, ADA, pharmacodynamics, and preliminary antiviral responses following single and/or multiple doses of RO7565020 in healthy participants and/or virologically suppressed participants with CHB. RO7565020 will be administered via SC injection in healthy participants and participants with CHB, and by IV infusion to healthy participants only. The study will be conducted in three parts: Part 1a is a SAD study in healthy participants with at least 8 participants per cohort. Part 1b is an optional, multiple-dose study with 8 healthy participants in 1 cohort. Part 2 is a SAD study in virologically suppressed participants with CHB with 6 participants in each cohort. Participants will be enrolled into Parts 2a and 2b on the basis of the baseline HBsAg level (cutoff: 3000 IU/mL). Part 3 is an optional, multiple-dose study with 6 virologically suppressed participants with CHB per cohort (see Figure 1).

A Dose Decision Team (DDT) will review emerging study data and make recommendations regarding dose escalation and overall study conduct (see Section 4.1.1.2). The dose escalation will be stopped according to stopping rules criteria (see Section 4.1.1.3). Additional dose cohorts that assess lower or repeat doses may be investigated; however, dose modifications of the RO7565020 doses of individual participants are not permitted during the study.

Part 1a – SAD in Healthy Participants

Part 1a is a 6:2 randomized, Sponsor-open (i.e., Investigator-blinded, participant-blinded), placebo-controlled SAD study in healthy participants to assess the safety, tolerability, pharmacokinetics, and immunogenicity (in the absence of HBsAg) following SC injection or IV infusion of RO7565020 or placebo. An ethnic-specific cohort is also included for the purpose of PK bridging between a global population and Chinese population.

Four provisional escalating dose levels are planned to be administered sequentially to 6 different cohorts of participants (see Table 6), The anticipated ascending-dose scheme is 70 mg SC, 230 mg SC, 360 mg SC, 360 mg IV, and 900–1500 mg IV or matching placebo. Cohort 6 (ethnicity bridging cohort: 360 mg SC or matching placebo) may be conducted in parallel with Cohort 4 after the preliminary safety evaluation in Cohort 3 is completed and considered safe.

Each participant within a given cohort will randomly receive single doses of RO7565020 or matching placebo at the assigned dose via SC injection or IV infusion (see Table 6).

Each cohort will enroll 8 participants to allow for a dose escalating decision. Sentinel dosing will be applied to each cohort, i.e., initially, 2 participants in each cohort will be randomized and dosed (1 with RO7565020 and 1 with placebo). Safety will be evaluated for at least 72 hours after the second sentinel participant has been dosed and if the safety data for the sentinel participants obtained in the 72-hour postdose period are judged acceptable by the Investigator, the remaining participants of the cohort will be dosed.

The study design is adaptive in nature and other intermediate doses may be investigated based on emerging safety and tolerability data. The IV formulation will be used to evaluate the absolute bioavailability of SC formulation, and to provide a higher PK exposure that covers the highest PK exposure (maximum concentration [C_{max}] and area under the time-concentration curve within a dosing interval [AUC_{tau}]) anticipated after multiple doses of SC administration in future Phase II studies.

Part 1b – Multiple Doses in Healthy Participants

Part 1b is an optional, 6:2 randomized, Sponsor-open, placebo-controlled multiple-dose study in healthy participants. If, for example, an unexpected impact on the PK profile due to ADA formation is observed in Part 1a, Part 1b might be initiated to further investigate the safety and pharmacokinetics of RO7565020 following multiple doses.

One dose cohort is planned for Part 1b, and each participant will randomly receive multiple doses of RO7565020 or matching placebo via SC injection. The dose and dosing frequency will be determined by emerging safety and PK data from Part 1a.

In this Part 1b cohort, sentinel dosing will be applied for each dosing to allow an evaluation of safety data for at least 72 hours after the first 2 participants have been dosed (1 with RO7565020 and 1 with placebo). If the safety data for the sentinel participants obtained in the 72-hour postdose period are judged acceptable by the Investigator, the remaining participants will be dosed.

Part 2 – SAD in Participants with CHB

Part 2 is an open-label, SAD study of RO7565020 administered by SC injection in participants with CHB who are virologically (HBV DNA) suppressed with stable NUC treatment, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir (ETV). Part 2 aims to assess the safety and tolerability including the potential for HBsAg:HBsAb complex-mediated immune reactions, pharmacokinetics, and pharmacodynamics of RO7565020 in participants with CHB. In addition, proof of mechanism will also be explored by measuring the changes in HBsAg level after treatment. Participants with 20 IU/mL $\leq$ HBsAg $\leq$ 3000 IU/mL will be enrolled into Part 2a. Participants with HBsAg $>$ 3000 IU/mL will be enrolled into Part 2b (upper limit of 10,000 IU/mL in Cohorts 1 and 2).

Three and four cohorts are planned for Part 2a and Part 2b, respectively. The provisional escalating dose levels are shown in Table 6. Before proceeding to higher dose levels, the safety and tolerability at lower dose levels will be reviewed by the DDT and considered to be safe.

Part 2a Cohort 1 will be initiated after at least 6 participants (5 on active treatment and 1 on placebo) in Part 1a Cohort 2 (i.e., a higher dose level in healthy participants) have completed the 28-day follow-up and the dose level is considered to be safe. The initiation of Part 2b (in participants with HBsAg $>$ 3000 IU/mL) will be staggered until at least 5 participants (all on active treatment) at the same dose level in Part 2a (HBsAg $\leq$ 3000 IU/mL) have completed at least 28 days of follow-up and the dose level is considered to be safe (see Section 4.1.1). Part 2b Cohort 1 (optional) is designed to assess the target-mediated drug disposition (TMDD) effect on the clearance of anti-HBs mAbs, and the need for this Cohort will be determined after the data from Cohort 1 (Part 2a) are available. If Part 2b Cohort 1 is not needed, Part 2b Cohort 2 will start after at least 5 participants in Part 2a Cohort 2 have completed at least 28 days of follow-up and the dose is considered to be safe. The conduct of Cohort 4 in Part 2b (optional) will be determined by whether a higher dose (720 mg or higher) is required in a high HBsAg population to achieve a meaningful HBsAg reduction and maintenance based on the neutralization potency of RO7565020 in the first 3 cohorts in Part 2b.

Each cohort will enroll 6 participants to allow for a dose-escalation decision. Sentinel dosing of the first participant will be applied to each cohort to allow an evaluation of safety data for at least 72 hours postdose. If the safety data of the sentinel participant obtained in the 72-hour postdose period are judged acceptable by the Investigator, the remaining participants can be dosed.

The HBsAg level of the first 2 participants recruited in Part 2b Cohort 3 and Part 2b Cohort 4 is required to be $\leq$ 10,000 IU/mL. A participant with HBsAg $>$ 10,000 IU/mL at screening will be on hold until at least 2 participants with HBsAg $>$ 3000 IU/mL but $\leq$ 10,000 IU/mL have been dosed and the dose is considered to be safe after 28 days of follow-up.

Part 3 (Optional) – Multiple Doses in Participants with CHB

On the basis of emerging data including safety, tolerability, PK and pharmacodynamic (PD) data from Parts 1 and 2, Part 3 may be initiated as an open-label cohort in participants with virologically suppressed CHB to assess safety, tolerability, pharmacokinetics, pharmacodynamics, and antiviral response after multiple doses of RO7565020 via SC injection, if, e.g., an unexpected PK/PD profile is observed due to ADA formation, or if the dose and dosing interval for the multiple-dose Phase II regimen could not be reliably determined from the single dose PK/PD data.

In Part 3, 6 eligible virologically suppressed participants with CHB are planned to be enrolled in each cohort, for a maximum of 2 cohorts. The dose level and frequency will be determined by the emerging data in Parts 1 and 2. Sentinel dosing will also be applied for each dosing in Part 3 to allow an evaluation of safety data for at least 72 hours after the first participant has been dosed. If the safety data for the sentinel participant obtained in the 72-hour postdose period are judged acceptable by the Investigator, the remaining participants can be dosed.

In Parts 2 and 3, all participants will continue to receive NUC therapy throughout the study, even if HBsAg loss is achieved. Participants should avoid changing NUC during the study including screening period, unless the Investigator considers it necessary for medical reason (e.g., virological breakthrough [Section 8.3.7], safety).

Table 6 Provisional Dose Regimens in Each Study Cohort

Study part	Study treatment	*Background* treatment
Part 1a (healthy participants)	• Cohort 1: 70 mg RO7565020 SC (starting dose) or placebo, single dose • Cohort 2: 230 mg RO7565020 SC or placebo, single dose • Cohort 3: 360 mg RO7565020 SC or placebo, single dose • Cohort 4: 360 mg RO7565020 IV or placebo, single dose (over 2-hour infusion) • Cohort 5: 900–1500 mg RO7565020 IV or placebo, single dose (over 2-hour infusion) • Cohort 6 (PK bridging cohort): 360 mg RO7565020 SC or placebo, single dose	N/A
Part 1b (healthy participants)	• Multiple doses (3 to 6 doses depending on dosing frequency). Dose level and dosing frequency will be determined using Part 1a data	N/A
Part 2a (participants with CHB)	• Cohort 1: 70 mg RO7565020 SC (starting dose), single dose • Cohort 2: 230 mg RO7565020 SC, single dose • Cohort 3: 360 mg RO7565020 SC, single dose	NUC
Part 2b (participants with CHB)	• Cohort 1 (optional): 70 mg RO7565020 SC, single dose • Cohort 2: 230 mg RO7565020 SC, single dose • Cohort 3: 360 mg RO7565020 SC, single dose • Cohort 4 (optional): 720 mg RO7565020 SC, single dose	NUC

Table 6 Provisional Dose Regimens in Each Study Cohort (cont.)

Study part	Study treatment	*Background* treatment
Part 3 (participants with CHB)	• Multiple doses (up to 6 doses depending on dosing frequency). Dose level and dosing frequency will be determined using Part 1 and Part 2 data	NUC

Abbreviations: CHB = chronic hepatitis B; IV = intravenous; N/A = not applicable; NUC = nucleos(t)ide analogue; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous.

Note: Depending on the evaluation of the safety and/or PK/PD data, the same dose may be repeated; the actual dose may be modified to a lower dose; or intermediate dose-escalation steps other than those anticipated above may be used at the discretion of the Investigator and the Sponsor.

4.1.1 Dose Escalation

4.1.1.1 Dose-Escalation Decision Criteria

The decision to escalate to the next dose level and cohort will be made by the DDT following a review of all available safety and tolerability data, including AEs, ECGs, vital signs, and laboratory safety test results (i.e., hematology, clinical chemistry and urinalysis, etc.) collected at least 28 days postdose from a minimum of 6 participants (5 on active treatment and 1 on placebo) in Part 1, or a minimum of 5 participants on active treatment in Part 2, as well as available serum PK, PD, and ADA data up to 28 days postdose from a minimum of 5 participants on active treatment.

In addition, all available safety, tolerability, PK, PD, and ADA data from all previous dose level(s) will be reviewed. Dose escalation will only occur if the previous doses were tolerated and stopping rules were not met.

Dose-escalation steps will not exceed 5-fold increments.

4.1.1.2 Dose Decision Team

A DDT will review emerging study data and make recommendations regarding dose escalation and overall study conduct to ensure participant safety while receiving study treatment. The DDT will consist of the Investigators and the Sponsor members, collectively having expertise in clinical science, clinical pharmacology, pharmacodynamics, statistics, and clinical safety and will include at least one physician. Additional advisors may be consulted as deemed appropriate. The DDT will review emerging data that become available and will be empowered to pause, stop, or continue the study, or to continue it with modifications. Additional information about the DDT can be found in a separate Dose Escalation Plan (DEP).

4.1.1.3 Stopping Rules Criteria

4.1.1.3.1 Cohort Stopping Rules

Part 1

Dose escalation will be stopped and dosing at a given level will be stopped if one of the following circumstances occurs in participants treated with RO7565020 within the same dose cohort:

- Severe non-serious adverse reactions (Grade 3 or above, as per Division of AIDS [DAIDS] grading, v2.1, considered to be related to RO7565020) in 2 or more participants receiving RO7565020 in the same cohort, independent of the system organ classes.
- Any serious adverse reaction in 1 participant (i.e., a serious AE [SAE] considered to be related to RO7565020).
- Grade 2 or above clinically significant laboratory abnormalities, vital sign change, or ECG change, of the same type in 3 or more participants receiving RO7565020 in the same cohort.
- Other findings, which at the discretion of the DDT, indicate that dose escalation or dosing at that dose level should be stopped.
- Dose escalation will also be stopped if increasing the dose does not result in a significant increase in serum exposure of RO7565020.

Parts 2 and 3

Dose escalation and dosing at a given level of RO7565020 will be temporarily halted if one of the following circumstances occurs. Dosing might be resumed if deemed appropriate following the DDT review of the available safety, PK, and PD data. Relevant reporting and discussion with relevant DDT personnel and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will take place before potential resumption of dosing.

- Severe non-serious adverse reactions (Grade 3 or above, as per DAIDS grading, v2.1, considered to be related to RO7565020) in 2 or more participants receiving RO7565020 in the same cohort, independent of the system organ classes
- Any serious adverse reaction in 1 participant (an SAE considered to be related to RO7565020)
- Other findings which, at the discretion of the DDT members, indicate that dose escalation or dosing at that level should be stopped

In case dose escalation is stopped, lower doses within the tolerated dose range could be investigated or a dose repeated in subsequent cohorts to increase the amount of data within this tolerated dose range.

4.1.1.3.2 Individual Participant Stopping Rules

Infusion of RO7565020 will be stopped immediately (for an individual participant in the IV cohorts), and the participant will be discontinued from further treatment with RO7565020 (for an individual participant in the multiple-dosing cohorts), if the participant experiences any of the following:

- Severe non-serious adverse reactions (Grade 3 as per DAIDS grading, v2.1, considered to be related to RO7565020)
- Serious adverse drug reaction (i.e., an SAE considered to be related to RO7565020)
- Other findings which, at the discretion of the DDT members, indicate that dosing should be stopped

4.1.1.4 Communication Strategy

Information will be communicated, as follows:

- For all participants, during dose escalation in the study, the Investigator(s) must confirm to the Sponsor that the participant has been dosed and provide a brief summary of the status of the participant in terms of safety and tolerability to RO7565020, communicated by email and/or telephone.
- In the event of a severe AE or an SAE, the Investigator will contact the Sponsor immediately to discuss participant status and action taken/to be taken.
- After at least 28 days postdose from a minimum of 6 participants (5 on active treatment and 1 on placebo) in Part 1, or a minimum of 5 participants on active treatment in Part 2: The Sponsor will organize a teleconference with the Investigators to discuss the safety and tolerability of RO7565020 and to discuss the dose(s) for the next cohort. If the teleconference occurs prior to the end of the dose evaluation period, the Investigator will provide a final status prior to the start of the next cohort.

  During each teleconference:

  - AEs (see Appendix 2) will be discussed along with the results of PK data (if available), in addition to safety laboratory results and any other available data that may assist the dose escalation decision process.
  - Dose escalation will only proceed to the next dose level if DDT are satisfied with the safety profile of the previous cohort and agree to move to the next dose level.
  - If other RO7565020 dose levels are explored, it will be documented in writing, and both the Sponsor and Investigators will approve the minutes of these meetings to confirm agreement.

In addition to these communications, the Sponsor and Investigators will be in regular contact throughout the study, 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.

4.2.1 Rationale for Study Population

Part 1 will be conducted in healthy male participants, and female participants of non-childbearing potential or who agree to take contraceptive measures as required by the study, 18 to 65 years of age. The absence of potentially confounding diseases and co-medications (except for hormonal contraceptives for female participants) in healthy volunteers allows for a clearer and more consistent assessment of drug disposition, safety, tolerability, and ADA formation.

Parts 2 and 3 will be conducted in virologically suppressed participants with CHB, between 18 and 65 years of age, with preserved liver function and without significant fibrosis/cirrhosis. This population is considered optimal to evaluate the proof of mechanism of RO7565020 in humans as the first patient population. The virologically suppressed participants have a more stable disease phenotype compared to treatment-naive patients who have elevated and fluctuating ALT levels, and the lower baseline HBsAg levels may increase the likelihood of attaining a treatment response. The study population is associated with a favorable benefit/risk profile and is considered appropriate for early phase clinical trials of novel CHB therapies within the current guidelines (FDA 2022).

As the participants enrolled in Parts 2a and 2b have different HBsAg levels at baseline, the proposed study will provide essential support for the selection of the RO7565020 multi-dose regimen for the future Phase II study in patients with CHB. Additionally, the safety, tolerability, and pharmacokinetics data, including the TMDD effect after single or multiple SC doses of RO7565020, will also provide essential information for supporting the future development of this target population.

4.2.2 Rationale for Control Group

In each cohort in Part 1a and in Part 1b, participants will be randomized (Sponsor-open, Investigator-blinded, and participant-blinded) at 6:2 to receive RO7565020 and placebo, respectively. This is considered sufficient to allow for unbiased comparisons of safety and tolerability of active treatment to placebo both within and across cohorts in absence of HBsAg.

It is considered unnecessary to include placebo controls in Parts 2 and 3, because placebo controls have negligible impact on HBsAg change over time, and the off-target safety profile at the same dose will have been assessed in healthy participants and the AEs in the presence of HBsAg would be most likely be of an immunological nature (e.g., as a consequence of HBsAg:HBsAb complex formation and possible tissue deposition) that can be easily attributed.

4.2.3 Rationale for Biomarker Assessments

4.2.3.1 HBV Dynamic Biomarkers

RO7565020 is a human IgG1 neutralizing antibody, which showed potent and cross-reactive in vitro neutralization against all main circulating viral genotypes of HBsAg. Therefore, the main virological endpoint in this study relies on measuring HBsAg at timepoints defined in the SoA (Section 1.3).

Additional well-established HBV dynamic biomarkers for the assessment of HBV treatment outcomes will include the time course of anti-HBs levels and the evolution of the HBeAg and anti-HBe statuses. In participants who are HBeAg-positive at study entry, a validated research-use-only (RUO) semi-quantitative calculation may be used to follow the time course of serum HBeAg levels over time. In order to evaluate the formation of HBsAg:HBsAb complexes, an assay is being developed by the Sponsor that may be used to either directly quantify the immune complexes or measure HBsAg independently of the putative formation of complexes (i.e., total HBsAg post-dissociation of HBsAg:HBsAb complexes), as appropriate. Additionally, quantification of HBsAg may be measured using a second assay designed to either evaluate a potential bias of the HBsAg quantitative assay being used or to measure a change in the affinity of RO7565020 to escape mutants that might be selected for by therapy with RO7565020.

Several HBV biomarkers have recently emerged in the field that may further support the demonstration of improved virus control. These novel biomarkers will not be used to screen participants and will not have an impact on any clinical decisions or other endpoint evaluation.

Among these, pregenomic HBV RNA, which bypasses reverse transcription and is released in plasma, may provide a direct measure of the transcriptional activity of cccDNA. Consistent with this view, in NUC-treated participants with suppressed HBV DNA, the presence of detectable circulating HBV RNA signals an increased probability of HBV DNA rebound upon NUC cessation (Wang et al. 2016; Fan et al. 2020; Seto et al. 2021; Kaewdech et al. 2020). In the course of this study, a validated real-time polymerase chain reaction-based investigational assay may be used to quantify HBV RNA.

Circulating hepatitis B core-related antigen (HBcrAg) levels provide one additional biomarker that could support demonstration of the achievement of virus control. HBcrAg is a composite circulating biomarker comprising hepatitis B core antigen (HBcAg, 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 cccDNA levels and activity and HBV treatment outcomes (Mak et al. 2018; Chen et al. 2017; Inoue and Tanaka 2020; Li et al. 2020). In the course of this study, a validated RUO method based on a quantitative enzyme-linked immunosorbent assay may be used to quantify HBcrAg in serum.

Antibodies against HBcAg (anti-HBc) are the first to appear during the acute phase of infection. The IgM anti-HBc levels gradually disappear and are followed by the production of IgG anti-HBc. Novel assays for the quantification of IgG or total anti-HBc have been developed. The levels of this biomarker have been shown to vary through the different phases of the CHB infection. They are higher during the immune clearance and reactivation phases than during the immune tolerance and inactive carrier phases. Moreover, high levels of IgG or total anti-HBc correlate with a higher rate of HBeAg seroconversion in HBeAg-positive patients treated with NUCs. In the course of this study, a validated RUO method may be used to quantify total anti-HBc in serum (Jia et al. 2014; Yuan et al. 2013; Fan et al. 2016).

The HBsAg messenger RNA contains three in-frame start codons that lead to the production of three HBsAg isoforms: S-HBsAg, M-HBsAg, and L-HBsAg, where S, M, and L indicate selective, medium, and large, respectively. The S-HBsAg contains four membrane-spanning domains as well as the “a”-determinant (i.e., the primary antigenic site of HBsAg). In addition to these domains, M-HBsAg contains an additional amino terminal preS2 sequence, and L-HBsAg contains both amino terminal preS1 and preS2 sequences (Bruss 2007; Brown et al. 1984; Patient et al. 2009; Laub et al. 1983). With spherical subviral particles (SVPs) forming the majority of circulating HBsAg and consisting of 95% of S-HBsAg, this isoform is the major circulating HBsAg isoform. However, while M-HBsAg and L-HBsAg are found during acute and chronic infection, their levels have been proposed to drop significantly in inactive HBV carriers, consistent with the reduced viremia observed in this patient population. Additionally, a recent study has observed that selective declines in M-HBsAg and L-HBsAg precede HBsAg loss during NUC therapy in HBeAg-positive HBV infection. (Pfefferkorn et al. 2018, 2021). Therefore, in the course of this study, an RUO method may be used to quantify the different HBsAg isoforms using a validated assay currently being developed by the Sponsor.

4.2.3.2 HBV Genotype

The initial participant population recruited in this study will be established on effective NUC therapy at study entry and will have circulating HBV DNA levels below the assay lower limit of quantification (defined as below 10 IU/mL) for at least 6 months, confirmed at screening. Response to therapy could potentially be modulated by the HBV genotype. To determine HBV genotype in participants with undetectable HBV DNA, Sanger or deep sequencing may be attempted in some participants using amplified HBV RNA from a plasma sample collected on Day 1 or at any follow-up timepoint, as appropriate. Alternatively, the HBsAg serotype may be determined as a surrogate for HBV genotype using the same sample.

4.2.3.3 HBV DNA Monitoring and Viral Resistance

During the study, participants will be monitored to ensure that HBV DNA suppression by the NUC therapy is maintained. Participants who experience HBV DNA breakthrough (HBV DNA > 100 IU/mL) while on NUC therapy will be recalled for repeat testing. If the

HBV DNA level is confirmed to be more than 100 IU/mL, the participants will be assessed for evidence of drug resistance using sequencing and potentially phenotyping. The sample will also be used to determine the HBV genotype. NUC and RO7565020 PK samples will also be collected.

Moreover, to evaluate the potential resistance to RO7565020 in absence of a concomitant DNA breakthrough, changes in the levels of free and total HBsAg and changes in the affinity of RO7565020 to potential escape mutants in the S gene that might have been selected for may be measured using baseline, end of follow-up, and/or intermediary timepoint samples. The characterization of such emerging mutations may be attempted through HBV RNA sequencing, if feasible.

4.2.3.4 Immunological Biomarkers

RO7565020 is a human neutralizing antibody (Ab) that shows potent reduction in circulating HBsAg in nonclinical models. The fully human origin of RO7565020 is expected to reduce immune-related risks (e.g., ADA or immune complex formation; Heyen et al. 2014; Vaisman-Mentesh et al. 2020). Nevertheless, soluble markers of immune activation and inflammation (soluble cytokines and chemokines which may include IFN-γ, tumor necrosis factor-α [TNF-α], interleukin [IL]-6 and IL-8) as well as complement components (e.g., C3a and SC-5b9) may be assessed. Measures of systemic immune activation and inflammation will be correlated with the safety profile of RO7565020 in participants. Additionally, specific cytokines and chemokines may be tested to explore correlations with immunological or virological data of interest in CHB cohorts.

Growing literature evidence shows that long-term exposure to high concentrations of viral antigens, in particular HBsAg, results in host immune response suppression, including T cell exhaustion, B cell impairment, and immune tolerance induced by other myeloid cells (e.g., natural killer [NK] cells; Iannacone and Guidotti 2022). It is hypothesized that reducing the levels of circulating HBsAg will in turn restore the immune response towards HBV. How this reduction in HBsAg may translate into the restoration of measurable HBV-specific immune responses in peripheral blood during or after the end of dosing is currently unclear. The transcriptional profile and inflammatory signature (single-cell RNA sequencing [scRNAseq]) may be assessed from blood in participants with CHB. Circulating immune phenotype, B and T cell activation status (flow cytometry) and HBV-specific cellular immune phenotype and function (e.g., Flurospot, tetramer staining, fluorescent bait) may be tested ex vivo in CHB participants using cryopreserved peripheral blood mononuclear cells (PBMCs) collected at timepoints indicated in the SoA (see Section 1.3). These analyses will be considered as an exploratory optional objective, taking into consideration the logistic and technical challenges that might be experienced with the collection of viable PBMCs during the conduct of a multi-center trial.

Whole blood samples for human DNA extraction will be taken from participants with CHB. The intended use of these is to determine human leukocyte antigen (HLA) types, necessary for the subsequent isolation and characterization of HBV-specific immune cells from PBMCs, using HLA-matching reagents (e.g., multimers). Any data arising from clinical genotyping will be subject to the confidentiality standards described in Appendix 1, Section 4.

4.2.4 Justification for Dose

The starting dose of 70 mg (SAD portions of Part 1 and Part 2) has been selected to balance considerations for an acceptable safety margin and the predicted efficacious dose in humans. RO7565020 was well tolerated at a dose level of 360 mg/kg when administered to cynomolgus monkeys via SC injection or IV once weekly for 3 weeks, thus 360 mg/kg was considered to be a no-observed-adverse-effect level (NOAEL) for both dose routes.

The observed PK exposure (e.g., area under the time-concentration curve from 0 to 21 days [$AUC_{0\text{-}21d}$] and C_{max}) at NOAEL is $>$ 100 times higher than the predicted AUC_{inf} and C_{max} values in humans at the proposed starting dose of 70 mg SC, and ~11 and 22 times higher than the predicted AUC_{inf} and C_{max} values, at the planned highest dose of 1.5 g IV in SAD (Part 1a), respectively.

Starting from a single dose of 70 mg in healthy participants also establishes a link to the starting dose in participants with CHB. Based on a PK/PD model, the starting dose of 70 mg in Part 2a is expected to produce a meaningful maximum decline ($\geq$ 1 log10 IU/mL) in free HBsAg concentrations in all participants with baseline HBsAg levels $\leq$ 3000 IU/mL after a single SC dose of RO7565020.

The planned higher doses (230 mg SC and 360 mg SC) in Part 2a and Part 2b are aiming to achieve greater and more sustained HBsAg reductions in participants with different baseline HBsAg level.

Switching to IV formulation in Part 1a is designed to test a higher dose in healthy participants, which exceeds the maximum SC dose (360 mg) that is feasible with one injection; Part 1a Cohort 5 (900–1500 mg) aims to cover the maximum PK exposure due to PK accumulation after multiple doses. In the meantime, absolute bioavailability of the SC formulation will be evaluated based on the PK data in Cohort 3 and Cohort 4, Part 1a.

Further details are provided in the RO7565020 IB.

4.3 DURATION OF PARTICIPATION

The duration of each study period is described in Table 7.

Table 7 Duration of Study Periods

Study Part	Screening	Treatment period	In-clinic period	End-of-study visit***
Part 1a	Up to 28 days	Day 1	Day −1 to Day 4	36 weeks after study treatment administration
Part 1b	Up to 28 days	Up to 169 days	Day −1 to Day 4, and 1 day after each administration for the following doses, including optional overnight stay*	36 weeks after the final study treatment administration
Parts 2a and 2b	Up to 56 days *(Pregnancy testing and liver function up to 14 days)*	Day 1	Day 1** to Day 4, including optional overnight stay*	24 weeks after study treatment administration (If HBsAg does not return to baseline level at follow-up Week 24, will have additional follow-up visits until returns to < 0.1 log below baseline for two consecutive visits, or up to 56 weeks postdose, whichever comes first.)
Part 3	Up to 56 days *(Pregnancy testing and liver function up to 14 days)*	Up to 337 days	Day 1** to Day 4, and 1 day after each administration for the following doses, including optional overnight stay*	24 weeks after last study treatment administration (If HBsAg does not return to baseline level at follow-up Week 24, will have additional follow-up visits until return to < 0.1 log below baseline for two consecutive visits, or up to 56 weeks post the final dose, whichever comes first.)

Abbreviations: ADA = anti-drug antibody; HBsAg = hepatitis B surface antigen; PK = pharmacokinetic.

Note: Participants who permanently discontinue from the study (or study treatment) due to Sponsor's decision (e.g., Sponsor prematurely terminates the study) will undergo safety follow-up for 24 weeks or longer if considered needed by Sponsor on the basis of the emerging data. Every 4 weeks (± 3 days) in the first 12 weeks post-final dose, then every 12 weeks (± 7 days).

* For Part 1b, all participants will stay at the clinic overnight on Day 1 after each dose. Optional overnight stay at the clinic on Day 2 and Day 3 after the first dose, i.e., on Day 2 and Day 3, participants can either stay at the clinic overnight or can be discharged after completion of the assessments and return the next morning for the subsequent assessments, at the Investigator's discretion.
For all cohorts in Part 2a and Cohorts 1 and 2 in Part 2b, all participants will stay at the clinic for at least 8 hours postdose for safety observation and sample collection. The overnight stay from Day 1 to Day 4 for sample collection and assessment is optional, at the Investigator's discretion.
For Cohorts 3 and 4 in Part 2b, all participants will stay at the clinic overnight on Day 1. The overnight stay on Day 2 and Day 3 for sample collection and assessment is optional, at the Investigator's discretion.

For Part 3, all participants will stay at the clinic for at least 8 hours after each dose for safety observation and sample collection. Overnight stay at the clinic on Day 1 after each dose and on Days 2 and 3 after the first dose is optional.

** Participants can stay at clinic the night before Day 1 (i.e., Day −1) if site prefers due to logistic reasons.

*** After completing the scheduled visits, an additional ADA and PK sample collection may be needed, depending on the emerging ADA data.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if the participant completed all phases of the study including the last visit.

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. Due to the exploratory nature of the trial, this study can be discontinued before all cohorts have been investigated. This will not constitute a premature discontinuation of the study.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be female and male healthy participants (Part 1) or virologically suppressed patients with CHB (Parts 2 and 3), between 18 and 65 years of age, inclusive, who fulfill all of the given inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted. All eligibility decisions are made by the Investigator. The Medical Monitor is available to the Investigator to answer any medical questions.

5.1 INCLUSION CRITERIA AND EXCLUSION CRITERIA FOR PART 1 (HEALTHY PARTICIPANTS)

5.1.1 Inclusion Criteria for Part 1

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

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to International Council for Harmonisation (ICH) and local regulations.

Age

2. Male and female participants 18 to 65 years of age (inclusive), at the time of signing the Informed Consent Form (ICF).

Ethnicity

3. Cohort 6 only: Chinese male and female participants. A Chinese subject is defined as his/her biological parents and grandparents are of Chinese ethnicity.

Type of Participants and Disease Characteristics

4. Healthy participants where the status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, clinical chemistry, serology, coagulation, and urinalysis.

Weight

5. A body mass index (BMI) between 18 and 32 kg/m^2, inclusive.

Sex and Contraception/Barrier Requirements

6. Biological Male and/or Female Participants

The reliability of sexual abstinence for the eligibility and enrollment of all participants 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.

a. **Biological Female Participants**

Biological female participants are eligible to participate if they are not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Participants of non-childbearing potential (PONCBP), as defined in Appendix 5.
- Participant of childbearing potential (POCBP), who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use at least one highly effective contraceptive method that results in a failure rate of < 1% per year until 24 weeks after final dose of study treatment. Examples of contraceptive methods with a failure rate of < 1% are in Appendix 5. The Investigator should evaluate with the participant the best contraceptive method based on anatomy and physiology, and lifestyle considerations when possible.
  - Have a negative pregnancy test (blood) within 28 days prior to the first study treatment administration.

b. **Biological Male Participants**

No contraception measures are needed.

5.1.2 Exclusion Criteria for Part 1

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

Medical Conditions

1. Pregnant (positive pregnancy test) or lactating women
2. Current infection with hepatitis A virus (HAV), HBV, hepatitis C virus (HCV), or HIV
3. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological, or allergic disease, metabolic disorder, cancer, or cirrhosis
4. History of immunologically mediated disease (e.g., inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, rheumatoid arthritis, multiple sclerosis, or any other autoimmune disease)
5. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study, including but

not limited to any major illness within 1 month prior to screening or any febrile illness within 1 week prior to screening and up to study treatment administration

6. History or presence of clinically significant ECG abnormalities based on the average of the triplicate ECG recordings (e.g., PQ/PR interval > 210 ms, QT corrected for heart rate using the Fridericia's correction factor [QTcF] > 450 ms for males and QTcF > 470 ms for females) or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death)

Prior/Concomitant Therapy

7. Use of any prescription drugs, herbal supplements, and/or over-the-counter (OTC) medication or dietary supplements (vitamins included) within the 2 weeks prior to the first dosing or within 5 half-lives of the medication prior to first dosing (whichever is longer). Vaccination is prohibited between 2 weeks before and 1 week after a dose of RO7565020.

Prior/Concurrent Clinical Study Experience

8. Are currently enrolled in, have participated in, or plan to participate in any other clinical study involving an investigational medicinal product (IMP) or medical device from within the last 90 days prior to screening or within 5 times the elimination half-life if known (whichever is longer) until completion of the follow-up visit.

Diagnostic Assessments

9. Confirmed (see Section 8.2.2) systolic blood pressure (SBP) greater than 140 or less than 90 mmHg, or diastolic blood pressure (DBP) greater than 90 or less than 50 mmHg, at screening
10. Clinically significant abnormalities (as judged by the Investigator) in laboratory test results (including complete blood count, chemistry panel, and urinalysis). In case of uncertain or questionable results, tests performed during screening may be repeated once to confirm eligibility prior to enrollment.
11. Evidence of HIV infection and/or positive result for human HIV antibodies
12. Presence of HBsAg, or positive HAV Ab IgM or positive HCV RNA test results at screening
13. Any suspicion or history of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink = 10 g alcohol) and/or any history or suspicion of regular consumption/addiction or drug abuse within 2 years prior to study treatment administration or a positive drug-screening test
14. Active smokers or use of tobacco and/or nicotine-containing products in the previous 3 months prior to screening. Urine cotinine levels will be measured at screening and on Day −1 for all participants. Smokers will be defined as any participant who reports tobacco use and/or who has a positive urine cotinine test.

Other Exclusions

15. Donation or loss of blood over 500 mL, or administration of any blood product, within 90 days prior to study treatment administration
16. Any clinically significant history of hypersensitivity or allergic reactions, either spontaneous or following study treatment administration, or exposure to food or environmental agents
17. History of hypersensitivity to any of the excipients (i.e., polysorbate 80, D-sucrose, and L-methionine) in the formulation of RO7565020
18. Participants under judicial supervision, guardianship, or curatorship
19. Participants who, in the opinion of the Investigator, should not participate in this study.
20. Participants with insufficient venous access

5.2 INCLUSION CRITERIA AND EXCLUSION CRITERIA FOR PARTS 2 AND 3 (PARTICIPANTS WITH CHB)

5.2.1 Inclusion Criteria for Parts 2 and 3

Participants are eligible to be included in Parts 2a, 2b, or 3 of the study only if all of the following criteria apply:

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. Participants must be between 18 and 65 years of age, inclusive, at the time of signing the ICF.

Type of Participants and Disease Characteristics

3. CHB infection (HBsAg-positive for $\geq$ 6 months)
    a) On NUC (ETV, TAF, or TDF) monotherapy (per local prescription information) for $\geq$ 12 months. Patients must be on the same NUC therapy for at least 3 months before screening.
    b) HBV DNA below the lower limit of quantification (LLOQ) or $<$ 10 IU/mL for $>$ 6 months prior to screening and confirmed at screening.
    c) ALT $\leq 1.5 \times$ upper limit of normal (ULN) for $>$ 6 months prior to screening and confirmed at screening. Total bilirubin within normal range at screening (isolated elevated bilirubin $\leq 1.5 \times$ ULN is acceptable for participants with Gilbert syndrome)

4. HBsAg titer at screening:

   Part 2a: 20 IU/mL ≤ HBsAg ≤3000 IU/mL

   Part 2b: HBsAg > 3000 IU/mL (< 10,000 IU/mL in Cohort 1 and Cohort 2, and first 2 participants in Cohort 3 and Cohort 4)

5. Screening laboratory values (hematology, chemistry, urinalysis) within normal ranges or judged not clinically significant by the Investigator

6. Liver biopsy, FibroScan, or equivalent test obtained within the past 6 months demonstrating liver disease consistent with chronic HBV infection without evidence of bridging fibrosis or cirrhosis (Metavir score ≥ 3, recommended cutoff for FibroScan 8.5 kPa)

Weight

7. BMI between 18 and 32 kg/m^2, inclusive

Sex and Contraception/Barrier Requirements

8. Biological Male and/or Female Participants

The reliability of sexual abstinence for the eligibility and enrollment of all participants 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.

a. **Biological Female Participants**

Biological female participants are eligible to participate if they are not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- PONCBP, as defined in Appendix 5.
- POCBP, who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use of at least one highly effective contraceptive method that results in a failure rate of < 1% per year until 24 weeks after final dose of study treatment. Examples of contraceptive methods with a failure rate of < 1% are in Appendix 5. The Investigator should evaluate with the participant the best contraceptive method based on anatomy and physiology, and lifestyle considerations when possible.
  - Have a negative pregnancy test (blood) within 28 days prior to the first study treatment administration.

b. **Biological Male Participants**

No contraception measures are needed.

5.2.2 Exclusion Criteria for Parts 2 and 3

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

Medical Conditions

1. Pregnant (positive pregnancy test) or lactating women
2. Anti-HBs antibody positive at screening
3. Current co-infection with other pathogens such as HAV, HCV, *hepatitis D virus* (HDV), *hepatitis E virus* (HEV), or HIV
4. Evidence of liver cirrhosis or decompensated liver disease such as ascites, esophageal or gastric varices, splenomegaly, nodular liver, jaundice, hepatic encephalopathy, or portal hypertension
5. History of or suspicion of HCC (e.g., elevated α-fetoprotein [AFP] levels, or suggestive lesions on abdominal ultrasound or other imaging)
6. History or other evidence of a medical condition associated with chronic liver disease other than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, nonalcoholic steatohepatitis, metabolic liver disease)
7. Expected to need systemic antiviral therapy other than that provided by the study at any time during their participation in the study, with the exception of oral/ topical therapy for HSV I or HSV II
8. History of immunologically mediated disease (e.g., inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, rheumatoid arthritis, multiple sclerosis, or any other autoimmune disease)
9. History of clinically significant and not adequately controlled cardiovascular, endocrine, gastrointestinal, renal, ocular, pulmonary, or neurological disease
10. History of clinically significant psychiatric disease
11. Evidence of an active or suspected cancer or a history of malignancy other than adequately treated basal cell carcinoma
12. History of having received or currently receiving any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids, IFN or PEG-IFN) within the 8 weeks prior to the first dose of study treatment or the expectation that such treatment will be needed at any time during the study. Eye drop-containing, topical, and infrequent inhaled corticosteroids are permissible up to 4 weeks prior to the first dose of study treatment.
13. History of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink = 10 g alcohol) and/or drug abuse within 1 year prior to study Day 1
14. Currently taking, or have received within 3 months of Day 1, systemic corticosteroids at a high dose (e.g., 40 mg prednisolone per day) for $>$ 7 days, or a low dose (e.g., 20 mg prednisolone per day) for $>$ 14 days

15. History of organ transplantation
16. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable)
17. Significant acute infection (e.g., influenza, COVID-19, local infection) or any other clinically significant illness within 2 weeks prior to study Day 1
18. Donation or loss of blood over 500 mL, or administration of any blood product, within 90 days prior to study treatment administration

Prior/Concomitant Therapy

19. Unable to comply with any drugs or nutrients listed in prohibited therapies (Section 6.5.2.2). Vaccination is prohibited between 2 weeks before and 1 week after a dose of RO7565020.

Prior/Concurrent Clinical Study Experience

20. Are currently enrolled in, have participated in, or plan to participate any other clinical study involving an IMP or medical device study from within the last 90 days prior to screening or within 5 times the elimination half-life if known (whichever is longer) until completion of the Follow-up visit.

Diagnostic Assessments

21. One or more of the following laboratory abnormalities at screening:
    a) Hemoglobin $<$ LLN; platelets $<$ LLN; INR $>$ 1.1 × ULN
    b) Total serum bilirubin $>$ ULN (or $>$ 1.5 x ULN for participants with Gilbert syndrome)
    c) Serum albumin $<$ LLN
    d) Positive results for antimitochondrial antibodies (AMA $>$ 1:80), antinuclear antibody (ANA $>$ 1:80), anti-smooth muscle antibody (ASMA $>$ 1:40), or anti-thyroperoxidase antibodies (a-TPO $\geq$ ULN)
    e) Abnormal thyroid-stimulating hormone (TSH)
    f) White blood cell count $<$ 2500 cells/µL; neutrophil count $<$ 1500 cells/µL ($<$ 1200 cell/µL if considered a physiological variant in a patient of African descent)
    g) Positive test for drugs of abuse and/or positive alcohol test at screening. For positive cannabinoids test, the eligibility is at the Investigator's discretion.
22. ECG at screening with clinically significant abnormalities, including QT corrected using Fridericia's formula (QTcF) interval $\geq$ 450 ms for males and $\geq$ 470 ms for females
23. Abnormal renal function including serum creatinine $>$ ULN or calculated creatinine clearance $<$ 70 mL/min (using the Cockcroft Gault formula)

Other Exclusions

24. History of intolerance to IV or SC injection
25. History of hypersensitivity to any of the excipients (i.e., polysorbate 80, D-sucrose, and L-methionine) in the formulation of RO7565020
26. Participants under judicial supervision, guardianship, or curatorship
27. Medical or social conditions that would potentially interfere with the participant's ability to comply with the study visit schedule or the study assessments

5.3 LIFESTYLE CONSIDERATIONS

Participants are expected to follow protocol requirements for contraception. There are no other lifestyle restrictions during the study.

5.3.1 Meals and Dietary Restrictions

There are no study-specific restrictions to meals and dietary requirements.

5.3.2 Caffeine, Alcohol, and Tobacco

The consumption of foods and beverages containing methylxanthines (e.g., tea, coffee and caffeinated soft drinks) will not be permitted 8 hours before study treatment administration, during the in-clinical period and 8 hours before each of the ambulatory visits, and will be restricted to a maximum of three cups of coffee or tea per day and 1 L per day of methylxanthine-containing drinks (e.g., cola) during the out-clinic time until follow-up.

Consumption of alcohol will not be allowed 48 hours before study drug administration and while resident in the clinical unit and 48 hours before each of the ambulatory visits and should be limited to a maximum of 2 units/day (1 unit = 10 mL of pure alcohol) during the out-clinic period until follow-up.

5.3.3 Activity

Participants are strongly recommended not to have intense physical activity 96 hours before each blood collection for clinical laboratory tests during the study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to study treatment (Part 1) or entered in the study (Parts 2 and 3). Screen failures may be tracked separately.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

If a subject fails an inclusion/exclusion criterion due to a transient and non-clinically significant condition at screening, the Investigator may repeat the relevant screening

assessment(s) within the screening period (28 days for Part 1 and 56 days for Parts 2 and 3). If the subject fails a second time, they will be classed as a screen failure.

Re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria but failed to be enrolled within 28 days (Part 1) or 56 days (Parts 2 and 3) after the start of screening period because of an administrative reason (e.g., study halt, or logistical, personal, or technical reasons). *Re-screening is also allowed for participants who failed screening because of a transient illness (e.g., influenza or COVID-19 infection).* To re-screen such a participant, all inclusion and exclusion criteria *need to* be re-evaluated and all applicable screening assessments repeated if done more than 28 days (Part 1) or 56 days (Parts 2 and 3) before enrollment. In addition, for Parts 2 and 3, the blood chemistry and pregnancy tests *need to* be *done* within 14 days before Day 1.

The patients who have failed the screening due to HBsAg level (e.g., not met the criterion of $\leq$3000 IU/mL in Part 2a, or not $>$3000 IU/mL in Part 2b, or above the upper limit of 10,000 IU/mL in Part 2b Cohorts 1 and 2) can be re-screened for other patients' parts or cohorts in this study. To re-screen such patients, all inclusion and exclusion criteria *need to* be re-evaluated and all applicable screening assessments repeated if done more than 56 days before Day 1 (the blood chemistry and pregnancy tests *need to* be *done* within 14 days).

For Part 2b Cohort 3 and Cohort 4, dosing of participants with HBsAg $>$ 10,000 IU/mL at screening will be on hold until at least 2 participants with 3000 IU/mL < HBsAg ≤ 10,000IU/mL have been dosed and confirmed safety by 28-day follow-up. All inclusion and exclusion criteria of these participants need to be re-evaluated before dosing. The applicable screening assessments need to be repeated if done more than 56 days before Day 1 (the blood chemistry and pregnancy tests *need to* be *done* within 14 days).

For re-screening, there is no need to repeat liver biopsy or transient elastography/ acoustic radiation force impulse (ARFI)/magnetic resonance imaging (MRI) assessment if done within 6 months and reliably documented.

In case of uncertain or questionable results, any of the tests performed during screening may be repeated once before study treatment administration to confirm eligibility or clinical significance.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using pre-screening enrollment logs, clinical database and IEC/IRB-approved newspaper/radio/social-media advertisements.

6. TREATMENTS

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

The IMP for this study *is* RO7565020, an HBsAg mAb. NUCs *(ETV, TDF, and TAF), as background treatment, are classified as authorized auxiliary medicinal products (AxMPs)/non-investigational medicinal products (NIMPs).* Appendix 6 identifies all investigational and non-investigational medicinal products for this study. RO7565020 administrations will be at the study center under supervision of site staff. NUCs will be self-administered by participants.

Cases of accidental overdose or medication error, along with any associated AEs, should be reported as described in Appendix 2, Section 5.2.

6.1 TREATMENTS ADMINISTERED

The treatments administered are summarized in Table 8. Guidelines for treatment interruption or discontinuation are provided in Section 6.6.1 or Section 7, respectively.

Please see RO7565020 IB and the pharmacy manuals for more details.

Table 8 Summary of Treatments Administered

Study treatment name:	RO7565020	Placebo	NUC (ETV, TAF, or TDF)
Use:	Experimental	Placebo comparator	*Background treatment*
Dose formulation:	Vial	Vial	Refer to local prescribing information.
Unit dose strength(s):	360 mg/2 mL	0 mg/20 mL	
Dose and regimen:	See details in Table 6	Not applicable	
Route of administration:	SC injection/ IV infusion	SC injection/ IV infusion	Oral
Source:	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	*Continued as prescribed by the treating physician, can be provided centrally or locally.*
Packaging and labeling:	Study treatment will be provided in a 2 mL glass vial. Each vial will be labeled as required per country requirement.	Placebo will be provided in a single-dose 20 mL glass vial.	Study treatment will be packaged and labeled *if* required per local regulation.

Abbreviations: ETV = entecavir; IV = intravenous; NUC = nucleos(t)ide analogue; SC = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

The packaging and labeling of the IMP will be done in accordance with the Sponsor's standard and local regulations. IMP packaging will be overseen by the Sponsor's clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The study site must follow all instructions included with each shipment of IMP. The Investigator or other authorized personnel (e.g., pharmacist) will acknowledge receipt of study treatment and confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMP received and that any findings, product complaints, or discrepancies have been reported and resolved before use of the IMP. All IMP 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 staff.

Only participants enrolled in the study may receive IMP, and only authorized staff may supply or administer IMP.

The Investigator is responsible for IMP accountability (i.e., receipt, reconciliation, and final disposition records). The authorized study personnel [e.g., pharmacist]) will maintain records of IMP delivery to the site, IMP inventory at the site, study treatment use by each participant, disposition or return of unused IMP. This will enable reconciliation of all IMP received, and ensure that participants are provided with the doses which are specified in the protocol.

IMP 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. 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. Accurate records of all IMP received at, dispensed from, returned to, and disposed of by the study site will be recorded on the drug accountability log.

Refer to the pharmacy manual for information on study treatment formulation, study treatment handling (including preparation and storage), and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

Participants in each cohort of Part 1a and Part 1b will be randomized to active treatment or placebo. The list of randomized treatment assignments will be generated by the Sponsor or its designee. The randomized treatment assignment will be allocated from

the list sequentially to subjects in the order in which they are randomized. For each dose cohort in Part 1a and Part 1b, the randomization will be designed such that of the first 2 participants, 1 will receive active drug and the other will receive placebo. The remaining 6 participants in the cohort will be randomized such that 5 receive active drug and 1 receives placebo. The treatment allocation will be managed by the unblinded pharmacist and will be based on the randomization code list.

Parts 2 and 3 are open label and participants will all receive active treatment. The specific treatment to be taken by a participant will be assigned using interactive (voice/web) response system (IxRS), according to specifications provided by the Sponsor to the external vendor. The site will contact the IxRS prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable electronic case report form (eCRF), if required.

6.3.2 Blinding

In each cohort of Part 1a and Part 1b, participants will be randomized to RO7565020 or placebo. The randomization numbers will be generated by the Sponsor or its designee. The study is observer-blind. This means that in the randomized cohorts (i.e., cohorts in Part 1a and Part 1b), the participant, the Investigator(s), and all individuals in direct contact with the participant at the investigative site will be blinded, except the pharmacist handling the study treatment and the unblinded study treatment administrator (if deemed necessary).

To allow informed recommendations or decisions regarding dose-selection 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, Clinical Scientist, Safety Science Lead, and the Clinical Biomarker Lead who perform this assessment, together with the Biostatistician, 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 study management team member. Likewise, the Bioanalyst and the Pharmacometrician will be unblinded. Other members of the Sponsor's project and study teams who do not have any direct contact with the participants may be unblinded at the Clinical Pharmacologist'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., Principal Investigator) who are involved in the dose decision process, but should not disclose individual treatment assignment.

Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved unblinded pharmacist will be responsible for the reconstitution and dispensation of all study treatment and an otherwise uninvolved unblinded study treatment administrator will be responsible for the study treatment administration, if deemed necessary. In the

event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

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.

If the Investigator wishes to know the identity of the study treatment for any reason other than a medical emergency, he/she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any non-emergency unblinding.

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 in the source documentation and eCRF, as applicable.

As per Health Authority reporting requirements, the Sponsor's drug safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Appendix 2) that are considered by the Investigator or Sponsor to be related to study treatment. The participant may continue to receive treatment, and the Investigator, participant, and the blinded Sponsor personnel as specified in the treatment assignment information dissemination form, with the exception of the drug safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

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 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.

Parts 2 and 3 are open label; blinding procedures are not applicable.

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

Any medication or vaccine (including OTC or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from 30 days prior to screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

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

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

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

6.5.1 Concomitant Medications for Part 1

6.5.1.1 Permitted Therapy for Part 1

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Paracetamol/Acetaminophen at doses of ≤ 2 g/day is permitted for use any time during the study.

6.5.1.2 Prohibited Therapy for Part 1

As a general rule, no other concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Participants should avoid taking prescription and non-prescription drugs (including vitamins and dietary or herbal supplements) within 2 weeks or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Vaccination is prohibited between 2 weeks before and 1 week after a dose of RO7565020.

6.5.2 Concomitant Medications for Parts 2 and 3

6.5.2.1 Permitted Therapy for Parts 2 and 3

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Paracetamol/Acetaminophen at doses of ≤ 2 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 Sponsor's Clinical Pharmacologist and Medical Monitor.

6.5.2.2 Prohibited Therapy for Parts 2 and 3

Use of the following therapies is prohibited (with the exception of medications to treat AEs), unless otherwise specified below, or the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

- Any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids, IFN or PEG-IFN) is prohibited at any time during the study and for at least 8 weeks prior to the first dose of study treatment. Eye drop-containing, topical, and infrequent inhaled corticosteroids are permissible up to 4 weeks.
- Any systemic antiviral therapy other than NUC (with the exception of oral therapy for HSV I or HSV II) is prohibited at any time during the study.

Participants should avoid taking non-prescription drugs (including vitamins and dietary or herbal supplements) within 2 weeks or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Vaccination is prohibited between 2 weeks before and 1 week after a dose of RO7565020.

Participants should follow the NUC prescribing information with respect to concomitant medication use while taking the NUC.

6.6 DOSE MODIFICATION AND TEMPORARY INTERRUPTION

In general, there will be no dose modifications for RO7565020 in this study.

6.6.1 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, Investigator, or Sponsor), an interruption of study treatment should be considered. Participants who have temporarily interrupted study treatment should restart it as soon as medically justified in the opinion of the Investigator.

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not intend to provide RO7565020 or NUC to participants after conclusion of the study or any earlier participant withdrawal.

The Sponsor will evaluate whether to continue to provide RO7565020 or NUC to participants after the main study is over, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

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

An excessive rate of participant 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 participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1, Section 4.

7.1 DISCONTINUATION OF STUDY TREATMENT

Reasons for discontinuation of study treatment RO7565020 may include, but are not limited to, 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 determination that treatment discontinuation is in the best interest of the participant.
- Pregnancy.
- Any other event that meets individual stopping criteria defined in Section 4.1.1.3.2.
- Safety and tolerability issues, e.g., acute reactions, not tolerable and not manageable with symptomatic treatment.

For Parts 2 and 3 only:

- Disease progression, e.g., any sign of development of liver cirrhosis (or liver imaging indicating cirrhosis), decompensation (e.g., ascites, variceal hemorrhage, Child-Pugh Class B or C clinical classification), or HCC
- Grade 4 ALT abnormal (i.e., $\geq 10 \times$ ULN) as defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE grading table) confirmed within 48 to 72 hours
- Grade 3 ALT abnormal (i.e., $> 5 \times$ to $< 10 \times$ ULN) combined with total bilirubin $> 2 \times$ ULN (of which $> 35\%$ is direct bilirubin), or Grade 3 ALT abnormal and INR > 1.5

Every effort should be made to obtain information on a participant who withdraws from the study treatment but has not withdrawn consent. A participant who discontinues study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.11.3) and may undergo follow-up assessments (see Section 8.11.4), unless the participant has withdrawn consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely due to safety reasons

will not be replaced. Participants who discontinue study treatment prematurely due to other reasons may be replaced.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason and without justification.

In addition, the Investigator can discontinue a participant from the study for medical conditions that the Investigator or Sponsor determines may jeopardize the participant's safety if the participant continues in the study.

If possible, information on the 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 up with for any reason after consent has been withdrawn. This includes the follow-up assessments.

When a participant voluntarily withdraws from the study, or is discontinued by the Investigator, samples collected until the date of withdrawal/discontinuation 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 be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples 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 may be replaced.

For data to be collected at the time of study discontinuation and any further evaluations that need to be completed, see the SoA (Section 1.3).

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, the participant 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 timepoints are summarized in the SoA (Section 1.3). Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

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 ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Efficacy assessments are not applicable for this study.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AEs, including SAEs and AEs of special interest (AESI); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical Examinations

A complete physical examination should be performed at screening and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal systems in addition to the head, eyes, ears, nose, throat, neck, and lymph nodes. Height and weight will also be measured and recorded. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

At subsequent visits (or as clinically indicated), symptom-directed physical examinations should be performed. Weight will also be measured and recorded according to SoA (Section 1.3).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.2 Vital Signs

Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm should be used for all blood pressure measurements. The non-infusion arm should be used during infusion in the IV cohorts. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, radio, cellular phones, conversation).

Vital signs (to be taken before blood collection for laboratory tests) will be measured after 5 minutes of rest and include temperature, SBP and DBP, pulse rate, and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG recordings will be obtained at specified timepoints (see Section 1.3). Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each specified timepoint (±5 minutes). Single 12-lead ECG recordings may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine or semi-supine position for at least 10 minutes, and the patient should remain in a supine or semi-supine position during recording. The same positioning should be maintained for each patient throughout the study. ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be performed within 2.5 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, average heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, and QTcF based on machine readings of triplicate ECG tracings should be recorded on the appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular postdose timepoint the mean QTcF is $>$500 ms or $>$60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint.

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 local laboratories process. If analysis is required to be done centrally, the samples and assays should be clearly identified, and instructions may be provided by the central laboratory manual according to the requirements from 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 eCRF. 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 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, AE, or dose modification), then the results must be recorded in the eCRF.

Results of clinical laboratory testing will be recorded on the eCRF or received as electronically produced laboratory reports submitted directly from the local or 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 laboratory results at screening is considered uncertain, screening laboratory tests may be repeated before enrollment 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, e.g., codeine, benzodiazepines, or opiates), the test could be repeated to confirm washout.

On the basis of 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 do not produce useful information.

8.2.5 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and 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 participant prior to the screening visit (see Section 6.5).

Demographic data will include age, sex, and self-reported race/ethnicity. The information about race/ethnicity of CHB participants is important because host genetics may modulate responses to study treatments. In addition, the information can be used to infer the likely HBV genotype where genotype information has not been obtained in routine clinical care, which is a common circumstance. There are different HBV variants with geographical distribution (Tanwar and Dusheiko 2012; Sunbul 2014) that show different transmission modalities (e.g., vertical, in childhood, in adulthood), disease course, and response to treatment. The relevance of HBV genotypes is that HBV genotypes have a distinct geographical distribution and are known to influence clinical and virological parameters to treatment responses to, for example, IFN (Rajoriya et al. 2017).

For the participants with CHB, the detailed HBV history will be documented, which will include date of HBV diagnosis, mode of HBV infection (if known), HBV genotype (if documented), all previous HBV treatments and outcomes of treatments, occurrence of NUC resistance (if any), previous evaluations of cirrhosis, and dates/outcomes of liver biopsies (if any).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

The Investigator and any qualified designees are responsible for ensuring that all AEs (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 AEs are provided in Appendix 3:

- Diagnosis versus signs and symptoms:
  - Infusion-/injection-related reactions
  - 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
- Lack of efficacy or worsening of the condition being studied
- Hospitalization or prolonged hospitalization

8.3.1 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 AEs at each participant's contact. All AEs, 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 SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the last scheduled follow-up visit.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period, defined as their last scheduled follow-up visit.

However, if the Investigator learns of any SAE (including a death) or other AEs 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 AE information at all participant evaluation timepoints.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow up on each AE until the event has resolved to baseline grade or better, 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 up on all SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (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 up on until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event details and outcome information (e.g., from hospital discharge summaries, consultant reports, and/or autopsy reports) to perform an independent medical assessment of the reported event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Immediate notification by the Investigator to the Sponsor of an SAE (regardless of relationship to study treatment) 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, IRB/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 an 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 notify the IRB/IEC, if appropriate according to local requirements.

For immediate (i.e., no more than 24 hours after learning of the event) and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, IRB and EC, see Appendix 2, Section 5.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be available separately.

8.3.5 Pregnancy

POCBP will be instructed to immediately inform the Investigator if they become pregnant during the study or within 24 weeks after the final dose of study treatment, whichever is longer.

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 24 weeks after the final dose of study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and follow up via the pregnancy reporting process as detailed in Appendix 5. All pregnancies reported during the study should be followed up until there is a pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5.

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

8.3.6 Adverse Events of Special Interest

AESI 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).

AESI for this study include the following:

- Cases of an elevated ALT or AST value in combination with either an elevated bilirubin value or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, defined as:

  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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.7 Management of Specific Adverse Events

Injection-site reactions or hypersensitivity reactions will be managed at the Principal Investigator's discretion with appropriate documentation that the treatment course was in reaction to evident findings (i.e., acetaminophen administered in response to documented fever or pain, graded use of antihistamine, glucocorticoids, or epinephrine for appropriately severe allergic findings, meperidine administered for documented rigors). If the participant experiences any suspected HBsAg-HBsAb immune complex mediated AEs (e.g., serum sickness; please refer to the RO7565020 IB for more information), an unscheduled sample will be collected (see Table 9), and the participant will be managed according to institutional practice at the Principal Investigator's discretion. No prophylactic treatments that could mask clinical findings that may emerge upon dosing with study drug will be administered without prior consultation with the Sponsor's Medical Monitor. If a study drug-related anaphylactic or serious hypersensitivity reaction occurs, administration of RO7565020 should be stopped immediately and permanently discontinued.

In the case of a possible event of ALT elevation or virological breakthrough during study treatment in Parts 2 and 3 in participants with CHB, please consider the following recommended guidelines for management of specific AEs (Table 9).

Table 9 Guidelines for Managing Specific Adverse Events

Event	Action to Be Taken
Injection-site reaction Infusion-related reaction Hypersensitivity reactions	• Manage according to institutional practice. • If the severity of the event is Grade ≥ 2, collect unscheduled safety samples including ADA, complement activation, CRP, hematology, blood chemistry, and coagulation.
Study drug-related anaphylactic or serious hypersensitivity reaction	• Stop administration of RO7565020 immediately and permanently discontinue RO7565020. • Manage according to institutional practice. • Collect unscheduled safety samples including ADA, complement activation, CRP, hematology, blood chemistry, and coagulation.
For Parts 2 and 3 only (participants with CHB)	
Suspected HBsAg-HBsAb immune complex mediated AEs (e.g., serum sickness)	• Manage according to institutional practice. • Collect unscheduled safety samples including ADA, complement activation, CRP, hematology, blood chemistry, and coagulation.

Table 9 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
For Parts 2 and 3 only (participants with CHB) (cont.)	
ALT elevations during treatment:	• If ALT elevation with preserved hepatic function (e.g., no significant changes in bilirubin, INR, PT, albumin, and/or ALP): o ALT 3–10 × ULN: Repeat ALT, LFTs (total bilirubin, direct bilirubin, AST, ALP, albumin), coagulation (INR, PT), and PD parameters (HBV DNA, HBsAg) every week until ALT < 3 × ULN. o ALT > 10 × ULN: Interrupt RO7565020 (in Part 3), and continue NUC treatment. Repeat ALT, LFTs, coagulation, and PD parameters twice weekly until ALT level < 10 × ULN, then weekly until ALT < 3 × ULN. Consider re-introducing RO7565020 on a case-by-case basis based on subsequent laboratory results. • If ALT elevation accompanied by declining liver synthetic and excretory functions (total bilirubin > 2 × ULN, or albumin < 3.0 g/dL, or INR > 1.5) or other signs of hepatic impairment (severe fatigue, vomiting): o Discontinue RO7565020 (in Part 3), and continue NUC treatment. o Repeat ALT, LFTs, coagulation, and PD parameters twice weekly until levels return towards baseline levels or normal range. o Investigate the participant for potential etiologies of the laboratory changes. o If alternative reasons/diagnoses cannot explain the laboratory changes, potential DILI will be considered. Notes: o Frequency of monitoring may need to be adjusted on the basis of clinical scenario and severity of injury. o As the central laboratory results generation and reporting will take time, additional local laboratory tests may be performed at the same time as the central laboratory test, and decision-making may be based on local laboratory results. o For marked and/or persistent ALT elevations, collect a spare serum sample (to allow retrospective evaluation of potential etiologies) and consider liver biopsy on a case-by-case basis (if deemed clinically relevant). • If ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected and managed as described below.

Table 9 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
For Parts 2 and 3 only (participants with CHB) (cont.)	
Virological breakthrough	• Participants with suspected virological breakthrough (HBV DNA > 100 IU/mL or > 1 log increase from nadir) during treatment will attend a study visit (scheduled or unscheduled) within 2 weeks for: o a confirmatory testing that HBV DNA > 100 IU/mL o testing of plasma drug levels of the NUC, and serum levels of RO7565020 o collection of an additional sample for potential resistance testing, and o thorough evaluation of compliance and factors that may be affecting treatment compliance • If virological breakthrough is confirmed: o The additional sample will be further tested for HBV genome characterization through HBV DNA and/or HBV RNA sequencing and where feasible phenotyping o The Investigator will manage the CHB participant's NUC treatment, according to current guidelines and local regulations (guided by participant's treatment history, assessment of compliance, HBV DNA levels, and any available result of drug resistance testing). Blood sample for NUC PK will be collected to confirm the NUC treatment compliance o Consider whether the study treatment RO7565020 can be continued (for Part 3 only)

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CHB = chronic hepatitis B; CRP = C-reactive protein; DILI = drug-induced liver injury; DNA = deoxyribonucleic acid; HBsAb = hepatitis B antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; INR = international normalized ratio; LFT = liver function test; NUC = nucleos(t)ide analogue; PD = pharmacodynamic; PT = prothrombin time; RNA = ribonucleic acid; ULN = upper limit of normal.

8.4 TREATMENT OF OVERDOSE

For this study, the dose of RO7565020 greater than the dose being studied will be considered an overdose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

The Sponsor does not recommend specific treatment for an overdose.

Decisions regarding dose interruptions will be made by the Investigator and the Sponsor on the basis of the clinical evaluation of the participant.

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 duration of the overdose, in the eCRF.
4. Obtain a blood sample for PK analysis as soon as possible.

8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate serum concentrations of RO7565020 will be collected as outlined in the SoAs (Section 1.3). PK samples at 5 minutes after the start of infusion and at the end of infusion on the day of IV administration of RO7565020 MUST NOT be taken from the same arm as that used for study treatment administration. In the case of a participant being unable to provide venous access on the opposite arm to that used for study treatment administration, the leg may be used for PK blood sampling. The date and time of each sample collection will be recorded in the eCRF. Serum concentrations of the total and active fraction of RO7565020 will be analyzed by fully validated assays (RDR 1119728 and RDR 1119729, respectively). During the course of the study, PK sampling timepoints may be modified after agreement between the Sponsor and Investigator on the basis of emerging data to ensure the pharmacokinetics of RO7565020 can be adequately characterized. Additional unscheduled PK samples will be taken at the time of treatment discontinuation if an infusion-related AE is reported (such as an infusion- or injection-related reaction [IRR]), SAE or an severe AE or a suspected virological breakthrough is reported (Section 8.3.7) or if an AE leading to dose interruption or delay of RO7565020 administration (Section 6.6.1) or an accidental overdose is reported (Section 8.4).

- Blood samples from participants treated with placebo 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 compound-related assay development and/or validation experiments or analyses.

The PK blood samples will be destroyed no later than 2 years after the date of the publication of the final clinical study report (CSR). For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).

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

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and archived in the Sponsor's and site study files. This will not constitute a protocol amendment. The

IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 IMMUNOGENICITY ASSESSMENTS

As RO7565020 is a human IgG1 antibody (anti-HBs neutralizing antibody Bc1.187), there is a risk that ADAs against RO7565020 could develop, potentially impacting on the pharmacokinetics of RO7565020, reducing its efficacy, and/or potentially resulting in safety events, such as symptomatic hypersensitivity reaction, including immune-complex reactions.

Antibodies to RO7565020 will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). After completing the scheduled visits, an additional ADA and PK sample collection may be needed, depending on the emerging ADA data.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against RO7565020 (RDR 1119730). The date and time of each sample will be recorded in the eCRF. All samples collected for detection of ADA to RO7565020 will also be evaluated for RO7565020 serum concentration to enable interpretation of the immunogenicity data.

If required, remaining volumes of ADA samples may also be used for assay development/validation experiments, for ADA characterization, for compound-related exploratory analyses, or to help develop further blood tests, after they are used for the mentioned intended uses.

The serum samples will be destroyed no later than 2 years after the date of final CSR or after approval by the study management team or earlier depending on local regulations. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).

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

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

8.7.1 HBV Biomarker Assessments

The following well-established HBV laboratory tests will be measured using plasma or serum samples, as appropriate: quantitative and qualitative HBsAg, quantitative anti-HBs, qualitative HBeAg, qualitative anti-HBe, and quantitative HBV DNA.

Additional HBV dynamic biomarkers may be measured in all or some participants, as appropriate. This may include but not be limited to semi-quantitative HBeAg (calculated from the qualitative assay), quantitative HBV RNA, quantitative HBcrAg, quantitative

total anti-HBc, total HBsAg (post-dissociation of HBsAg:HBsAb complexes), and the HBsAg isoforms using plasma or serum samples.

8.7.2 HBV Genotype

In addition to gathering the HBV genotype through the collection of the medical history from the participants with CHB, the HBV genotype will be determined through HBV RNA sequencing. HBV RNA will be extracted and amplified using the plasma sample collected on Day 1. If this sample is not collected at that visit, it can be collected at any other scheduled visit. If the amplification yields enough HBV RNA material, RNA-based sequencing will be attempted to determine the HBV genotype. The HBV genotype may also be inferred using alternative approaches, such as serovariant determination.

8.7.3 Viral Resistance Monitoring

In some participants, HBV genome (DNA and/or RNA) sequencing may be done as appropriate to identify emerging mutations that may be leading to drug resistance. In the event of a confirmed HBV DNA breakthrough, as defined in Section 8.3.7, HBV DNA will be extracted and amplified using the plasma sample collected for the confirmatory HBV DNA quantification. If the amplification yields enough HBV DNA material, DNA sequencing of either the whole HBV genome or selected regions of interest will be attempted to determine genotype and mutations with potential to be associated with drug resistance and, where feasible, phenotyping. If this process fails, extraction, amplification, and sequencing may be attempted at a later timepoint.

Moreover, changes in the distribution of free and total HBsAg in relation with RO7565020 PK and changes in the affinity of RO7565020 to potential escape mutants in the S gene that might have been selected for by therapy with RO7565020 may be measured using baseline, end of follow-up, and/or intermediary timepoint samples. Further characterization of such emerging mutations may be attempted through HBV RNA sequencing, if feasible.

8.7.4 Exploratory Immunology Biomarkers

Biomarkers of systemic inflammation and immune activation will comprise assays to quantify cytokine/chemokine panels in blood (such as IFN-γ, TNF-α, IL-6, and IL-8), as well as complement activation markers (such as C3a and SC5b-9).

Immune phenotype, B and T cells activation status (by flow cytometry), transcriptional profile and inflammatory signature (scRNAseq) may be assessed in blood from participants with CHB.

Ex vivo HBV-specific cellular immune responses in CHB participants may be measured in samples collected at sites with appropriate capability to perform the PBMC isolation procedure. These cells may be used to evaluate ex vivo HBV-specific cellular immune response by standard immune assays. These analyses will be considered as an

exploratory optional objective due to the logistic and technical challenges that might be experienced with obtaining viable PBMC during the conduct of a multi-center trial.

8.7.5 Genetic and Genomic Analyses

8.7.5.1 Clinical Genotyping

A whole blood sample for germline DNA analysis will be taken once, at baseline or before study treatment administration. If this sample is missed, it can be collected at any other scheduled visit. DNA may be used to determine alleles at genes coding for human leukocyte antigens (i.e., HLA gene family). This information would be used for adapting the methodology of subsequent HBV-specific immune cell evaluations.

To identify these variants and polymorphisms, genome-wide methods may be used.

Given the complexity and exploratory nature of genome-wide analyses, neither genomics data nor analyses will be shared with Investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples, including samples for analyses of inherited human DNA, will be subject to the confidentiality standards described in the sample documentation and in Appendix 1, Section 1.4.

8.7.5.2 Transcriptome Analysis

RNA extraction and subsequent gene expression profiling may be performed from leftover samples to identify biomarker signatures predictive or associated with treatment response/safety. These assessments may be performed in some of the participants if safety or activity rationales develop, pending approval from country health authorities and local ethic committees as appropriate.

Given the complexity and nature of these analyses, genetic and genomic data and analyses will not be shared with Investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the confidentiality standards described in Appendix 1, Section 1.4.

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

The samples may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to RO7565020, identifying biomarkers useful for predicting and monitoring RO7565020 safety, assessing PD effects of RO7565020, and investigating mechanism of therapy resistance. Additional markers may be measured if a strong scientific rationale develops.

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

On the basis of 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 or may be tested only in some of the participants and/or some of the scheduled visits.

Unless otherwise specified below, all samples will be destroyed no later than 5 years after the date of final CSR. For participants who consent to RBR in countries where this applies, leftover samples will be transferred to RBR (Section 8.9).

Any remaining samples after the specified analyses may also be used for additional exploratory biomarker profiling or/and (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to HBV.

Details on processes for collection and shipment of these samples can be found in separate sample documentation.

8.8.1 Mandatory Samples

The following samples for PD and biomarker research are required and will be collected from all participants:

8.8.1.1 Blood Sampling

Samples will be collected for the measurement of the HBV dynamic markers, the HBV genotype, the viral resistance monitoring, and the exploratory immunology biomarkers (see Sections 8.7.1, 8.7.2, 8.7.3,and 8.7.4) according to the SoA (Section 1.3).

A mandatory whole blood sample will also be taken for germline DNA extraction and clinical genotyping of the human leukocyte antigen gene family from every participant. If the sample is missed on Day 1, it can be collected at any other scheduled visit. The whole blood sample for clinical genotyping and derived analytical material will be destroyed immediately after the publication of the associated report.

8.8.1.2 Urine Sampling

Urine samples will be collected according to the SoA (Section 1.3) for safety assessment.

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from participants who give specific consent to participate in this optional RBR in countries where this applies. Samples collected for RBR can be used (but are not thus limited) to achieve the following objectives:

- To study the association of biomarkers with efficacy or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.
- To increase knowledge and understanding of disease biology and drug safety.
- 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.

8.9.2 Sample Collection

For Parts 2 and 3, leftover plasma, serum, blood, and urine samples (including derivatives of these, such as DNA or RNA extracts or PBMCs prepared from blood) will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7565020, diseases, or drug safety. Additional whole blood samples for RBR will be collected from RBR-consenting participants according to SoA table (Section 1.3).

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

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

The repository samples will be subject to the confidentiality standards (as described under “Confidentiality” in Appendix 1).

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economic/medical resource utilization and health economic parameters are not evaluated in this study.

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 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 all pre-treatment assessments (related to entry criteria) must be completed and reviewed by the Investigator 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 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.

In Part 1a and Part 1b, screening and pre-treatment assessments will be performed within 28 days prior to Day 1, unless otherwise specified. In Parts 2 and 3, screening and pre-treatment assessments will be performed within 56 days prior to Day 1, unless otherwise specified.

8.11.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per the SoA (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 SoAs.

Exceptional measures during the COVID-19 pandemic, such as adjustments in study visits, may be considered (see Section 8.11.6)

8.11.3 Assessments at Study Completion/Early Termination Visit

Participants who prematurely discontinue study treatment but remain in the study should continue to attend the follow-up visits. All follow-up assessments must be performed as per SoA (Section 1.3).

8.11.4 Follow-Up Assessments

Follow-up assessments must be performed as per SoA (Section 1.3). After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

8.11.5 Assessments at Unscheduled Visits

If clinically indicated, any assessment or sample specified in the SoAs (Section 1.3) can be performed any time as unscheduled assessment or sample at the discretion of the Investigator. Unscheduled eCRFs will be used to record any assessments performed during an unscheduled visit.

For unscheduled sample collection related to specific safety events, please see Section 8.3.7. For unscheduled PK sample collection, please see Section 8.2.3 and Section 8.5.

8.11.6 Exceptional Measures during COVID-19 Pandemic

If COVID-19 pandemic related special restriction happens, exceptional measures, such as adjustments in study visits, may be considered if in the overall best interest of the participant. Adjustments may include:

- Use of alternative facility for assessments (e.g., local laboratory or imaging centers).
- Replacement of a study visit with alternative methods for assessments (such as phone contacts or virtual visits to assess safety).
- Postponement of a study visit or of individual assessments.
- Temporary suspension of sample collection.

A robust benefit–risk assessment should be performed by the Investigator and discussed with the Medical Monitor. This assessment will be fully documented, and any deviations to the protocol will be recorded in accordance with the Sponsor standard procedure.

9. STATISTICAL CONSIDERATIONS

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.

Approximately 48 to 56 healthy participants and 30 to 54 participants with CHB (depending on whether the optional cohorts are conducted) are planned to be enrolled in this study.

In Part 1a, 8 participants with 6:2 ratio (active treatment versus placebo) are planned to be enrolled into each cohort. Six cohorts are planned. Additional cohort(s) with intermediate dose level(s) is/are allowed.

In Part 1b, 8 participants with 6:2 ratio (active treatment versus placebo) are planned to be enrolled if considered to be necessary based on the data of Part 1a.

In Part 2a and 2b, 6 CHB participants (all active treatment) per dose cohort are planned to be enrolled. Seven cohorts are planned including 2 optional cohorts.

In the optional Part 3, 6 CHB participants (active treatment) in each cohort ($\leq$2 cohorts) are planned to be enrolled if considered necessary based on the data of Parts 1 and 2.

Dose escalation decisions will be made based on data from 5 or 6 participants from each cohort. With 5 participants per dose cohort, there is an at least 80% chance to observe at least one AE that has an incidence rate of 28% in the population; with 6 participants per dose cohort, there is an at least 80% chance to observe at least one AE that has an incidence rate of 24% in the population.

Participants who discontinue study prematurely or withdraw consent from the study for non-safety reason may be replaced in order to obtain the required participant numbers for a dose decision. Additional participants may be enrolled in additional dose cohorts that assess lower or repeat doses. In Parts 2 and 3, except for the replacements, additional participants may be enrolled in some cohorts in case the variability in PK and PD is too high in participants with CHB.

9.3 ANALYSIS SETS

For purposes of analysis, the following populations are defined in Table 10.

Table 10 Analysis Sets

Participant Analysis Set	Description
PD	The analyses of the viral dynamic response will include all participants with CHB who received at least one dose of study treatment (RO7565020 or placebo). Participants will be analyzed according to the treatment group to which they were randomized/assigned.
Safety	All participants randomized/assigned to study treatment and who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
PK	All participants who have received at least one dose of study treatment and who have data from at least one postdose sample will be included in the PK analysis set. Participants will be excluded from the PK analysis set if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Immunogenicity	Participants who had at least one ADA assessment will be included and analyzed according to the treatment they actually received. The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetics; PD = pharmacodynamics.

9.4 STATISTICAL ANALYSES

Statistical summaries will be descriptive in nature and will be reported separately for each part of the study within the CSR. All study participants who are randomized to receive placebo within one part will be pooled as respective placebo control groups for each part.

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 age, gender, race, ethnicity, country of origin, weight, height, BMI, HBV baseline characteristics (e.g., HBsAg levels), HBV history (e.g., duration of HBV diagnosis, HBV treatment history, and liver fibrosis status), and, where measurable (participants with detectable HBV RNA), the viral genotype. For Part 1a and Part 1b, all participants who are randomized to receive SC or IV placebo will be pooled as respective SC or IV 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 subjects in each category will be summarized.

9.4.2 Safety Analyses

All safety analyses will be based on the safety analysis set (see Table 11). Participants will be summarized by cohort. In addition, all study participants who are randomized to receive SC or IV placebo will be pooled as respective SC or IV placebo control groups, according to each part of the study.

The safety data, including AEs, injection-site reactions, reasons 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 11 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. AEs will be summarized by mapped term and appropriate thesaurus level. Frequency and severity of adverse events will be summarized.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units) by individual outputs with flagging of abnormal results. Summary tables of absolute value and change from baseline over time will be displayed. Shifts in DAIDS grades v2.1 from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. For details on standard reference ranges and data transformation and the definition of laboratory abnormalities, see Appendix 4.
Vital signs	Vital sign data will be presented with flagging of values outside the normal ranges and flagging of abnormalities. Mean changes from baseline and absolute value over time will be provided.
ECG data analysis	ECG data will be presented using appropriate outputs, as detailed in Section 9.4.2.1.
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented using appropriate outputs.

Abbreviations: AE = adverse events; DAIDS = Division of AIDS; ECG = electrocardiogram; eCRF = electronic case report form; SI = Système International d'Unités.

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 timepoint, the average of these measurements will be used as the value at that nominal timepoint in all summaries. In addition, QTcF will be categorized at each timepoint as $\leq$ 450 ms, $>$ 450 to 480 ms, $>$ 480 to 500 ms and $>$ 500 ms and summarized. Similarly, a summary will be provided of the QTcF changes from baseline at each timepoint categorized as $<$ 30 ms, 30 to 60 ms, and $>$ 60 ms. Changes of the overall ECG interpretation and T-wave and U-wave morphology will be summarized.

9.4.3 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis set. All PK parameters will be presented by listings and descriptive summary statistics (arithmetic means, geometric means, medians, ranges, standard deviations, and coefficients of variation) separately by group or cohorts.

Individual and mean serum total and active RO7565020 concentration versus time data will be tabulated and plotted on linear or semi-logarithmic scales by dose level, and/or by route of administration in different parts.

PK parameters will be read directly from the serum total and active concentration-time profiles, or calculated using standard non-compartmental methods. The following PK parameters will be computed for RO7565020 as appropriate.

- Time to maximum concentration (t_{max})
- Maximum serum concentration observed (C_{max})
- AUC from 0 to last sampling point or last quantifiable sample, whichever comes first (AUC_{last})
- AUC from 0 to infinity (AUC_{inf})
- Terminal half-life ($t_{1/2}$)
- Volume of distribution (Vss) and clearance (CL) (IV only)
- Apparent clearance (CL/F) and apparent volume of distribution (Vz/F) (SC only)

Further data analysis to estimate the dose-exposure relationships and the potential impact of TMDD and of ADAs on PK of RO7565020 will be also conducted as appropriate.

Calculations of additional PK parameters and population pharmacokinetic (popPK) analysis at the end of the dose escalation will be performed as data allow it. Population and individual PK parameters will be estimated, and the influence of various covariates

(such as age, sex, body weight and baseline HBsAg levels [only in Parts 2 and 3]) on these parameters will be investigated in an exploratory way.

The details of the popPK and any other exploratory data analyses will be reported in documents separate from the CSR.

9.4.4 Immunogenicity Analyses

The immunogenicity analyses will include all participants with at least one ADA assessment, irrespective of whether or not the participant receives any treatment (Shankar et al. 2014).

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after study treatment administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized.

- Participants are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study treatment administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold (e.g., $\geq$ 0.60-titer units) greater than the titer of the baseline sample (treatment-enhanced ADA response).
- Treatment-induced ADA responses will be further categorized as either:
  - Transient ADA response: defined as a) ADA negative or no ADA available at baseline, and b) at least one post-treatment ADA-positive sample, and c) only one ADA-positive sample or the time between the first and last ADA-positive sample is less than 16 weeks and d) the last ADA sample is negative
  - Persistent ADA response: defined as a) ADA negative or missing data at baseline, and b) post-treatment ADA-positive samples over 16 weeks or more or the last ADA timepoint is positive (Shankar et al. 2014)
- Participants are considered to be ADA negative if they are ADA negative; if they have missing data 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 at least 4 fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

9.4.5 Pharmacodynamic Analyses

Viral dynamic response analysis will be done for the participants with CHB enrolled in Part 2a, Part 2b, and Part 3, and will be based on the PD analysis set (see Table 10). Descriptive statistics will be utilized to summarize the viral dynamic response outcome

measure of serum HBsAg and HBeAg (Table 12), and the exploratory viral dynamic endpoints of HBV RNA, HBcrAg, total HBsAg, HBsAg isoform (Table 13).

Table 12 Viral Dynamic Response Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
HBsAg change from baseline	Time course profile: summary descriptive statistics by cohort (including mean, standard deviation, median, minimum, and maximum) (in log10 IU/mL and % change from baseline) at each timepoint.
Maximum reduction of HBsAg	Summary descriptive statistics by cohort (including mean, standard deviation, median, minimum, and maximum) (in log10 IU/mL and % reduction).
HBsAg loss and HBsAg seroconversion	Proportion of HBsAg loss and HBsAg seroconversion at each timepoint. Percentages are based on PD analysis set.
HBeAg loss and HBeAg seroconversion	Proportion of HBeAg loss and HBeAg seroconversion at each timepoint. Percentages are based on PD analysis set.

Abbreviations: HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; PD = pharmacodynamic.

Table 13 Exploratory Viral Dynamic Response Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Baseline and change from baseline of HBV RNA, HBcrAg, and total HBsAg	Time course profile: summary descriptive statistics by cohort (including mean, standard deviation, median, minimum, and maximum) (in log10 IU/mL) at each timepoint.

Abbreviations: HBcrAg = hepatitis B core-related antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

9.4.6 Pharmacokinetic/ Pharmacodynamic Relationships

In order to inform the design and selection of dose regimens in further clinical trials, exploratory analysis between PK and/or PD, antiviral response and/or safety by modeling and simulation (e.g., using nonlinear mixed effects modeling and/or physiologically-based pharmacokinetic [PBPK] analysis) based on study data may be applied if considered appropriate.

The details of PK/PD modeling results will be reported in documents separate from the CSR.

9.4.7 Other Analyses

Data from exploratory biomarkers will be listed, and descriptive statistics, by cohorts and between participants with CHB and healthy participants (when available), at each

timepoint, will be applied in relation to viral and immune markers and potentially PK parameters. Graphic displays may be used as appropriate.

This exploratory study will have ongoing safety assessment and safety data reviews for the purpose of dose escalation/decisions that do not qualify as formal interim analyses (IAs). Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim analyses. The decision to conduct an optional IA and the timing of the analysis will be documented in the Sponsor's electronic trial master file (eTMF) prior to the conduct of the IA. The IA will be performed and interpreted by Sponsor's study team personnel, who will have full access to trial data. Access to treatment assignment information will follow the Sponsor's standard procedure.

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 or who discontinued and completed the study will be summarized and listed.

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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) and Appendix 3 (Procedures of recording AEs), Appendix 4 (Clinical laboratory tests), Appendix 5 (Contraceptive guidance and collection of pregnancy information), Appendix 6 (Investigational medicinal product and auxiliary medicinal product designations), and Appendix 7 (List of abbreviations).

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 (GCP) 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 International Council for Harmonisation (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. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the E.U./EEA will comply with the E.U. Clinical Trial Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations.

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Master Informed Consent Forms (ICFs), any information to be given to the participant (e.g. advertisements, diaries etc.), and relevant supporting information must be submitted to the Institutional Review Board (IRB)/ethics committee (EC) by the Principal Investigator or the Sponsor, as required by local laws and regulations 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 or the Sponsor, as required by local laws and regulations, 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 (AEs) 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 Child's Assent or Caregiver's 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 Code of Federal Regulations (CFR) Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 (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. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant.

The ICFs must be signed and dated by the participant 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 ICFs 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 ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, 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 ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant. All signed and dated ICFs 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.

Participants who are re-screened are required to sign a new ICF.

Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the Research Biosample Repository (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 samples 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 samples. 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 electronic case report form (eCRF).

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

For sites in the United States, each ICF may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply, except that IRB review and approval may not be required per study site policies.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's 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 samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the study 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 study is closed. A participant's withdrawal from Study BP44118 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study BP44118. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

Confidentiality for Research Biosample Repository

Data generated from RBR samples 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 samples is confidential and may only be disclosed to third parties as permitted by the ICF (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 sample 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 sample data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with GCP by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as compliance to authorized use of samples as specified in this protocol and in the ICF. The Sponsor's 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 the Sponsor. 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 1 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 eCRF 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 case report form (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.

2.1.3. 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, COAs (paper or eCOA), 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, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

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.

2.1.4. 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.

2.1.5. Safety Biomarker Data

Adverse Event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations. 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local Health Authorities.

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 competent authorities according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any protocol amendments will be prepared by the Sponsor. 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 participants 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 on the basis of 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 multi-center studies 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 (ICMJE) 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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study Investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to first participant entry into the study, the Sponsor will identify and evaluate potential risks associated with critical study processes and data, as well as implement controls for the communication, review, and reporting of these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

Risk control includes the selection of risk-based parameters and establishing associated quality tolerance limits. Detection of deviations from defined quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the management and review of quality tolerance limits will be provided in a separate Quality Tolerance Limit plan.

2.3.5. 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.

3. ADMINISTRATIVE STRUCTURE

Not applicable.

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 AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.
- Emerging data and/or prioritization of assets.

If general study stopping criteria are met, the study will be paused and the Sponsor will conduct a full review of all available safety data. The study will resume if the Sponsor and Investigator agree and after informing and receiving agreement from relevant Health Authorities and Ethics Committees.

If the study is placed on hold, or if the Sponsor decides to discontinue the study or the development program, the Sponsor shall promptly inform the Investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

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 International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP), an **adverse event** (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

An AE 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:

- 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 (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent preexisting 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.
- AEs 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).

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder 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 preexisting 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 an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE 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 during 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.

- **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

  – elevated ALT or AST ($>3\times$ ULN and $>3\times$ baseline) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia (potential Hy's law).

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 electronic case report form (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 the 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 the Medical Monitor.

The Investigator will attempt to establish a diagnosis of the event on the basis of 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 terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, severe, or according to a predefined grading criteria) (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS]); 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 AE recorded on the eCRF.

SAEs 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 DAIDS (v2.1) will be used for assessing severity for adverse events. Table 1 will be used for assessing severity for AEs that are not specifically listed in the DAIDS.

Table 1 DAIDS Adverse Event Severity Grading Scale for Events Not Specifically Listed in DAIDS Toxicity Grading Scale

Grade	Description
1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
4	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
5	Death

Abbreviation: DAIDS = Division of AIDS

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see above). DAIDS v2.1 grading scale is available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Developed by the DAIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services.

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 AE 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, or reintroduction 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 participant 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 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.

If a participant dies during participation in the study or during a recognized follow-up period, when possible the Investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

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 study. 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:

- SAEs
- AEs of special interest (AESI; see Section 8.3.6)
- 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 on the basis of 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 SAEs to the local Health Authority and Institutional Review Board (IRB)/ethics committee (EC).

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND 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 SAEs caused by a protocol-mandated intervention should be reported. The Clinical Trial Adverse Event/Special Situations 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 SAEs and AESI (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 Clinical Trial Adverse Event/Special Situations 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 SAE occurring after the end of the AE reporting period, and 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 Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to Investigators.

6. SPECIAL SITUATIONS (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 (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration).

After initiation of study drug, special situations associated with RO7565020/matching placebo and any associated AEs will be reported until 6 months after the final dose of study drug.

Special situations, regardless of whether they result in an AE, should be recorded on the Special Situations eCRF. If there are any associated AEs, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated AEs should be reported within 30 days after the Investigator becomes aware of the situation. However, if an associated AE fulfills seriousness criteria or qualifies as an AE of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the Investigator becomes aware of the event), as described in Section 5.1 of this appendix.

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

The Sponsor will promptly evaluate all SAEs and AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs/ ECs, and applicable Health Authorities on the basis of applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events through use of the reference safety information (RSI) in the documents listed below:

Drug	Document
RO7565020	Investigator's Brochure RO7565020
RO7565020 placebo	Investigator's Brochure RO7565020

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.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events (AEs) on the Adverse Event electronic case report form (eCRF). Avoid colloquialisms and abbreviations.

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION REACTIONS/ INJECTION REACTIONS

AEs associated with the intravenous infusion or injection that occur during or within 24 hours after study treatment administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than as an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-/ injection-related reaction or anaphylactic reaction).

1.2. OTHER ADVERSE EVENTS

For AEs other than infusion-related or injection reactions, 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 AEs based on signs and symptoms should be nullified and replaced by one AE report that is 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, AEs 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 AEs 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 AEs 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 AE is one that extends continuously, without resolution, between participant evaluation timepoints. 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 AE is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE 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 AE.

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 AE. 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 AE. A vital sign result should be reported as an AE 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 AE.

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 FUNCTION TESTS

Parts 1a and 1b:

The finding of an elevated ALT or AST ($>3\times$ULN) 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 (as defined by Hy's Law). Therefore, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN.
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice.

Parts 2 and 3:

The finding of an elevated ALT or AST in combination with either an elevated total bilirubin or clinical jaundice in the absence of cholestasis or other causes of

hyperbilirubinemia is considered to be an indicator of potential severe liver injury. Therefore, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 5 \times$ ULN value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin).
- Treatment-emergent ALT or AST $> 5 \times$ ULN value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious AE (SAE) or a non-serious AE of special interest (see Section 8.3.6).

7. DEATHS

All deaths that occur during the protocol-specified AE 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 chronic hepatitis B.

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 AE 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. LACK OF EFFICACY OR WORSENING OF CHRONIC HEPATITIS B

Lack of efficacy in terms of changes in HBsAg does not qualify as an adverse event in this study.

Medical occurrences or symptoms of deterioration in the course of chronic hepatitis B should be recorded as an AE 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 chronic hepatitis B on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., progression of chronic hepatitis B).

Hepatitis B virological breakthrough and abnormal liver function tests (see Section 8.3.7) should be reported as adverse events.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAEs in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., for study treatment administration).
- 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 (e.g., when elective surgery became necessary because of the expected normal progression of the disease).

  The participant has not suffered an AE.

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

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

Appendix 4
Clinical Laboratory Tests

Urinalysis, urine pregnancy test, alcohol, cotinine, and drugs of abuse screens will be performed locally. The other tests detailed in Table 1 will be performed by the local or central laboratory, depending on study parts/cohorts (e.g., for Parts 2 and 3, these tests will be performed by central laboratory). If the local laboratory results are used, the results must be captured in source documentation and entered into the electronic case report form (eCRF) or electronic transfer to the Sponsor.

For the study parts/cohorts using a central laboratory, local laboratory results may be required in the event that the central laboratory results are not available in time for *determination of study eligibility,* study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis be obtained at the same time. Additionally, if the local laboratory results are used to make *these determinations*, 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 Section 5.2 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, mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]).
Clinical chemistry	• Sodium, potassium, chloride, bicarbonate, phosphate, magnesium, calcium • Glucose, lipase • Total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH, gamma-glutamyl transferase (GGT), creatine kinase/creatine phosphokinase (CK/CPK), and amylase • Uric acid, urea, blood urea nitrogen (BUN), creatinine and cystatin C, estimated glomerular filtration rate (eGFR), calculated creatinine clearance (using the Cockcroft Gault formula)
Coagulation	• INR, aPTT, PT.

Laboratory Assessments	Parameters
Viral serology and virology	• HIV (specific tests HIV-1 antibody, HIV-2 antibody or HIV-1/2 antibody, or any confirmatory test approved by Health Authorities), hepatitis A virus (HAV IgM antibody), hepatitis B surface antigen (HBsAg) quantitative, hepatitis B surface antibody (HBsAb) quantitative, hepatitis C virus (HCV) antibody, HCV RNA (if HCV antibody positive), hepatitis D virus (HDV) antibody *(Parts 2 and 3 only)*, hepatitis E virus (HEV) antibody or HEV RNA *(Parts 2 and 3 only)*. • HBV DNA quantitative
Lipids	• Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Thyroid hormones	• Free T4, TSH, free T3.
Pregnancy test	• All biological female participants will have a blood pregnancy test at screening (in Parts 2 and 3, if two tests at screening, the one within 14 days before dosing should be a blood test). 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. • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase. • If there is a clinically significant positive result, 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. • Microscopic examination (RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal
Other screening tests	• Urine drug abuse screen, including cannabinoids, amphetamines and/or methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates • Urine cotinine test • Alcohol test (breath or urine)
Others	• Auto-antibodies (ANA, AMA, ASMA, a-TPO) • C3, C4, and total hemolytic complements (CH50) • C-reaction protein (CRP) • Glutamate dehydrogenase (GLDH) for Parts 2 and 3 (exploratory) • α-fetoprotein

Abbreviations: ALT = alanine aminotransferase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; ASMA = anti-smooth muscle antibody; AST = aspartate aminotransferase; a-TPO = anti-thyroid peroxidase; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PT = prothrombin time; RBC = red blood cell; TSH = thyroid-stimulating hormone; WBC = white blood cell.

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

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

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific laboratory tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these 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, alkaline phosphatase, and total bilirubin. The standard reference ranges for these parameters have a lower limit of zero; therefore, only the upper limits of the ranges will be used in transforming the data.

Definition of Laboratory Abnormalities

For all laboratory parameters included in the analysis described above, 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 statistical outputs of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. 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 and Barrier Methods Guidance

1. DEFINITIONS

- **Participant of Childbearing Potential (POCBP)**

A participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Participants in the following categories are considered to be of Non-Childbearing Potential (PONCBP)**

o Pre-menarchal

o Premenopausal biological females 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.

o Postmenopausal participants:

- A postmenopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Participants 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. Only discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Biological Female Participants**

POCBP are eligible to participate if they agree to use highly effective method of contraception that results in a failure rate of < 1% per year until 24 weeks after the final dose of study treatment, consistently and correctly as described in Table 1 below.

Per International Council for Harmonisation (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] (Failure rate of < 1% per year when used consistently and correctly)
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: o Oral o Intravaginal o Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: o Oral o Injectable
Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion/ligation **Azoospermic partner (vasectomized or due to medical cause)** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the POCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** 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.
Effective Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[b] • Cap, diaphragm, or sponge with spermicide[b]

Abbreviation: POCBP = Participant of childbearing potential.

a) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraception method.

   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.

b) A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods (i.e., when the risk of teratogenicity and genotoxicity is unlikely).

3. PREGNANCY TESTING

For POCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to the SoA (see Section 1.3). If a highly sensitive 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 partner who becomes pregnant while the male participant is in this study or within 6 months after the final dose of study treatment (see Section 8.3.5 Pregnancy). This applies only to male participants who receive RO7565020.

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 and an Authorization for Use and Disclosure of Infant Health Information to allow for follow-up on her pregnancy and the infant health information respectively. 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 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.

Information on the status of the infant health at the 6th and 12th month after the date of birth will be forwarded to the Sponsor by using Infant Clinical Trial Follow-up Reporting Form when the authorization for infant health follow-up has been obtained.

- **Participants who become pregnant**

The Investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the Clinical Trial Pregnancy Reporting 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. 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. The Investigator will collect follow-up information on the participant and the neonate which will be forwarded to the Sponsor. When permitted by the site, the pregnant participant would need to sign an Authorization for the Use and Disclosure of Infant Health Information to allow for follow-up on the infant. Information on the status of the infant health at the 6th and 12th month after the date of birth will be forwarded to the Sponsor by using Infant Clinical Trial Follow-up Reporting Form when the authorization for infant health follow-up has been obtained.

While pregnancy itself is not considered to be an adverse event (AE) or serious AE (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 participant who becomes pregnant while participating in the study will discontinue study treatment.

Additionally, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5 ABORTIONS

Any spontaneous abortion in a participant exposed to study treatment or the partner of a male participant exposed to study treatment should be classified as an SAE (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 embryofetal toxicity should also be classified as an SAE, 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 or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting and is not considered an AE but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a participant or partner of a male participant exposed to study treatment should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 6
Investigational Medicinal Product and *Non-Investigational* Medicinal Product Designations

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
RO7565020	IMP (test product)	*Unauthorized*	Not applicable
RO7565020 placebo	IMP (placebo)	*Unauthorized*	Not applicable
ETV	*Authorized AxMP (background treatment)*	*Authorized*	*Yes*
TDF	*Authorized AxMP (background treatment)*	*Authorized*	*Yes*
TAF	*Authorized AxMP (background treatment)*	*Authorized*	*Yes*

Abbreviations: AxMP = auxiliary medicinal product; EEA = European Economic Area; ETV = entecavir; IMP = investigational medicinal product; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in the UK*	*Used within Marketing Authorization*
RO7565020	*IMP (test product)*	*Unauthorized*	*Not applicable*
RO7565020 placebo	*IMP (placebo)*	*Unauthorized*	*Not applicable*
ETV	*NIMP (background treatment)*	*Authorized*	*Yes*
TDF	*NIMP (background treatment)*	*Authorized*	*Yes*
TAF	*NIMP (background treatment)*	*Authorized*	*Yes*

Abbreviations: ETV = entecavir; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate, UK = United Kingdom.

Appendix 7
Abbreviations

Abbreviation	Definition
AAV	adeno-associated virus
Ab	antibody
ADA	anti-drug antibody
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
AFP	α-fetoprotein
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANA	antinuclear antibody
ARFI	acoustic radiation force impulse
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
a-TPO	anti-thyroperoxidase
AUC_{0-21d}	area under the time-concentration curve from 0 to 21 days
AUC_{inf}	area under the time-concentration curve from 0 to infinity
AUC_{last}	area under the time-concentration curve from 0 to last sampling point or last quantifiable sample, whichever comes first
AUC_{tau}	area under the time-concentration curve within a dosing interval
AxMP	*auxiliary medicinal product*
BMI	body mass index
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
CL	clearance
CL/F	apparent clearance
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DDT	Dose Decision Team
DEP	Dose Escalation Plan

DNA	deoxyribonucleic acid
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
eTMF	electronic trial master file
ETV	entecavir
E.U.	European Union
FcRn	neonatal Fc receptor
FIH	First-in-human
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSV	herpes simplex virus
IA	interim analysis
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-/injection-related reaction
IV	intravenous
IxRS	interactive (voice/web) response system
LLN	lower limit of normal

LLOQ	lower limit of quantification
LPLO	last participant, last observation
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NIMP	*non-investigational medicinal products*
NK	natural killer
NOAEL	no-observed-adverse-effect level
NUC	nucleos(t)ide analogue
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamic
PEG	pegylated
PK	pharmacokinetic
POCBP	participant of childbearing potential
PONCBP	participant of non-childbearing potential
popPK	population pharmacokinetic
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBR	Research Biosample Repository
RNA	ribonucleic acid
RUO	research-use-only
SAD	single-ascending dose
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
scRNAseq	single-cell RNA sequencing
siRNA	short interfering RNA
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
SVP	subviral particle
$t_{1/2}$	terminal half-life
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
t_{max}	time of maximum concentration observed
TMDD	target-mediated drug disposition
TNF	tumor necrosis factor

TSH	thyroid-stimulating hormone
ULN	upper limit of normal
U.S.	United States
Vss	volume of distribution
Vz/F	apparent volume of distribution
WHO	World Health Organization
YTE	M252Y/S254T/T256E (mutation)

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