Official Title: A Randomized, Sponsor-Open, Placebo-Controlled Study to Evaluate Safety, Tolerability and Pharmacokinetics and Pharmacodynamics of Subcutaneous Administration of RO7062931 With Single Ascending Doses in Healthy Volunteers and Multiple Doses and Modified Regimens in Virologically Suppressed Patients With Chronic Hepatitis B Virus Infection

NCT Number: NCT03038113

Document Date: Protocol Version 4: 12-March-2019

PROTOCOL

TITLE:	**A RANDOMIZED, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACOKINETICS AND PHARMACODYNAMICS OF SUBCUTANEOUS ADMINISTRATION OF RO7062931 WITH SINGLE ASCENDING DOSES IN HEALTHY VOLUNTEERS AND MULTIPLE DOSES AND MODIFIED REGIMENS IN VIROLOGICALLY SUPPRESSED PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION**
PROTOCOL NUMBER:	BP39405
VERSION:	*4*
TEST PRODUCT:	RO7062931
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 24-October 2016
DATE AMENDED:	Version 2: 10-April-2017 *Version 3: 30-November-2018* Version *4*: See electronic date stamp below

Approver's Name	**Title**	**Date and Time (UTC)**
[redacted]	Company Signatory	12-Mar-2019 10:11:46

PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACOKINETICS AND PHARMACODYNAMICS OF SUBCUTANEOUS ADMINISTRATION OF RO7062931 WITH SINGLE ASCENDING DOSES IN HEALTHY VOLUNTEERS AND MULTIPLE DOSES AND MODIFIED REGIMENS IN VIROLOGICALLY SUPPRESSED PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION**
PROTOCOL NUMBER:	BP39405
VERSION NUMBER:	*4*
TEST PRODUCT:	RO7062931
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL AMENDMENT, VERSION *4*: RATIONALE

The following sections summarize the rationale for the changes made to the protocol.

Substantial changes

Protocol BP39405 has been amended to incorporate the following changes:

- Study Part 2c with up to four cohorts was added to evaluate the efficacy and safety of RO7062931 when administered with Standard of Care (SoC) for up to 48 weeks.

  a) Preliminary results from Part 2a and 2b of the study with RO7062931 administered over a short duration of 28 days showed that RO7062931 is associated with good safety and tolerability profile, and proof-of-mechanism (PoM) was demonstrated with dose-dependent declines in hepatitis B surface antigen (HBsAg) compared with the placebo group.

[redacted]

- Up to date non-clinical and clinical information was added to support the extension of the treatment duration in Part 2c.
- Clarification and additional information regarding the management of ALT abnormalities was added.
- Dose modifications guidance for the management of PEG-IFN side effects was added.
- For consistency and comparability of hepatitis B virus (HBV) clinical data, the severity of adverse events will be graded according to Division of AIDS (DAIDS).

[redacted]

- A rationale was provided about why NUCs are classed as non-investigational medicinal products (NIMP) and about peginterferon (PEG-IFN) is classed as an IMP in this study. Accordingly, the dosage form of PEG-IFN and packaging and labeling instructions have been provided.

Non-Substantial Changes

- It was clarified that NUC/PEG-IFN are marketed and commercially available and consequently, no post-study medication or drug reimbursement after the trial is provided as part of the protocol.
- A clarification was provided that herbal therapy or substances *(*e.g. tea)/supplements/traditional Chinese medicines), as well as over the counter (OTC drugs), may affect laboratory values and consequently lead to screening failures/patient withdrawal from study treatment. Therefore, Investigators have been instructed to carefully review the intake of such therapies with the patient and advise them to refrain from taking them, if considered necessary.
- For patients in Part 2C taking NUC or PEG-IFN during the study, it was added that prescribing information or PEG-IFN Investigator Brochure should be followed as a guide as to whether concomitant medications are permitted or prohibited and that the sponsor may be contacted in case of doubt regarding potential prohibited concomitant medications.
- Some formatting and typographical errors have been corrected.

PROTOCOL AMENDMENT, VERSION 4: SUMMARY OF CHANGES

All changes made to the protocol are shown in italics.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol.

1.2.1 Previous Non-Clinical Studies

[…]

[redacted]

[redacted]

1.2.2 Previous Clinical Studies

This Phase I study (BP39405) is the first-in-human study with RO7062931. One further clinical study with RO7062931 in Chinese Healthy Volunteers is currently ongoing.

Preliminary data from BP39405 study indicates that RO7062931 is safe and well tolerated:

- *In the BP39405 study Part 1, 60 healthy volunteers in total, in six SAD cohorts (0.1, 0.3, 1.0, 2.0, 4.0, and 3.0 mg/kg) received a single dose of RO7062931 or placebo. Blinded data review demonstrated no dose dependency in the incidence and intensity of AEs. A total of 78 non-serious AEs were reported in 40 out of 60 HVs; the majorities (74) of those AEs were mild in intensity and 4 were of moderate in intensity.*

- *In Part 2a and Part 2b of the BP39405 study, at the cut-off date of 22 November 2018, 54 patients were enrolled. Part 2a enrolled 27 patients in four cohorts for monthly dosing (0.5, 1.5, 3.0 mg/kg of RO7062931 or placebo). Part 2b enrolled further 27 patients in three cohorts exploring 3 mg/kg weekly (QW) or bi-weekly dosing (Q2W) of RO7062931. There was no dose-dependent or regimen-dependent increase in the frequency or severity of AEs. A total of 82 AEs were reported in 32 of the 54 CHB patients; most AEs were mild and had resolved, and five AEs observed in 4 CHB patients were moderate in intensity.*

- *There were no severe or SAEs, AEs leading to treatment withdrawal, or AEs of special interest. No particular pattern or significant changes were observed for vital signs, ECGs parameters, laboratory safety test results, or urine microscopy. No patients discontinued study medication due to safety reasons.*

- *In addition, proof-of-mechanism (POM) in CHB patients has been demonstrated with dose-dependent declines in HBsAg observed in patients treated with RO7062931 compared to placebo. Similar HBsAg declines were observed regardless of HBeAg status.*

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

Study BP39405 is the first clinical study of RO7062931, designed to assess: the safety, tolerability and pharmacokinetics (PK) of subcutaneously administered single-ascending doses (SAD) in healthy volunteers (HVs; Part 1); and safety, tolerability, PK, and pharmacodynamic (PD) effects of subcutaneously administered multiple doses to CHB patients *for a short duration of treatment (Part 2a and Part 2b) and for an extended duration of treatment (Part 2c).* In this protocol, both healthy volunteers and patients are referred to as study subjects.

[…]

[redacted]

[…]

Part ~~2~~*2a/2b* will involve patients with CHB infection who have responded to standard treatment with NUC inhibitors of HBV reverse transcriptase. [redacted] However, the results from Part ~~2~~*2a/2b* will provide essential information for selecting doses for future clinical trials and for supporting the development of a new treatment for chronic HBV infection.

Part 2c of the study will assess the efficacy and safety of RO7062931 when administered with Standard of Care (SoC; NUC with/without PEG-IFN) for up to 48 weeks. Preliminary data from Part 2a/2b have demonstrated POM and RO7062931 administration in CHB patients is associated with a good safety and tolerability profile following 4 weeks of treatment. [redacted]

1.3.2 Benefit-Risk Assessment

~~No~~*Before initiation of this first-in-human study, no* prior clinical experience with RO7062931 ~~exists~~*existed*. The evaluation of the potential risks of treatment and the specific tests, observations, and precautions required for clinical studies with RO7062931 ~~are~~*were* based on information from non-clinical toxicology and safety pharmacology studies as well as prior experience with other oligonucleotide therapeutics. Safety and tolerability will be carefully assessed, and study subjects (referring to both healthy volunteers and patients in the protocol) will be closely monitored. The RO7062931 Investigator Brochure, Section 6 summarizes the key risk management activities to consider when administering this novel compound to study subjects.

[…]

The good safety and tolerability observed to date in CHB patients, the preliminary encouraging dose dependent declines in HBsAg levels, and the favorable results from pre-clinical chronic toxicity studies, support an evaluation of RO7062931 treatment at a dose level of up to 4mg/kg/week and for up to 48 weeks treatment duration when administered with standard of care (SoC) therapies. Consistent with current guidelines (FDA 2018), non-clinical combination studies of RO7062931 with approved SoC therapies (i.e. NUC or PEG-IFN) were not conducted, as available nonclinical data does not suggest a potential for serious synergistic toxicity.

For further information please refer to the latest RO7062931 Investigator Brochure.

3.1.1 Overview of Study Design

The study will be conducted in two parts, of which Part 1 will be in healthy volunteers and Part 2 will be in CHB patients (see Figure 1). Both parts of the study are randomized. Part 1 will evaluate the safety, tolerability and PK of RO7062931, and if applicable metabolite(s), following SC administration of single doses in healthy volunteers. Part 2 will evaluate the safety, tolerability PK and PD (viral dynamics) following administration of multiple SC doses of RO7062931 in CHB patients *over short treatment duration (Figure 1) and extended treatment durations (Figure 2)* (see Section 4.6).

The header of Figure 1 was changed to reflect the fact that there will be short treatment durations in Part 1, 2a, and 2b, in contrast to the newly added Part 2c.

Figure 2 was added to describe the study design for the newly added Part 2c with extended treatment durations.

The total duration of the study for each HV in Part 1 will be ≥ 16 weeks.

- Part 1 (1 dose)
  - Screening: Up to 28 days;
  - In Clinic period: Days – 1 to 3;
  - Safety Follow-up: up to at least Day 85.

The total duration of the study for each patient in Part 2 will be ≥ 24 weeks~~.~~*, except for Part 2c where the total duration may be ≥ 52 weeks.*

- Part 2a (2 doses, Q1M)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days – 1 to 2 and Days 29 to 30;
  - Safety Follow-up: up to at least Day 113.
- Part 2b (3 doses, Q2W)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days – 1 to 2 and Days 29 to 30;
  - Safety Follow-up: Up to at least Day 113.
- Part 2b (4 doses, QW)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days –1 to 2 and Days 22 to 23;
  - Safety Follow-up: Up to at least Day 106.
- Part 2b (5 doses, QW)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days – 1 to 2 and Days 29 to 30;
  - Safety Follow-up: Up to at least Day 113.
- *Part 2c (QW)*
  - *Screening: Up to 28 days;*
  - *Treatment period: Up to 48 weeks;*
  - *Follow-up period: Up to 24 weeks.*

3.1.1.2 Part ~~2~~2*a/2b*: Proof-of-Mechanism in CHB Infected Patients

Part ~~2~~2*a/b* is a multi-center randomized, Sponsor-open, Investigator-blinded, subject-blinded, placebo-controlled, adaptive, parallel multiple-dose study in chronically HBV infected patients, with the aim to study the safety, tolerability, PK of RO7062931(and if applicable metabolite[s]), and the relationship between RO7062931 dose, dose regimen and viral dynamic response. ~~Part 2 is comprised of two subparts.~~

[…]

In Part 2b, a dose identified from the dose-response analysis of Part 2a (based on either HBsAg decline or maximum dose evaluated and well tolerated) will be tested in different dosing regimens administered weekly (QW) or bi-weekly (Q2W). The total dose ~~*of 16 mg/kg per month or 400*~~*of* 400 mg per day will not be exceeded. The selection of dosing regimens will be guided by the analysis of safety, PK and PD data of all previous cohorts in Part 2.

[…[

Visits and assessments will be performed as indicated in the SoA tables (see Appendix 1 to *Appendix 14*).

All doses in Part ~~2a~~2 will be lower than, or equal to, the doses studied and considered to be well-tolerated in Part 1. Subsequent doses and regimens for Part 2b*/2c* will be selected on the basis of the analysis of Part 2a data. Part 2b will be initiated once Part 2a data have been analyzed. ~~For all parts of the study, the~~*The* total dose will not exceed ~~16 mg/kg per month or~~ 400 mg per day.

[…]

3.1.1.3 Part 2c: Extended Duration of RO7062931 Therapy in CHB Infected Patients

Part 2c *is an adaptive, open-label, non-controlled, multi-arm, multi-center, study to evaluate the efficacy and safety of RO7062931 following subcutaneous administration on top of SoC therapies (a NUC with/without PEG-IFN) in NUC-suppressed or treatment-naïve CHB patients (Figure 2). Both HBeAg positive and negative patients will be enrolled.*

- *Cohort 9 will enroll NUC-suppressed CHB patients. Patients will receive RO7062931 on top of a NUC for up to 24 weeks. RO7062931 will be administered at a dose determined from study Parts 2a and 2b.*

- *Cohort 10 will enroll NUC-suppressed CHB patients. Patients will receive RO7062931 on top of a NUC plus PEG-IFN for up to 48 weeks. RO7062931 will be administered at a dose determined from study Parts 2a and 2b.*

- *Cohort 11 and 12 (optional cohorts) may enroll treatment-naïve immune-active CHB patients and/or different treatment combinations or treatment duration.*

All cohorts will initially enroll approximately 8 CHB patients per cohort. Initially the enrollment will occur sequentially (Cohort 9 will be followed by Cohort 10, see Section 4.3). At the end of treatment (either 24 or 48 weeks depending on cohort), all study treatment (RO7062931 and PEG-IFN) will be discontinued and all patients will be followed up for at least 24 weeks post-treatment follow up.

Based on emerging and accumulated PK, PD, efficacy and safety data from this study or other related studies, the initial cohorts may be expanded to enroll a total of 30 CHB patients. Enrollment of the expanded cohorts may be either sequential or parallel.

3.1.2 Dose-Review/Escalation Decisions

[…]

For Part ~~2~~*2a/2b*

- All available safety information, including AEs, ECGs, vital signs, clinical laboratory test results collected up to Day 57 visit (exception: Day 50 for the cohort with 4 doses given QW).
- Adequate data over the first week in Part 2a to characterize the RO7062931 PK and predict exposure in cohorts with different regimens or doses used in Part 2b.
- HBsAg levels at least by two weeks after the last dose.

For Part 2c

- *Commencement of optional cohorts, or expansion of existing cohorts, will be determined based on accumulated safety, tolerability, PK, and PD data from this study.*

Dose-escalation in Part 1 will not be implemented as planned in healthy volunteers dosed with RO7062931, and dosing for a treatment arm/cohort in Part 2 will be discontinued, if one of the below criteria is fulfilled, unless it is obvious that the occurrence is not considered to be related to RO7062931.

Dose-escalation will be stopped if at a dose level, more than 2 of 8 healthy volunteers receiving RO7062931 in Part 1, or, within a treatment arm/cohort in Part 2 more than 2 of 6 patients experience:

- Severe or clinically significant (as defined by the Investigator) RO7062931-related AEs of the same character, or
- ~~Clinically~~ *S*ignificant RO7062931-related laboratory abnormality of the same character, or
- Clinically significant RO7062931-related changes in vital signs or ECGs of the same character (e.g., QTcF $>$ 500 msec, or $>$ 60 msec longer than the pre-dose baseline, within the first 48 hours post-dose).
- Within two consecutive dose cohorts, four occurrences of any of the above conditions in HVs receiving active drug.

[…]

3.2 RATIONALE FOR STUDY DESIGN

A two-part study design has been chosen to characterize RO7062931 in this clinical trial. In Part 1, safety and PK of single RO7062931 doses will be characterized in healthy volunteers to determine the best liver-targeted dose to be evaluated in CHB patients. In Part 2, safety, PK, HBsAg decline and other possible PD effects will be assessed following multiple RO7062931 doses in CHB patients and data will be obtained to further refine the dose and dosing regimen. *Part 2c will evaluate the efficacy and safety of RO7062931 when administered with SoC for up to 48 weeks.*

3.2.1 Rationale for Dosage Selection

[…]

[redacted]

3.2.2 Rationale for Study Population

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

Part ~~2~~*2a/2b* will be conducted in nucleoside/nucleotide suppressed CHB infected patients. Only in this patient population can the pharmacodynamic effects of RO7062931 in humans be tested. The PK and safety of RO7062931 will also be evaluated in this population. The results will provide essential information for supporting the future development, such as dose-selection for a Phase II study in CHB patients.

Part 2c of the study will be conducted in NUC-suppressed or potentially treatment-naïve immune-active CHB patients, and will include both HBeAg positive and HBeAg negative patients. These patient populations are considered appropriate for trials of novel CHB therapeutics regimen, as highlighted in current guidelines (FDA 2018).

3.2.3 Rationale for Control Group

This phase I study is designed to be adequate and well-controlled. In Part 1, randomization to RO7062931 or placebo will occur in a 4:1 ratio within each of the up to 8 cohorts planned. This is considered sufficient to allow for comparisons of safety and tolerability of active to placebo both within and across cohorts.

In Part 2a, randomization to 3 doses of active or placebo will occur in a 1:1:1:1 ratio. In Part 2b, randomization to active or placebo will be 3:1 (within cohorts). The assessment of dynamic changes of HBsAg in CHB patients, will allow estimating the effect of RO7062931 over placebo. The control patients will also allow for the comparisons of safety of active with placebo.

It is not considered necessary to include controls within the cohorts of Part 2c. Part 2a and 2b have shown that placebo controls have negligible change in HBsAg levels over time. This information can be leveraged in Part 2c for interpretation of HBsAg dynamics. The safety data from Part 2c will be compared qualitatively against Part 2a and Part 2b placebo data and against well-established historical safety profiles of SoC therapies.

3.2.4 Rationale for Biomarker Assessments

[…]

Based on nonclinical data (and class effect [Kynamro Solution for injection 189 mg, CHMP-EMA Assessment Report 2013]) RO7062931 is considered of to be low risk for acute reactions; however, cytokines and complement activation will be measured and sentinel dosing will be implemented.

[redacted]

[redacted]

[redacted]

[…]

3.3.2.2 Pharmacodynamic Outcome Measures (Part 2 only)

In Part 2, blood samples for quantitative and qualitative determination of viral dynamic response measurements of, but not limited to, HBsAg, HBV DNA, ~~TNA,~~*HBV RNA,* HBeAg, ~~HBcAg~~*HBcrAg*, anti-HBe, anti-HBc*,* and~~,~~ anti-HBs and HBsAg/anti-HBs complex, will be collected at the time-points indicated in the Schedule of Assessment tables (see Appendix 1 to see Appendix 1 to *Appendix 14*) and as detailed in Section 4.6.1.5.4.

The PD outcome measure to support the secondary objective is the change in quantitative HBsAg over time. Derived endpoints of quantitative HBsAg will include:

- Quantitative HBsAg *(qHBsAg)* (log10) and its change from baseline
- Maximum change from baseline in quantitative HBsAg across all time-points
- Rate of decrease for HBsAg at each time-point
- *Proportion of patients with undetectable qHBsAg (< 0.05 IU/mL)*

3.3.3 Exploratory Outcome Measures

Exploratory PD outcome measures:

These will include but may not be limited to HBeAg, qualitative HBsAg, anti-HBs, anti-HBe, and maintenance of HBV DNA levels less than 90IU/mL *(for Part 2c lower limit of quantification [LLOQ]).*

Viral resistance monitoring will be performed in any patient who experiences viral breakthrough. Please see Section 4.6.1.5.4.

[redacted]

Exploratory safety outcome measures

[redacted]

Exploratory PK outcome measure:

[redacted]

[redacted]

4.2 STUDY POPULATION

[…]

4.2.2 Inclusion Criteria

[…]

4.2.2.2 ~~Parts 2~~*Part 2a and Part 2b* - CHB patients only:

[…]

4.2.2.3 Part 2c – CHB patients only:

1. *Ability and willingness of patients to provide written informed consent.*
2. *Adult male and female patients, 18 to 65 years of age, inclusive.*
3. *A BMI between 18 to 32 kg/m² inclusive.*
4. *CHB infection (HBsAg-positive for ≥ 6 months).*
5. *For cohorts only enrolling NUC-suppressed CHB patients, patients must meet the following criteria:*
   a. *Patients treated with a single NUC (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate) for ≥12 months. Patients must be on the same NUC therapy for at least 3 months before screening.*
   b. *HBV DNA <LLOQ at screening and in preceding 6 months (at least one measurement >30 days prior to screening).*
   c. *ALT ⩽ 2 x ULN for >6 months prior to screening and confirmed at screening. Total bilirubin within normal range at screening except for patients with Gilbert's syndrome (TB ≤ 47 µmol/L [2.75 mg/dL]).*

6. *For Cohorts only enrolling treatment-naïve and immune-active patients (e.g., Cohort 11), patients must meet the following criteria:*

   a. *HBV DNA at screening ≥2 x 10^4 IU/mL for HBeAg positive patients, or ≥2 x 10^3 IU/mL for HBeAg negative patients.*

   b. *Elevated serum ALT >2 ULN to ⩽ 5 ULN, 2 values within 6 months, at least one of which is at screening and both results must be at least 14 days apart. Total bilirubin within normal range at screening, except for patients with Gilbert's syndrome (TB ≤ 47 µmol/L [2.75 mg/dL]).*

7. *Screening laboratory values (hematology, chemistry, urinalysis) obtained up to 28 days prior to first study treatment within normal ranges, with the exception of otherwise specified criteria or judged to be not clinically significant by PI and Medical Monitor.*

8. *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 3, recommended cut-off for fibroscan 8.5 kPa).*

9. *Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by FSH, or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization (removal of ovaries and/or uterus).*

   All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

   With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus spermicide during the treatment period and up to 6 months after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2.3 Exclusion Criteria

[…]

4.2.3.2 ~~Parts 2~~*Part 2a and Part 2b* - CHB patients only:

[…]

4.2.3.3 Part 2c - CHB patients only:

1. *Women who are lactating.*
2. *History or other evidence of bleeding from esophageal varices.*
3. *Evidence of liver cirrhosis or decompensated liver disease such as ascites, esophageal or gastric varices, splenomegaly, nodular liver, jaundice, hepatic encephalopathy, portal hypertension.*
4. *One or more of the following laboratory abnormalities at screening:*
   a) *Total serum bilirubin > ULN (exception Gilbert's disease).*
   b) *(INR >1.1 ULN.*
   c) *Serum albumin <3.5 g/dL (<35g/L).*
   d) *AFP >13 ng/mL (if >ULN, hepatic imaging must exclude hepatocellular carcinoma [HCC]).*
   e) *Positive results for anti-mitochondrial antibodies (AMA >1:80), anti-nuclear antibody (ANA) (>1:80), anti–smooth muscle antibody (ASMA >1:40), anti-thyroperoxidase antibodies (a-TPO), anti-thyroglobulin, or anti-platelet antibodies.*
   f) *Thyroid stimulating hormone (TSH) within normal ranges.*
   g) *Platelet count <100,000 cells/mm^3.*
   h) *Hemoglobin <12 g/dL (females) or <13 g/dL (males).*
   i) *White blood cell count <2500 cells/mm^3.*
   j) *Neutrophil count <1500 cells/mm^3 (<1200 cell/mm^3 if considered a physiological variant in a patient of African descent).*
5. *History or other evidence of a medical condition associated with chronic liver disease other than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, nonalcoholic steatohepatitis, etc.).*
6. *History of thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests (TSH).*
7. *Documented history or other evidence of metabolic liver disease within one year of randomization.*
8. *Positive test for hepatitis A (IgM anti-HAV), hepatitis C (quantitative anti-HCV), hepatitis D (total anti-HDV), hepatitis E (IgM and IgE anti-HEV), or human immunodeficiency virus (anti-HIV1/anti-HIV2).*
9. *Expected to need systemic antiviral therapy other than that provided by the study at any time during their participation in the study, with the exception or oral therapy for HSV I or HSV II.*
10. *History of significant gastrointestinal disease (including but not limited to gastric ulcers).*

11. *History of clinically significant cardiovascular, endocrine, renal, ocular, pulmonary, psychiatric, or neurological disease.*
12. *Evidence of an active or suspected cancer or a history of malignancy other than adequately treated basal cell carcinoma.*
13. *History of organ transplantation.*
14. *Participation in an investigational drug or device study within 30 days prior to screening or previous treatment with an investigational agent for HBV (6 months prior to screening).*
15. *Taking any drugs or nutrients listed in prohibited medications and prohibited food sections.*
16. *Significant acute infection (e.g., influenza, local infection) or any other clinically significant illness within 2 weeks of randomization.*
17. *ECG at screening with clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia's formula) ≥450 msec for males and ≥470 msec for females.*
18. *Abnormal renal function including serum creatinine >ULN or calculated creatinine clearance <70 mL/min (using the Cockcroft Gault formula).*
19. *Donation or loss of blood over 500 mL within 3 months prior to randomization.*
20. *Administration of any blood product within 3 months prior to randomization.*
21. *History of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink = 10 grams of alcohol) and/or drug abuse within one year of randomization; positive test result for drugs of abuse or alcohol breath test at screening.*
22. *Subjects under judicial supervision, guardianship, or curatorship.*
23. *Medical or social conditions that would potentially interfere with the subject's ability to comply with the study visit schedule or the study assessments.*

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

~~This study is~~*Part 1, Part 2a, and Part 2b are* Sponsor-open, Investigator-blinded, subject-blinded. This means that the study subjects will be blinded, the Investigator(s), site staff observing the subjects will be blinded and the Sponsor will be unblinded. *Part 2c is open-label.*

In Part 1, the site pharmacist and the study drug administrator will be unblinded. For Part*s* ~~2~~ *2a and 2b*, the site Pharmacist will be unblinded. Members of the Sponsor's study team who do not have direct contact with the Investigator or study site staff will be unblinded. This does not include any CROs and any sponsor staff in direct contact with the investigators and the study sites, who will remain blinded. *Part 2c of the study is a non-randomized, non-controlled, open-label study; therefore site staff observing the patients, patients, and the Sponsor will be unblinded.*

[…]

Part 2c

For Part 2c, the IxRS will be used to register patients to the open-label cohorts. Additionally, IxRS will be used to dispense RO7062931 and PEG-IFN for patients. The Sponsor may postpone or stop enrolment of, or only enroll certain patient subgroups, in order to evaluate pharmacodynamic parameters in different patient subgroups. The initial 8 patients of cohort 9 will be enrolled prior to the enrollment of the initial 8 patients in cohort 10. Either or both of these cohorts may be expanded up to a maximum of 30 patients in total. Assignment of patients at this expansion stage may be sequential or in parallel. Enrolment of subsequent cohorts 11 and 12 may be sequential or parallel.

The treatment allocation will be managed by the Pharmacist and will be based on the IxRS assignment.

The Principal Investigator(s) will receive a set of sealed treatment codes for Part 1. These may have the form of sealed envelopes or scratch codes. If the identity of the test medication needs to be known in order to manage the study subject's condition (in the case of a serious adverse event), the treatment code for that study subject may be broken. For Part*s* ~~2~~*2a and 2b*, the Investigator(s) will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly before the code is broken, if possible. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

[…]

4.4.1.2 Standard of Care (NUC and PEG-IFN)

As NUCs (entecavir, tenofovir alafenamide or tenofovir disoproxil fumarate) are to be used as background SoC therapies, they are classed as non-investigational medicinal product (NIMP). Please see local prescribing information for additional information.

As PEG-IFN is not licensed for use in CHB patients receiving NUC therapy, it is thus classed as an IMP.

PEG-IFN is a clear and colourless to light yellow sterile liquid provided in prefilled syringes for single use. Each prefilled syringe of 0.5 mL solution contains 180 µg peginterferon alfa-2a.

The list of excipients is as follows: sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid, and water for injections.

The packaging and labeling of PEG-IFN will be in accordance with Roche standard and local regulations. Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage. Study drug should be stored under the recommended storage conditions (2 to 8°C, protected from light). For further details, see the packaging label.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

4.4.2 Dosage, Administration and Compliance

4.4.2.1 RO7062931 and Placebo

[…]

For Part 2c:
All RO7062931 administrations will be via the SC route utilizing sterile technique. RO7062931 doses will be administered SC once weekly for up to 24 weeks in Cohort 9 and for up to 48 weeks in Cohort 10. All RO7062931 doses will be administered at the study clinic in the morning by investigational staff and should be administered in the fasted state either two hours before or two hours after a morning meal.

For cohorts involving PEG-IFN, RO7062931 and PEG-IFN SC doses should be administered at different sites (e.g. left thigh and right thigh), and the administration sites should be rotated on a weekly basis between doses. This will allow to better characterize and minimize the risk of injection site reactions. For convenience, consider SC treatment administrations in the same morning as the NUC administration and PEG-IFN SC administration should be at least 1 hour after RO7062931 SC administration.

PEG-IFN administration
All PEG-IFN administrations will be administered via the SC route utilizing sterile technique. PEG-IFN at a dose of 180 mcg will be administered once weekly for up to 48 weeks. PEG-IFN will be administered weekly at study clinic.

Specific guidelines for adjusting the doses of PEG-IFN for adverse event management are provided in Section 5.2.1.3. If PEG-IFN is interrupted or discontinued permanently, patients should continue treatment with RO7062931 and NUC until the end of the treatment period.

For further information on the PEG-IFN, please refer to PEG-IFN Investigator Brochure.

NUC administration

NUC will be administered per local label or as per prescribing information and should be taken in the morning of RO7062931 or RO7062931 and PEG-IFN administration. NUC administration during the study, including the follow-up period, should be captured in the site documentation and eCRF. This information should include information about any missing doses during treatment and follow-up period.

For further information on the NUCs used in this study, please follow local prescribing information.

4.4.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (RO7062931 ~~and~~, placebo, *and PEG-IFN*) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, to confirm the shipment condition and content. Any damaged shipments will be replaced.

[…]

4.4.5 Post-Trial Access to NUC/PEG-IFN

NUC or PEG-IFN are marketed drugs and commercially available. No post-study medication or drug reimbursement is provided as part of this protocol. The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition.

4.5 CONCOMITANT THERAPY AND FOOD

There are no concomitant treatment restrictions at this time as no drug-drug interactions are foreseen for RO7062931. In Part 1, there are some restrictions for healthy volunteers that should be maintained.

[…]

- *Herbal therapy or substances (e.g. tea)/supplements/traditional Chinese medicines, as well as OTC drugs, may affect patient laboratory values. Abnormal values may lead to screening failures or patient withdrawal from study treatment. As such, patients at screening should be carefully questioned regarding such practices/habits and should be advised to refrain from them, if deemed necessary.*

4.5.2 Prohibited Therapy

As a general rule, no concomitant medication will be prohibited. All concomitant medications need be discussed with the Sponsor prior to enrolling study subjects.

For patients in Part 2c who take NUC or PEG-IFN during the study, please follow the prescribing information or the PEG-IFN Investigator Brochure, to guide as to whether concomitant medications are permitted or prohibited.

In case of doubt, the Sponsor may be contacted regarding potential prohibited concomitant medications, which may be allowed if the rationale is discussed, agreed and documented between the Investigator and Sponsor Medical Monitor.

4.6.1.5.1 Safety Laboratory Assessments

[…]

The following blood and urine samples will be collected:

- Hematology: leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).
- Blood chemistry: ALT, AST, total and indirect bilirubin, ALP, blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT) (at Screening only), *glutamate dehydrogenase (GLDH),* creatine phosphokinase (at Screening only), total protein, albumin, creatinine~~,~~ *and calculated creatinine clearance (using the Cockcroft Gault formula),* glomerular filtration rate (GFR) calculated *(MDRD4 method),* uric acid, cystatin c, fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, sodium, chloride, potassium, calcium, magnesium, phosphate and bicarbonate.
- Coagulation: prothrombin time (PT), International Normalized Ratio (INR), activated partial thromboplastin time (aPTT)
- Urinalysis: A mid-stream, clean catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocytes, specific gravity and pH. Urine will be also sent to the laboratory to perform microscopy to examine urine sediment for casts and cells. If there is a clinically significant positive dipstick result, (i.e., confirmed by a positive repeated sample), urine will be sent to the laboratory for culture. If there is an explanation for the positive dipstick result, e.g., menses, it should be recorded. Urine color may be evaluated from urinalysis or urine PK samples if considered necessary.
- Viral serology: Human immunodeficiency virus (HIV-1 Antibody, HIV-2 Antibody), hepatitis A virus (HAV IgM Antibody), hepatitis B virus (surface antigen, HBsAg), hepatitis C virus (~~HCV RNA or HCV antibody)~~ *quantitative HCV antibody), hepatitis D (total HDV antibody) (Part 2c), and hepatitis E virus (IgM and IgG HEV antibodies) (Part 2c).*
- *Auto-antibodies at Screening: AMA, ANA, ASMA, a-TPO, anti-thyroglobulin, and anti-platelet antibodies (Part 2c).*

- Pregnancy test

  For all women enrolled in the study: Blood sample for determining beta-human chorionic gonadotropin (β-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.
- Alpha fetoprotein: At Screening only for HBV patients.
- *Thyroid function test: TSH (Part 2c).*
- Hormones: FSH (females only to confirm post-menopausal status, performed at Screening only).
- Drugs of abuse (urine): Cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates.
- Alcohol breath or blood test will be performed.

4.6.1.5.2 Pharmacokinetic Assessments

[…]

[redacted]

Sparse sampling for tenofovir (including tenofovir alafenamide, if approved for HBV and applicable), entecavir, adefovir and telbivudine will be collected~~.~~ *for Parts 2a and 2b and entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate for Part 2c.*

[…]

4.6.1.5.3 Assessments for Inflammatory Markers, Autoantibodies and Anti-Drug Antibodies (ADA)

[…]

Inflammatory Markers

Blood samples for assessing inflammatory markers will be obtained for all study subjects at pre-specified time-points (see SoA, Appendix 1 to see Appendix 1 to *Appendix 14*). In addition, in case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected as close to the onset of the AE as possible. Blood samples (both planned and unscheduled) will be taken to assess: complement, CRP, ESR, gamma globulin and other inflammatory biomarkers (such as, but not limited to, IL-6, IL-8, IL12, MCP1, TNFα).

For patients in Part 2c, a baseline (Day 1, pre-dose) sample for inflammatory markers will be assessed. In case an immune AE/AE suggestive of immunological involvement occurs, the samples collected at the other time-points as well as an unscheduled sample collected as close to the onset of the AE as possible will be assessed.

Auto-antibodies

Blood samples for assessing autoantibodies will be obtained for all study subjects before dosing, at baseline (also see SoA, Appendix 1 to see Appendix 1 to *Appendix 14*). In addition, in case *of* an autoimmune driven AE/-AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected as close to the onset of the AE as is possible. The panel of autoantibodies to be assessed will be: anti-nuclear antibodies, anti-ds-DNA antibodies, anti-histone antibodies, anti-ssDNA antibodies, anti-neutrophil cytoplasmic antibody, anti-cardiolipin antibodies, *and* rheumatoid factor.

ADA Assessment

Blood samples will be collected from all subjects at each time-point as specified in the SoA tables (see Appendix 1 see Appendix 1 to *Appendix 14*). All ADA blood samples ~~should~~*will* be collected prior to dosing of investigational drug.~~ ADA blood samples will be stored and will only be~~ analyzed~~ in case there is an immune driven AE/AE suggestive of immunological, anti drug involvement or in case of an atypical PK result~~.

4.6.1.5.4 Pharmacodynamic Assessments

During the course of the study, PD sampling time-points may be modified on the basis of emerging data to ensure the pharmacodynamics of RO7062931 can be adequately characterized.

Blood samples for pharmacodynamics assessments will be collected as indicated in the SoA tables (see Appendix 1 to see Appendix 1 to *Appendix 14*). Samples for laboratory tests as specified below will be sent to one or several central laboratories or to the Sponsor for analysis. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

In Part 2c, based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for PD evaluation may be stopped at any time if the data from the samples collected does not produce useful information.

Handling of residual samples is described in Section 4.6.1.5.

4.6.1.5.5 Clinical Genotyping

A blood sample will be taken pre-dose on Day 1 for DNA extraction from all subjects. If, however, the genetic blood sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study. [redacted]

The sample collected for DNA extraction may be used for whole exome and/or whole genome sequencing and other genetic analysis and may be sent to one or more laboratories for analysis. These assessments will be performed if safety or scientific rationales develop.

Handling of residual samples is described in Section 4.6.1.5.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.6.1.5.6 Other Assessments

[redacted]

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

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pretreatment Assessments

[…]

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 *Part 2c and* 56 days for Part*s* ~~2 screening period.~~*2a and 2b).* If the subject fails a second time, they will be classed as a screen failure and cannot be re-screened. Re-screening is allowed for subjects who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized within 28 days ~~for Part 1 or 56 days for Part 2~~ after the start of *the* screening period *for Part 1 and Part 2c or within 56 days after the start of the screening period for Parts 2a and 2b*. In order to re-screen such a subject, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated if done more than 28 days *before randomization* for Part 1 and *Part 2c or more than* 56 days *before randomization* for Part*s* ~~2 before randomization~~*2a and 2b*. There is no need to repeat alpha-fetoprotein test if done for the study in central laboratory within 6 months before re-screening.

4.6.2.2 Assessments during Treatment

Under no circumstances will study subjects who enroll in *any part of* 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 SoA tables (see Appendix 1 to see Appendix 1 to *Appendix 14*).

4.6.2.3 Follow-Up Assessments and Study Completion

Study subjects who complete the study or discontinue from the study early will be asked to return to the clinic after the last dose of study drug for a follow-up visit.

All follow up assessments must be performed as per SoA tables (see Appendix 1 to Appendix 14).

Adverse events should be followed as outlined in Section 5.5.

4.7.1.1 Discontinuation from Study Drug

Study subjects must discontinue study drug if they experience any of the following:

- Pregnancy
- A serious adverse event (SAE) considered by the Investigator to be related to treatment with RO7062931.

- ~~If a dose of RO7062931 is omitted.~~

Study subjects who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit and may undergo follow-up assessments. The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

Study subjects who discontinue study drug prematurely for safety reasons will not be replaced. Study subjects who discontinue study drug prematurely for non-safety reasons may be replaced. The Sponsor should be informed of subjects' discontinuations from the study or from the study drug.

Part 2: CHB Patients
Individual patients must discontinue RO7062931/placebo if they experience any of the following:

- Safety and tolerability issues, e.g., acute reactions, not tolerable and not manageable with symptomatic treatment.
- Grade 4 ALT (i.e., $\geq 10 \times$ ULN) as defined by the Division of Acquired Immunodeficiency Syndrome (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE grading table) confirmed within 48-72 hours *(not for Part 2c)*.
- Grade 3 ALT (i.e., $>$ 5x *to* $< 10 \times$ ULN) combined with total bilirubin $> 2 \times$ ULN (of which $>$ 35% is direct bilirubin), or Grade 3 ALT and INR $>$ 1.5.
- Any other confirmed (within 48-72h) Grade 4 laboratory abnormality deemed clinically significant (based on Investigator's assessment).
- Development of liver decompensation (ascites, varices, Child-Pugh Class B or C clinical classification).
- ~~Renal~~*Grade 3 renal* adverse events defined as creatinine ~~1.5 × ULN or~~ increase ~~of~~ $\geq$ 50% from baseline *and/or eGFR* $<$*60 ml/min/1.73 m*^{2}.
- Development of resistance in a CHB patient is suspected if the patient experiences an increase in serum HBV DNA of $>$ 1 log10 (10-fold) over nadir during the treatment period, i.e., virological breakthrough.
- NUC analogue discontinuation due to safety issues or resistance development.

All prematurely discontinued patients will have assessments performed at the end of treatment with RO7062931/placebo listed in the SoAs tables. If a patient discontinues study drug between study visits, he/she should be called for an unscheduled visit to have these assessments performed.

All patients who discontinued the study treatment prematurely should complete the 4-week follow-up period (starting from the date of the last dose taken) *and continue safety follow up* as per SoAs (see Appendix 1 to *Appendix 14*). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest 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 Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- *Cases of an isolated elevated ALT or AST ≥ 10 ULN (Section 5.2 and 5.3.5.6).*
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Severe injection site reactions
- ~~Hepatic flare, defined as ALT≥10×ULN~~
- ~~Renal~~*Grade 3 renal* adverse events defined as creatinine ~~1.5 ×ULN or~~ increase ~~of~~ ≥50% from baseline *and/or eGFR <60 mL/min/1.73 m²*.

5.2.1 Management of Specific Adverse Events

~~Hepatic flares are identified by an abrupt elevation of serum ALT (defined as ALT≥10×ULN), will be conducted for the duration of the study.~~

5.2.1.1 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation (within 48 to 72 hours) of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs, and discontinuation of all study medications (RO7062931, NUC, or PEG-IFN, where applicable) must be considered.

In this study, a potential DILI is defined as follows:

- *For healthy volunteers (Part 1): ALT > 3 × ULN accompanied total bilirubin > 2 × ULN*

- *For CHB patients (Part 2): ALT > 3 × baseline / ULN (whichever is higher) accompanied by total bilirubin >2 × ULN*

AND

- *No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to acute viral hepatitis, cholestasis, pre-existing hepatic disease excluding HCV/HEV or the administration of other drug(s), herbal medications, or substances known to be hepatotoxic.*

5.2.1.2 Alanine Transaminase (ALT) Elevations

Abrupt elevation of serum ALT above normal is known to occur spontaneously in patients with CHB during the course of disease, and/or during anti-viral therapy. Transient ALT elevations are not always harmful and may be due to:

- *The underlying disease*

- *Immune clearance of infected hepatocytes*

- *Drug-induced immune-mediated hepatitis*

- *DILI*

Isolated ALT elevations of 2-3 times the baseline value that are self-limited ~~are likely to~~ *may* reflect *a desirable* treatment-*related immunologic* response rather than drug toxicity. *However,* progressive increases~~, increases inconsistent with the time course of a "flare",~~ or ALT elevations associated with increases in bilirubin ~~and~~ *without* alkaline phosphatase *increase*, should *primarily* be *considered* ~~treated as~~ adverse events*, i.e. potential DILI.*

In the event of ALT elevation > 5x ULN, more frequent monitoring of liver tests should be performed based on medical judgment and other causes of ALT elevations should be investigated. For patients with ALT > 5 × ULN, the following management plan is recommended:

ALT elevations during treatment

- *Isolated ALT elevation with preserved hepatic function (e.g. no significant changes in bilirubin, INR/PT, albumin, and ALP):*

- *Closely monitor liver function tests (LFTs) (i.e. ALT/AST, bilirubin, albumin, ALP and INR/PT):*
    - *ALT 5 to 10 x ULN: Repeat LFTs every week.*
    - *ALT >10 x ULN: Temporarily interrupt RO7062931 or RO7062931 and PEG-IFN treatment and repeat LFTs twice weekly until ALT level < 5 x ULN. Continue NUC treatment. Consider re-introducing RO7062931 or RO7062931 and PEG-IFN therapy following discussion with medical monitor based on subsequent laboratory results.*

- *ALT flare accompanied by declining liver synthetic and excretory functions (increased bilirubin >2 x ULN, or albumin decline >0.5 g/dL, or INR >1.5) or other signs of hepatic impairment (severe fatigue, nausea, vomiting, right upper quadrant pain):*
    - *RO7062931 or RO7062931 and PEG-IFN will be permanently discontinued, continue NUC treatment.*
    - *Closely monitor LFTs:*
        - *ALT 5 to 10 x ULN: Repeat LFTs every week.*
        - *ALT >10 x ULN: Repeat LFTs twice weekly until ALT level < 5 x ULN.*
            - *Investigate the participant for potential etiologies of the laboratory changes.*
            - *If alternative reasons/diagnoses cannot explain the laboratory changes, a potential DILI will be considered.*

If ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected (see Section 4.6.1.5.4).

ALT elevations during follow-up

- *Isolated ALT elevation with preserved hepatic function:*
    - *ALT 5 to 10 x ULN: Repeat LFTs every week.*
    - *ALT >10 x ULN: Repeat LFTs twice weekly until ALT level <5 x ULN.*

- *ALT elevation accompanied by declining liver synthetic and excretory functions:*
    - *ALT 5 to 10 x ULN: Repeat LFTs and ALT/AST every week.*
    - *ALT >10 x ULN: Repeat LFTs and ALT/AST twice weekly until ALT level < 5 x ULN.*
    - *Investigate the CHB patient for potential etiologies of the laboratory changes.*
    - *If alternative reasons/diagnoses cannot explain the laboratory changes, a potentially delayed DILI will be suspected and CHB patient will be monitored accordingly.*

In participants who have not discontinued NUC therapy, if ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected (see Section 4.6.1.5.4).

The Investigator should aim to exclude development of decompensated liver disease. Patients who develop signs of decompensated liver disease (e.g., ascites, variceal hemorrhage, Child-Pugh Class B or C clinical classification [*Appendix 16*]) should discontinue study treatment (Section 4.7.1.1). Patients who develop flares should be monitored more closely with additional unscheduled visits and laboratory assessments.

~~No dose modification of RO7062931/placebo for safety reasons is expected in the study.~~ At the discretion of the Investigator, study treatment can be discontinued.

5.2.1.3 Dose Modifications with PEG-IFN

The intention of Part 2c of the protocol is that patients remain on PEG-IFN until the completion of the allocated treatment period. However, it is possible that some patients will encounter transient or prolonged adverse effects or abnormal laboratory values at some juncture during their participation in the trial leading to potential need for adjustment of the PEG-IFN dosage.

If severe adverse reactions or laboratory abnormalities develop during PEG-IFN therapy, the dose should be modified until the adverse reactions abate. If intolerance persists after dose adjustment, PEG-IFN therapy should be discontinued.

When dose modification of PEG-IFN is required for adverse reactions (clinical and/or laboratory), an initial dose reduction to 135 mcg (adjustment to the corresponding graduation mark for the prefilled syringes) is recommended. Dose reduction to 90 mcg (adjustment to the corresponding graduation mark for the prefilled syringes) may be needed if the adverse reaction persists or recurs. Following improvement of the adverse reaction, re-escalation of the dose may be considered. Table 1 provides guidelines for dose modifications and discontinuation of PEG-IFN for haematological laboratory abnormalities.

Table 1 PEG-IFN Hematological Dose Modifications Guidelines

Laboratory Values	***Recommended Dose***
ANC < 750 cells/mm³	*Reduce to 135 mcg*
ANC < 500 cells/mm³	*Discontinue treatment until ANC values return to more than 1000 cells/mm³. Reinstitute at 90 mcg and monitor ANC.*
Platelets < 50,000 cells/mm³	*Reduce to 90 mcg*
Platelets < 25,000 cells/mm³	*Discontinue treatment*

For patients who discontinue PEG-IFN early due to intolerability or if stopping criteria are met, then NUC and RO7062931 should be continued up to 48 weeks. The reasons for discontinuation of PEG-IFN and length of treatment duration will be recorded in the eCRF.

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing adverse event severity in the study *for Part 1 and Parts 2a and 2b*.

Table *2* **Adverse Event Severity Grading Scale**

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

For Part 2c, DAIDS toxicity grading scales (Appendix 18) will be used to assess adverse event severity.

5.3.5.6 ~~Abnormal Liver Function Tests~~*Alanine and Aspartate Transaminase (ALT/AST) Elevations*

For Part 1:
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 *(Hy's Law).* Therefore, investigators must report as an adverse event 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.

For Part 2:

~~The~~*CHB patients may have elevated baseline ALT levels without an increase in bilirubin. However, 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~~.~~ *or worsening of disease.* Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT ~~or AST~~ > 3 × Baseline and >3 x ULN value in combination with total bilirubin > 2 × ULN ~~(of which ≥ 35% is direct bilirubin).~~.
- Treatment-emergent ALT ~~or AST~~ > 3 × Baseline and >3x ULN value in combination with clinical jaundice.
- ~~Treatment emergent ALT ≥ 10 × ULN~~

**For Part 2c (treatment- naïve and immune-active CHB patients), the threshold of ALT >3 × ULN baseline will be capped at 10 × ULN.*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.11 Overdoses

Study drug *(including IMP and NIMP)* overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

[…]

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female subjects of childbearing potential will not be allowed to participate in this study. Although highly unlikely, female subjects will be instructed to immediately inform the Investigator if they become pregnant during the study or within 105 days after the last dose of study drug *(Parts 2a and 2b) or within 6 months after last dose (Part 2c).* A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

6.1 DETERMINATION OF SAMPLE SIZE

[…]

For Part~~s 2~~*2a and 2b* of the study, the PoM in CHB infected patients, a sample size of no more than 80 patients with CHB has been chosen (6 patients [Part 2a] and 8 patients [Part 2b] per dose cohort). It is anticipated that this sample size will allow characterization of the PK/PD (viral dynamic response) relationship, as well as safety and tolerability, in patients with CHB.

For Part 2c, approximately 16 patients will be enrolled into the initial 2 cohorts (8 patients in each cohort). If utilized, approximately 8 patients will be enrolled to each of the Cohorts 11 and 12. The sample size supports the assessment of response rate of undetectable qHBsAg at Week 24 follow-up in Cohorts 10, 11, and 12.

A sample size of 8 ensures that the associated lower 90% confidence limit is above 10%, if the observed response rate is at least 38% (i.e. at least 3/8), assuming a binomial distribution. This sample size is also considered reasonable to support the safety and tolerability objectives of all cohorts, as well as to allow characterization of the qHBsAg profiles in Cohort 9.The cohorts may be expanded up to 30 subjects if warranted by emerging PD and/or safety data. A sample size of 30 ensures that the associated lower 90% confidence limit is above 20%, if the observed response rate is at least 37% (i.e. at least 11/30).

6.6.2 PK/Viral Dynamic Response Analyses

The relationship between RO7062931 and dose, and metabolite(s) and dose if applicable, and the change of HBsAg at each time-point and rate of decrease will be explored by graphical analysis. The relationship between RO7062931 PK and urinary parameters and HBsAg will also be explored by graphical analysis. Assuming a monotonic relationship between HBsAg decrease and dose/plasma RO7062931, an appropriate exposure/dose-response model may be fitted to the data from Part 2a. This model may be used to guide dose selection for Part 2b*, and will be further developed with data from Parts 2b and 2c*.

6.6.3 Efficacy Analyses

The proportion of patients with undetectable qHBsAg and associated 95% binomial confidence intervals will be calculated at 24 week after the end of treatment. Patients with missing HBsAg measures at 24 weeks visit after the end of treatment and thereafter will be treated as non-responders.

6.7 PHARMACOKINETIC ANALYSES

Non-compartmental analysis using WinNonlin software will be used to calculate PK parameters where appropriate. Summary descriptive statistics of plasma PK parameters including C_{max}, T_{max}, AUC_{inf}, AUC_{last}, and $t_{1/2}$ for RO7062931 and any metabolites when available will be presented by cohort/treatment arm including mean, standard deviation (SD), coefficient of variation (CV), medians and ranges. Note: the geometric *or arithmetic* mean and associated CV% will be used to describe C_{max}, AUC_{inf}, AUC_{last}~~;~~ ~~arithmetic means~~ *and $t_{1/2}$. Median values* will be used to describe T_{max} ~~and $t_{1/2}$~~. Where appropriate, data may be pooled and analyzed, for example, all single dose data may be pooled. Listings, summary tables and graphs (individual plots and/or mean plots) by treatment group will be provided. Descriptive statistics of urine PK parameters for RO7062931 and any metabolites will be presented, where available. PK and PD data from this study may be used to develop a population PK/PD model.

Where appropriate, listings and summary tables of nucleoside/nucleotide-analogues, tenofovir, tenofovir, alafenamide, entecavir, adefovir, or telbivudine concentrations will be provided based on the sparse sampling throughout the study.

[redacted]

6.11 INTERIM ANALYSES

No interim analysis is planned for Part 1s 2a, and 2b of this study.

In Part 2c, administrative interim analyses will be conducted at Weeks 12 and 24 for the initial 8 enrolled in both Cohorts 9 and 10. Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional administrative interim PD analyses. The decision to conduct additional interim analyses and the timing of the analyses will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

10. REFERENCES

[…]

[redacted]

Investigator's Brochure PEG-Interferon.

[…]

Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med. 1966; 274(9): 473-81.

U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment. Guidance for Industry. Draft Guidance. November 2018. (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM624695.pdf)

Appendices:

Further appendices were added to the Schedule of Assessments regarding Part 2c of the study, i.e. QW Doses for 24 and 48 Weeks, Main and Detailed Tables and Division of AIDS (DAIDS) Table for Grading the Severity of Adverse Events (Appendices 11 to 14 and Appendix 18).

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PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACOKINETICS AND PHARMACODYNAMICS OF SUBCUTANEOUS ADMINISTRATION OF RO7062931 WITH SINGLE ASCENDING DOSES IN HEALTHY VOLUNTEERS AND MULTIPLE DOSES AND MODIFIED REGIMENS IN VIROLOGICALLY SUPPRESSED PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION**
PROTOCOL NUMBER:	BP39405
VERSION:	*4*
TEST PRODUCT:	RO7062931
PHASE:	I
SPONSOR:	F. Hoffmann-La Roche Ltd

–

OBJECTIVES

Primary Objective:

The primary objectives of this study are:

- To assess the safety and tolerability of RO7062931 compared to placebo after single-ascending subcutaneous (SC) doses in healthy volunteers (HVs).
- To assess the safety and tolerability of RO7062931 compared to placebo after multiple SC doses in chronic Hepatitis B (CHB) patients.

Secondary Objectives

The secondary objectives for this study are as follows:

For Part 1:

- To assess plasma and urine pharmacokinetics (PK) of RO7062931, and if applicable metabolite(s), after single-ascending SC doses.

For Part 2:

- To assess the plasma and urine PK of RO7062931 and if applicable metabolite(s), after multiple SC doses.
- To study HBsAg dynamics after SC administration of RO7062931.

Exploratory Objectives

The exploratory objectives of this study are as follows:

- Pharmacodynamics (PD) exploratory objectives:
  - For Part 2: to explore the effect of multiple doses of RO7062931 on viral and anti-viral parameters other than quantitative HBsAg during and after the end of treatment in CHB patients.

- To explore the effects of RO7062931 doses on further exploratory biomarkers.

- PK exploratory objective:

[redacted]

STUDY DESIGN

Description of Study

The study will be conducted in two parts, of which Part 1 will be in healthy volunteers and Part 2 will be in patients with CHB virus infection. Both parts of the study are randomized and Sponsor-open. Part 1 will evaluate the safety, tolerability and PK of RO7062931, and if applicable metabolite(s), following SC administration of single doses in healthy volunteers. Part 2 will evaluate the safety, tolerability PK and PD (viral dynamics) following administration of multiple SC doses of RO7062931 in CHB patients *over short term duration and extended treatment durations*.

Part 1 is an adaptive single ascending dose (SAD) study with an adaptive dose-escalation schedule. The first cohort will receive a single dose of 0.1 mg/kg RO7062931 or placebo using a randomization ratio of 4:1. The range of doses for subsequent cohorts is suggested to be 0.3 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg, but will be adapted during the study based on assessment of emerging safety, tolerability, and PK data. In advance of evaluation of the safety and tolerability of lower doses in healthy volunteers, the 4 mg/kg dose may be considered the top dose evaluated in this study. [redacted] However, at this dose, AEs are expected to be mild and within this protocol higher doses may be evaluated if this dose is found to be safe and well tolerated. Since the monkey is considered a more clinically-relevant species for oligonucleotide safety assessment in humans, doses would not be escalated beyond the HED [redacted]. The use of a Bayesian analysis, specifically a continual reassessment method (CRM) analysis will be explored as a tool to help to guide the selection of these additional doses. Each cohort will have sentinel dosing (two subjects at least one of which will receive RO7062931) to monitor acute reactions.

Part 2*a/b* is an adaptive, parallel multiple-dose study in patients with CHB. In Part 2a, CHB patients will receive two monthly doses (Q1M) of RO7062931. Part 2a is planned to consist of 4 parallel cohorts of three RO7062931 dose levels and one placebo. [redacted] In addition to safety, PK will be evaluated in the first two patients of each dose cohort prior to subsequent randomization of the remaining patients in the cohort, to confirm that RO7062931 exposure is comparable as found for the HVs. [redacted] Thus, Part 2 may run in parallel with additional doses in healthy volunteers in Part 1 that will be used to provide additional safety data.

In Part 2b, each patient will be randomized to active *treatment* or placebo in each dose cohort/level in a 3:1 ratio. A dose identified from the dose-response analysis of Part 2a (based either on HBsAg decline or maximum dose evaluated and well tolerated), will be tested in different dosing regimens administered weekly (QW) or bi-weekly (Q2W). The selection of dosing regimens will be guided by the analysis of safety, PK and PD data of all previous cohorts in Part 2. A response-adaptive approach will be explored to help guide the selection of the doses to be studied based on criterion that optimizes the dose- PD response parameters (D-optimality), as well as criterion that optimizes the target dose (TD-optimality). *The* total dose will not exceed 400 mg per day *for Part 2c of the study*.

Part 2c is an adaptive, open-label, non-controlled, multi-arm, multi-center, study to evaluate the efficacy and safety of RO7062931 following subcutaneous administration on top of Standard of Care (SoC) therapies (a nucleoside/nucleotide analogue[NUC] with/without pegylated interferon [PEG-IFN]) in NUC-suppressed or treatment-naive CHB patients. Both HBeAg positive and negative patients will be enrolled. Cohort 9 will enroll NUC-suppressed CHB patients and patients will receive RO7062931 on top of a NUC for up to 24 weeks. Cohort 10 will enroll NUC-suppressed CHB patients and patients will receive RO7062931 on top of a NUC plus PEG-IFN for up to 48 weeks. For Cohorts 9 and 10, RO7062931 will be administered at a dose determined from study Parts 2a and 2b. Cohorts 11 and 12 (optional cohorts) may enroll treatment-naïve immune-active CHB patients and/or different treatment combinations or treatment duration.

NUMBER OF PATIENTS

In Part 1 of the study, up to 8 cohorts of 10 HVs are planned. HVs will at each dose level be randomized to either active treatment (eight HVs per cohort) or placebo (two HVs per cohort).

For Part*s 2a and 2b* of the study, in CHB infected patients, a sample size of no more than 80 patients with CHB was chosen (6 patients [Part 2a] and 8 patients [Part 2b] per dose cohort).

For Part 2c, approximately 16 patients will be enrolled into the initial 2 cohorts (8 patients in each cohort). If utilized, approximately 8 patients will be enrolled to each of the Cohorts 11 and 12.

Depending on evaluation of safety, tolerability and PK data from all previous cohorts of the study, one or more additional cohorts may be studied.

TARGET POPULATION

The target population consists of male and female HVs/ patients diagnosed with chronic hepatitis B infection, between the age of 18 and 65, inclusive.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

Study subjects must meet the below criteria for study entry.

Part 1 - Healthy volunteers only:

1. Able to participate and willing to give written informed consent and to comply with the study restrictions.
2. Healthy male and female (of non-childbearing potential) subjects. Health status is defined by absence of any active or chronic disease following a detailed medical and surgical history, concomitant drug use (including hormonal supplements), a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.
3. 18 to 65 years of age, inclusive.
4. A Body Mass Index (BMI) between 18 to 30 kg/m^2 inclusive and a body weight of at least 50 kg.
5. Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH], or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

   All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and up to 105 days after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the healthy volunteer. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

Part 2a and Part 2b **- CHB patients only:**

1. Ability and willingness of patient to provide written informed consent.
2. Adult male and female (of non-childbearing potential) patients, aged 18-65 years (inclusive).
3. A BMI between 18 to 32 kg/m^2 inclusive.
4. Chronic hepatitis B infection.
5. Positive test for HBsAg for more than 6 months prior to randomization.
6. HBsAg titer $\geq 10^3$ IU/mL at screening.
7. On entecavir, tenofovir, adefovir or telbivudine treatment for at least 6 months prior to randomization and will remain on stable treatment during the study.
8. HBV DNA $\leq$ 90 IU/mL for at least the preceding 6 months.
9. Screening laboratory values (hematology, chemistry, urinalysis) obtained up to 56 days prior to first study treatment within normal ranges, with the exception of otherwise specified criteria or judged to be not clinically significant by Principal Investigator (PI) and Medical Monitor.
10. Alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP) at screening $\leq 1.5 \times$ upper limit of normal (ULN); normal values for total bilirubin and prothrombin time (PT)/International Normalized Ratio (INR)/activated partial thromboplastin time (aPTT) tests at screening (except for patients with Gilbert's syndrome TB $\leq$ 47 μmol/L [2.75 mg/dL]).
11. 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 ($\geq$ Metavir 3, recommended cut-off for Fibroscan 8.5 kPa).
12. Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by FSH, or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

    All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

    With female partners of childbearing potential or pregnant female partners, men must

remain abstinent or use a condom during the treatment period and up to 105 days after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Part 2c - CHB patients only

1. *Ability and willingness of patients to provide written informed consent*
2. *Adult male and female patients, 18 to 65 years of age, inclusive.*
3. *A BMI between 18 to 32 kg/m^2 inclusive.*
4. *CHB infection (HBsAg-positive for ≥ 6 months)*
5. *For Cohorts only enrolling NUC-suppressed CHB patients, patients must meet the following criteria:*
   a. *Patients treated with a single NUC (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate) for ≥12 months. Patients must be on the same NUC therapy for at least 3 months before screening.*
   b. *HBV DNA <LLOQ at screening and in preceding 6 months (at least one measurement >30 days prior to screening).*
   c. *ALT ≤ 2 x ULN for >6 months prior to screening and confirmed at screening. Total bilirubin within normal range at screening, except for patients with Gilbert's syndrome (TB ≤ 47 µmol/L [2.75 mg/dL]).*
6. *For cohorts only enrolling treatment-naïve and immune-active patients (e.g., Cohort 11), patients must meet the following criteria:*
   a. *HBV DNA at screening ≥2 x 10^4 IU/mL for HBeAg positive patients, or ≥2 x 10^3 IU/mL for HBeAg negative patients.*
   b. *Elevated serum ALT>2 ULN to ⩽ 5 ULN, 2 values within 6 months, at least one of which is at screening and both results must be at least 14 days apart. Total bilirubin within normal range at screening, except for patients with Gilbert's syndrome (TB ≤ 47 µmol/L [2.75 mg/dL).*
7. *Screening laboratory values (hematology, chemistry, urinalysis) obtained up to 28 days prior to first study treatment within normal ranges, with the exception of otherwise specified criteria or judged to be not clinically significant by PI and Medical Monitor.*
8. *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 3, recommended cut-off for fibroscan 8.5 kPa).*
9. *Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH], or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization*

(removal of ovaries and/or uterus).

All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus spermicide during the treatment period and up to 6 months after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion criteria:

Study subjects who meet any of the below criteria will be excluded from study entry.

Part 1 - Healthy volunteers only:

1. Women who are lactating.
2. Any suspicion or history of alcohol and/or other substance abuse or dependence in the past 6 months.
3. Positive urine drug and alcohol screen (barbiturates, benzodiazepines, methadone, amphetamines, methamphetamines, opiates, cocaine, cannabinoids and alcohol), or positive cotinine test at screening or Day – 1.
4. Positive result on hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) 1 and 2.
5. Confirmed (e.g., two consecutive triplicate measurements) average systolic blood pressure (SBP) > 140 or < 90 mmHg, and diastolic blood pressure (DBP) > 90 or < 45 mmHg at Screening.
6. Confirmed (e.g., two consecutive triplicate measurements) average resting pulse rate (PR) > 90 or < 45 beats per minute (bpm) at Screening.
7. A personal history of unexplained blackouts or faints, or known risk factors for Torsade de Pointes (e.g., hypokalemia, heart failure). Clinically significant abnormal ECG, including arrhythmias or marked QT abnormalities (QTcF < 300 msec or > 450 msec at Screening).
8. ECG morphology at screening that renders measurement of QT interval imprecise (e.g., neuromuscular artifact that cannot be readily eliminated, indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves, arrhythmias, etc.).
9. Screening or baseline ECG evidence of atrial fibrillation, atrial flutter, complete right or left bundle branch block, Wolff-Parkinson-White syndrome, or cardiac pacemaker.
10. Personal or family history of congenital long QT syndrome or sudden death.
11. Any out of range findings in liver function tests, INR and renal function tests or any clinically significant abnormalities (as judged by the Investigator) in the physical examination and in the remaining laboratory test results (including hepatic and renal panels, complete

blood count, chemistry panel and urinalysis) at screening and on Day-1.

12. Participation in an investigational drug or device study within 90 days prior to screening or 5 times the half-life of the investigational drug (whichever is longer).
13. Donation of blood over 500 mL within three months prior to screening.
14. Concomitant disease or condition (including allergic reactions against any drug, or multiple allergies) that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the healthy volunteers in this study.
15. Any major illness within the one month preceding the Screening visit, or any febrile illness within the two weeks preceding the screening visit.
16. Alcohol consumption of more than 2 standard drinks per day on average; 1 standard drink equals 10 grams of alcohol (for further guidance please see Appendix 9).
17. Hypersensitivity to the excipients of the study drug.
18. Healthy volunteers under judicial supervision, guardianship or curatorship.

Part 2a and Part 2b **- CHB patients only:**

1. Women who are lactating.
2. History or other evidence of bleeding from esophageal varices.
3. Decompensated liver disease (e.g., Child-Pugh Class B or C clinical classification [see Appendix 10] or clinical evidence such as ascites or varices).
4. 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, non-alcoholic steatohepatitis, etc.).
5. Documented history or other evidence of metabolic liver disease within one year of randomization.
6. Positive test for hepatitis A (IgM anti-HAV), hepatitis C, or HIV.
7. Documented history of infection with hepatitis D virus.
8. 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 Herpes simplex virus (HSV) I or HSV II.
9. History of or suspicion of hepatocellular carcinoma or alpha fetoprotein (AFP) $\geq$ 13 ng/mL at Screening.
10. 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).
11. History of clinically significant and not adequately controlled cardiovascular, endocrine, gastrointestinal, renal, ocular, pulmonary, or neurological disease.
12. Evidence of an active or suspected cancer or a history of malignancy other than adequately

treated basal cell carcinoma.

13. History of having received (in the last 6 months) or currently receiving any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic corticosteroids).
14. History of organ transplantation.
15. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
16. Significant acute infection (e.g., influenza, local infection) or any other clinically significant illness within 2 weeks of randomization.
17. Clinically relevant ECG abnormalities on screening ECG including arrhythmias or marked QT abnormalities (QTcF $<$ 300 msec or $>$ 450 msec) at Screening.
18. Any of the following laboratory parameters at screening:
    a) White blood cells (WBC) $<$ 3,000 cells/ mm^3
    b) Neutrophil count $<$ 1500 cells/mm^3
    c) Platelet count $<$ 140,000 cells/mm^3
    d) aPTT $>$ 40 seconds, INR $>$ 1.2
    e) Hemoglobin (Hgb) $<$ 12 g/dL in females or $<$ 13 g/dL in males.
19. Abnormal renal function including serum creatinine $>$ ULN or calculated creatinine clearance $<$ 70 mL/min (using the Cockcroft Gault formula).
20. Participation in an investigational drug or device study within 30 days prior to randomization.
21. Donation or loss of blood over 500 mL within 3 months prior to starting study medication.
22. Administration of any blood product within 3 months of randomization.
23. History or evidence of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink equals 10 grams of alcohol, for further guidance please see Appendix 9) and/or drug abuse within one year of randomization; positive test result for drugs of abuse at Screening.
24. Patients under judicial supervision, guardianship or curatorship.
25. Medical or social conditions that would potentially interfere with the patient's ability to comply with the study visit schedule or the study assessments.

Part 2c – CHB patients only

1. *Women who are lactating*
2. *History or other evidence of bleeding from esophageal varices.*
3. *Evidence of liver cirrhosis or decompensated liver disease such as ascites, esophageal or gastric varices, splenomegaly, nodular liver, jaundice, hepatic encephalopathy, portal hypertension.*
4. *One or more of the following laboratory abnormalities at screening:*

a) *Total serum bilirubin > ULN (exception Gilbert's disease).*

b) *(INR >1.1 ULN.*

c) *Serum albumin <3.5 g/dL (<35g/L).*

d) *AFP >13 ng/mL (if >ULN, hepatic imaging must exclude hepatocellular carcinoma [HCC]).*

e) *Positive results for anti-mitochondrial antibodies (AMA >1:80), anti-nuclear antibody (ANA) (>1:80), anti–smooth muscle antibody (ASMA >1:40), anti-thyroperoxidase antibodies (a-TPO), anti-thyroglobulin, or anti-platelet antibodies*

f) *Thyroid stimulating hormone (TSH) within normal ranges.*

g) *Platelet count <100,000 cells/mm^3*

h) *Hemoglobin <12 g/dL (females) or <13 g/dL (males).*

i) *White blood cell count <2500 cell/mm^3.*

j) *Neutrophil count <1500 cell/mm^3 (<1200 cell/mm^3 if considered a physiological variant in a patient of African descent).*

5. *History or other evidence of a medical condition associated with chronic liver disease other than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, nonalcoholic steatohepatitis, etc.).*
6. *History of thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests (thyroid-stimulating hormone [TSH].*
7. *Documented history or other evidence of metabolic liver disease within one year of randomization.*
8. *Positive test for hepatitis A (IgM anti-HAV), hepatitis C (quantitative anti-HCV), hepatitis D (total anti-HDV), hepatitis E (IgM and IgE anti-HEV), or human immunodeficiency virus (anti-HIV1/anti-HIV2).*
9. *Expected to need systemic antiviral therapy other than that provided by the study at any time during their participation in the study, with the exception or oral therapy for HSV I or HSV II.*
10. *History of significant gastrointestinal disease (including but not limited to gastric ulcers).*
11. *History of clinically significant cardiovascular, endocrine, renal, ocular, pulmonary, psychiatric, or neurological disease.*
12. *Evidence of an active or suspected cancer or a history of malignancy other than adequately treated basal cell carcinoma.*
13. *History of organ transplantation.*
14. *Participation in an investigational drug or device study within 30 days prior to screening or previous treatment with an investigational agent for HBV (6 months prior to screening)*
15. *Taking any drugs or nutrients listed in prohibited medications and prohibited food sections.*
16. *Significant acute infection (e.g., influenza, local infection) or any other clinically*

significant illness within 2 weeks of randomization.

17. *ECG at screening with clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia's formula) ≥450 msec for males and ≥470 msec for females.*
18. *Abnormal renal function including serum creatinine > ULN or calculated creatinine clearance < 70 mL/min (using the Cockcroft Gault formula).*
19. *Donation or loss of blood over 500 mL within 3 months prior to randomization.*
20. *Administration of any blood product within 3 months prior to randomization.*
21. *History of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink = 10 grams of alcohol) and/or drug abuse within one year of randomization; positive test result for drugs of abuse or alcohol breath test at screening.*
22. *Subjects under judicial supervision, guardianship, or curatorship.*
23. *Medical or social conditions that would potentially interfere with the subject's ability to comply with the study visit schedule or the study assessments.*

LENGTH OF STUDY

The total duration of the study for each HV in Part 1 will be ≥ 16 weeks, and for each patient in Part 2 ≥ 24 weeks *(for Cohort 8, ≥ 23 weeks)* , *except for Part 2c where the total duration may be ≥ 52 weeks,* divided as follows:

Screening: Up to 28 days (Part 1) and 56 days (Part *2a and 2b*) *and up to 28 days (Part 2c);*

In Clinic period:

- Part 1 (1 dose): Days – 1 to 3
- Part 2a (2 doses Q1M): Optional for Days – 1 to 2 and Days 29 to 30
- Part 2b (3 doses, Q2W): Optional for Days – 1 to 2 and Days 29 to 30
- Part 2b (4 doses, QW): Optional for Days – 1 to 2 and Days 22 to 23
- Part 2b (5 doses, QW): Optional for Days – 1 to 2 and Days 29 to 30

Treatment period:

- *Part 2c (QW): Up to 48 weeks*

Safety Follow-up: up to at least 84 days after *the* last dose of study drug *for Part 1, up to at least 112 days after the last dose of the study drug for Part 2a (2 doses, Q1M) and Part 2b (3 doses, Q2W and 5 doses QW), up to at least 105 days after the last dose of the study drug for Part 2b (4 doses, QW), and up to 24 weeks after the last dose of the study drug for Part 2c.*

END OF STUDY

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

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events, including adverse events of special interest.
- Incidence of laboratory abnormalities based on hematology, blood chemistry, coagulation and urinalysis test results.
- ECGs.
- Vital signs, including blood pressure, heart rate and temperature.

PHARMACOKINETIC OUTCOME MEASURES

The PK evaluations for this study are as follows:

Blood and urine samples will be collected to evaluate the RO7062931 and if applicable metabolite(s) PK, as specified in the Schedule of Assessment tables. Plasma and urine concentrations will be measured by specific validated methods.

The following plasma and urine PK parameters will be calculated for RO7062931 (and its metabolites, as appropriate), when possible, using non-compartmental methods:

- C_{max}: maximum plasma concentration.
- t_{max}: time to reach the maximum plasma concentration.
- $AUC_{0\text{-}inf}$: area under the plasma concentration-time curve from time zero to infinity.
- $AUC_{0\text{-}last}$: area under the plasma concentration-time curve from time zero until the last quantifiable time-point.
- Additional PK parameters may be calculated from available data including:

  k (terminal elimination rate constant),

  $t_{1/2}$ (terminal elimination half-life),

  CL (total clearance

  V_{ss} (volume of distribution).
- Urine PK parameters may be calculated with available data including:

  A_e - cumulative amount of drug excreted in urine over a 24 hour period or over defined time periods linked to the pools of urine collected.
- In Part 2: sparse sampling for tenofovir (including tenofovir alafenamide, if approved for HBV and applicable), entecavir, adefovir and telbivudine will be made to determine patient compliance.

PHARMACODYNAMIC OUTCOME MEASURES

In Part 2, blood samples for quantitative and qualitative determination of viral dynamic response measurements of, but not limited to, HBsAg, HBV DNA, *HBV RNA*, *HBcrAg*, HBeAG, anti-HBe, anti-HBc and, anti-HBs and HBsAg/anti-HBs complex, will be collected at the time-points indicated in the Schedule of Assessment tables and as detailed in Section 4.6.1.8.

The PD outcome measure to support the secondary objective is the change in quantitative HBsAg over time. Derived endpoints of quantitative HBsAg will include:

- Quantitative HBsAg *(qHBsAg)* (log10) and its change from baseline
- Maximum change from baseline in quantitative HBsAg across all time-points
- Rate of decrease for HBsAg at each time-point.
- *Proportion of patients with undetectable qHBsAg (< 0.05 IU/mL)*

All other PD outcome measures are considered exploratory.

EXPLORATORY OUTCOME MEASURES

Exploratory PD outcome measures:

These will include but may not be limited to HBeAg, qualitative HBsAg, anti-HBs, anti-HBe, maintenance of HBV DNA levels less than 90IU/mL *(for Part 2c LLOQ)*.

Viral resistance monitoring will be performed in any patient who experiences viral breakthrough.

[redacted]

Exploratory safety outcome measures

[redacted]

[redacted]

- Assessments for inflammatory markers, autoantibodies and anti-drug antibodies (ADA)

Exploratory PK outcome measure:

[redacted]

INVESTIGATIONAL MEDICINAL PRODUCT(S)

The investigational medicinal products (IMPs) in this study are RO7062931, placebo*, and PEG-IFN* and will be provided by the Sponsor. All study drug administration will occur at the study clinic in the morning by investigational staff. SC doses will be administered at an appropriate body site. The drug should be administered concomitantly with the nucleosides/nucleotides taken by the patient.

NUCs (entecavir, tenofovir alafenamide or tenofovir disoproxil fumarate) to be used as background SoC therapies in Part 2c are classed as non-investigational medicinal product.

PROCEDURES

A Schedule of Assessments (SoA) is provided.

ROCHE RESEARCH BIOSAMPLE REPOSITORY (RBR)

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

Unused residual PD serum, plasma and blood samples will be retained as well as specimens will be collected from patients who give specific consent to participate in this optional Research Biosample Repository. Collected specimens will be used to study the association of biomarkers with efficacy, adverse events, or disease progression, to study drug response, including drug effects and the processes of drug absorption and disposition, and to increase the knowledge and understanding of the disease biology. These samples will also aid in the development of biomarker or diagnostic assays and establish the performance characteristics of these assays. The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Leftover serum and plasma samples to assess protein biomarkers including, but not limited to proteomics.

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood for DNA extraction to assess for biomarkers, including but not limited to the following: single nucleotide polymorphisms (SNPs)

The samples collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

STATISTICAL METHODS

All study subjects randomized to receive placebo will be pooled as control group for Part 1. Patients receiving placebo in Part 2b will be pooled with the placebo cohort from Part 2a.

PHARMACODYNAMIC ANALYSES

Viral Dynamic Response Analyses

Descriptive statistics will be used to summarize the viral dynamic response outcome measure of quantitative HBsAg (log10), actual and change from baseline in quantitative HBsAg at each time-point by dose group. Rate of decrease in quantitative HBsAg will also be summarized using descriptive statistics.

PK/Viral Dynamic Response Analyses

The relationship between RO7062931 and dose, and metabolite(s) and dose if applicable, and the change of HBsAg at each time-point and rate of decrease will be explored by graphical analysis. The relationship between RO7062931 PK and urinary parameters and HBsAg will also be explored. An appropriate exposure/dose-response model may be fitted to the data from Part 2a. This model may be used to guide dose selection for Part 2b*, and will be further developed with data from Parts 2b and 2c*.

PHARMACOKINETIC ANALYSES

Pharmacokinetic parameters as defined will be determined using standard non-compartmental methods for both RO7062931 and any metabolite(s) when available. Descriptive statistics of urine PK parameters for RO7062931 and any metabolite(s) will be presented, where available. PK and PD data from this study may be used to develop a population PK/PD model.

Where appropriate, listings and summary tables of nucleoside/nucleotide-analogues, tenofovir, tenofovir alafenamide, entecavir, adefovir, or telbivudine concentrations will be provided based on the sparse sampling throughout the study.

Study subjects will be excluded from the pharmacokinetic analysis population if they significantly violate the eligibility criteria or the protocol, or if data are unavailable or incomplete which may influence the pharmacokinetic analysis.

SAFETY ANALYSES

All study subjects who receive at least one dose of study drug will be included in the safety analysis. The safety endpoints include, but may not be limited to, incidence of adverse events (including injection site reactions [ISRs]), treatment discontinuations due to adverse events, change from baseline by time in laboratory parameters and incidence of clinically significant laboratory abnormalities, change from baseline by time *of* ECG parameters and abnormalities*,* and vital signs and abnormalities.

OTHER ANALYSES

The exploratory safety parameters for liver and kidney biomarker data will be summarized using descriptive statistics and explored graphically. For inflammatory markers, autoantibodies and ADA, at minimum, any data collected and available at the time of database closure will be summarized, if applicable, and explored graphically.

Bayesian adaptive methodology (continual re-assessment method [CRM]) will be explored to help guide selection of doses and dosing regimen to be studies in Part 1 and Part 2b of this study. [redacted] The Power model method will be used to aid assessment of dose-proportionality.

In Part 2b, for the first two cohorts, a repeated measures dose-response model will be fitted to the data observed in Part 2a to model the relationship between quantitative HBsAg decline over time and dose. The dose selected to be studied in different dosing regimens in the first two cohorts of Part 2b will be the lowest dose that yields the greatest decline at any time-point. For the exploratory part of Part 2b, a response-adaptive approach will be explored to help guide the selection of the doses to be studied using criterion that optimizes the dose-response parameters (D-optimality) as well as criterion that optimizes the target dose (TD-optimality).

SAMPLE SIZE JUSTIFICATION

In Part 1 of the study, the planned sample size of 8 active per cohort was chosen not only to allow adequate assessment of safety and tolerability but also to increase the precision of the estimates of mean PK and urinary parameters, [redacted]

In Part *2a and 2b* of the study, it is anticipated that the sample size will allow characterization of the PK/PD (viral dynamic response) relationship, as well as safety and tolerability, in patients with CHB.

For Part 2c, approximately 16 patients will be enrolled into the initial 2 cohorts (8 patients in each cohort). If utilized, approximately 8 patients will be enrolled to each of the Cohorts 11 and 12. The sample size supports the assessment of response rate of undetectable qHBsAg at Week 24 follow-up in Cohorts 10, 11 and 12.

CONCOMITANT MEDICATIONS

There are no concomitant treatment restrictions at this time as no drug-drug interactions are foreseen for RO7062931.

In Part 1, there are some restrictions for healthy volunteers regarding prescribed or over-the-counter medication (including herbal remedies, vitamins, fish oils and protein powders), taken within 2 weeks prior to first study drug administration with the exception of hormone replacement therapy, which is allowed throughout the study. Paracetamol (up to 1 g per day) will be allowed. In the event that a healthy volunteer requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor. For study subjects taking nucleosides/nucleotides food restrictions may apply.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAV	Adeno-associated virus
ADA	Anti-drug antibody
AE	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AMA	*Anti-mitochondrial antibodies*
ANA	***Anti-nuclear antibody***
[redacted]	[redacted]
ASMA	*Anti-smooth muscle antibody*
AST	Aspartate aminotransferase
a-TPO	*Anti-thyroglobulin*
AUC	Area under the curve
BP	Blood pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
cccDNA	Covalently closed circular DNA
CHB	Chronic Hepatitis B
CL	Clearance
CNS	Central nervous system
CRO	Contract research organization
DAIDS	Division of AIDS Table
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLE	Dose-limiting event
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
ESF	Eligibility screening form
EU	European Commission
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GalNAc	N-Acetylgalactosamine

GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HBcAg	Hepatitis B core antigen
HBcrAg	Hepatitis B core-related antigen
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HAV	Hepatitis A
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCG	Human Chorionic gonadotropin
HDL	High-density lipoproteins
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
HSV	Herpes simplex virus
HV	Healthy volunteer
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IxRS	Interactive (voice/web) response system
LDL	Low-density lipoproteins
LFT	*Liver function test*
LNA	Locked nucleic acid
LPLV	Last patient, last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MTD	Maximum tolerated dose
NIMP	*Non-investigational medicinal product*
NOAEL	No-observed-adverse-event level
NUC	*Nucleoside/nucleotide analogue*
OTC	Over-the-counter
PD	Pharmacodynamic
PEG-*IFN*	Pegylated interferon

PK	Pharmacokinetic
PoM	*Proof of mechanism*
PT	Prothrombin time
qHBsAg	*Quantitative HBsAg*
Q1M	Once a month
QW	Once a week
Q2W	Once every two weeks
QRS	QRS complex
RBR	Research Biosample Repository
RNA	Ribonucleic acid
SAD	Single-ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Saturation dose
SoA	Schedule of Assessments
SoC	*Standard of Care*
SSO	*Single stranded oligonucleotide*
SUSAR	Suspected unexpected serious adverse reactions
TK	Toxicokinetics
TSH	*Thyroid stimulating hormone*
ULN	Upper limit of normal
WBC	White blood cell
WGS	Whole genome sequencing

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Hepatitis B virus (HBV) infection is a major cause of both acute hepatitis and chronic liver diseases, including cirrhosis and hepatocellular carcinoma. Approximately two billion people worldwide have serological evidence of past or present HBV infection, and around 240 million people are chronic hepatitis B surface antigen (HBsAg) carriers. An estimated 686,000 people die each year due to the acute or chronic consequences of hepatitis B (WHO 2016; EASL 2012).

Antiviral therapy of CHB aims to improve quality of life and survival of the patients by preventing progression of liver damage to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death. Sustained suppression of HBV replication is associated with biochemical remission, histological improvement and delayed disease progression (EASL 2009).

Chronic HBV infection is a dynamic process with several stages, during which CHB may be present either as HBV e antigen (HBeAg)-positive or HBeAg-negative. Current guidelines specify the ideal endpoint of therapy for CHB patients as the loss of HBsAg with or without HBsAg seroconversion (EASL 2012). For HBeAg-positive patients, HBeAg seroconversion is indicative of better prognoses, including lower rates of cirrhosis and slower disease progression. Other clinically meaningful endpoints, irrespective of HBeAg status, are HBV DNA suppression and alanine aminotransferase (ALT) normalization, which indicate the virological and biochemical responses to therapies, respectively.

Currently, there are two types of drugs available for the treatment of CHB: subcutaneously administered interferon preparations (IFN; conventional or pegylated IFN [PEG-IFN]) and orally administered nucleoside/nucleotide analogues (NUC), including adefovir, telbivudine, tenofovir, entecavir, and lamivudine. Although nucleos(t)ide treatment is highly effective at normalizing liver enzymes (biochemical response) and in lowering HBV DNA level to undetectable levels (virological response), chronic HBV infection cannot be completely eradicated with currently approved therapeutics due to the persistence of HBV covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes (Lucifora et al 2014). Signs of infection return to pre-treatment levels (relapse) if nucleos(t)ides are discontinued in the majority of cases. Therefore, few individuals achieve a functional or clinical cure with current therapies (sustained HBsAg and HBV DNA loss with or without HBsAg seroconversion occurs in $<$ 15% after five years following treatment discontinuation) *(EASL 2012)*. Moreover, PEG-IFN is associated with significant safety and tolerability risks, while NUC analogues frequently require prolonged or indefinite therapy and some are associated with high risk of resistance.

1.2 BACKGROUND ON RO7062931

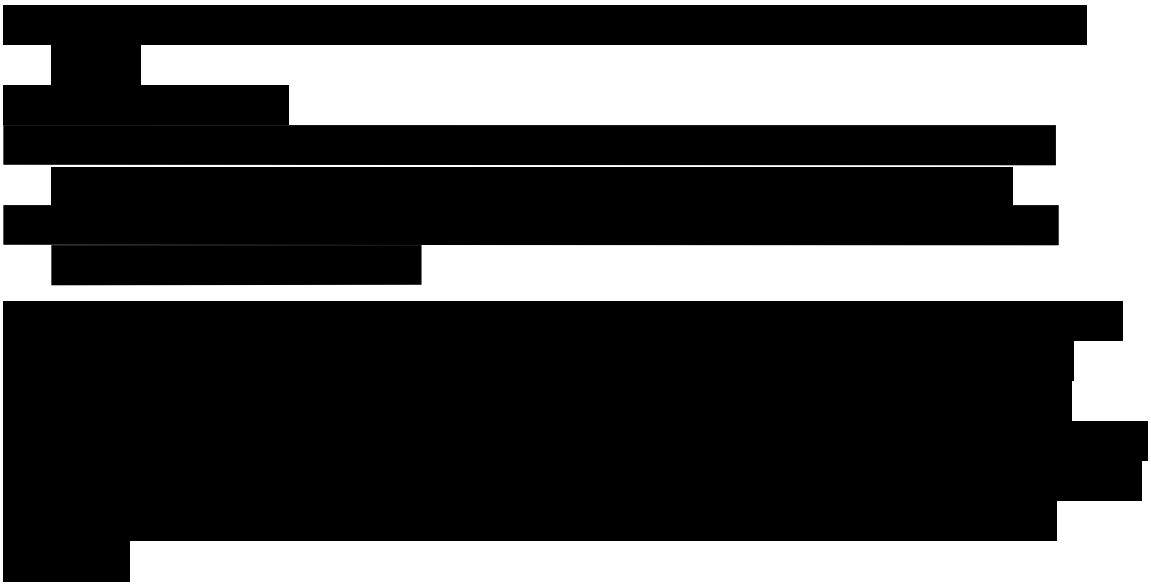
RO7062931is [redacted], intended for the treatment of CHB infections. Chronicity in CHB is believed to be perpetuated, at least in part, by protein products expressed from the HBV genome which are derived from translation of four mRNA species transcribed from the cccDNA template located in the nucleus of actively infected hepatocytes. [redacted]

See the RO7062931 Investigator Brochure (IB) for details on non-clinical and clinical studies.

1.2.1 Previous Non-Clinical Studies

RO7062931 has shown potent antiviral activity through the inhibition of [redacted]. RO7062931 is [redacted] active in vitro against [redacted] genotypes A, B, C, D and NUC analog-resistant HBV. In mice infected with a recombinant adeno-associated virus (AAV) carrying a replicable HBV genome (AAV-HBV), administration of RO7062931 reduced [redacted].

The pharmacokinetics (PK) and toxicokinetics (TK) of RO7062931 were studied in rats and cynomolgus monkeys following subcutaneous (SC) injections. Similar plasma PK characteristics were observed for RO7062931 across the species. [redacted]



RO7062931 is not expected to interfere with the activity of cytochrome (CYP) P450 enzymes and/or drug transporters.

1.2.2 Previous Clinical Studies

This Phase I study (BP39405) is the first-in-human study with RO7062931. One further clinical study with RO7062931 in Chinese Healthy Volunteers is currently ongoing.

Preliminary data from BP39405 study indicates that RO7062931 is safe and well tolerated:

- *In the BP39405 study Part 1, 60 healthy volunteers in total, in six SAD cohorts (0.1, 0.3, 1.0, 2.0, 4.0, and 3.0 mg/kg) received a single dose of RO7062931 or placebo. Blinded data review demonstrated no dose dependency in the incidence and intensity of AEs. A total of 78 non-serious AEs were reported in 40 out of 60 HVs; the majorities (74) of those AEs were mild in intensity and 4 were of moderate in intensity.*

- *In Part 2a and Part 2b of the BP39405 study, at the cut-off date of 22 November 2018, 54 patients were enrolled. Part 2a enrolled 27 patients in four cohorts for monthly dosing (0.5, 1.5, 3.0 mg/kg of RO7062931 or placebo). Part 2b enrolled further 27 patients in three cohorts exploring 3 mg/kg weekly (QW) or bi-weekly dosing (Q2W) of RO7062931. There was no dose-dependent or regimen-dependent increase in the frequency or severity of AEs. A total of 82 AEs were reported in 32 of the 54 CHB patients; most AEs were mild and had resolved, and five AEs observed in 4 CHB patients were moderate in intensity.*

- *There were no severe or SAEs, AEs leading to treatment withdrawal, or AEs of special interest. No particular pattern or significant changes were observed for vital signs, ECGs parameters, laboratory safety test results, or urine microscopy. No patients discontinued study medication due to safety reasons.*

- *In addition, proof-of-mechanism (PoM) in CHB patients has been demonstrated with dose-dependent declines in HBsAg observed in patients treated with RO7062931 compared to placebo. Similar HBsAg declines were observed regardless of HBeAg status.*

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Study BP39405 is the first clinical study of RO7062931, designed to assess: the safety, tolerability and pharmacokinetics (PK) of subcutaneously administered single-ascending doses (SAD) in healthy volunteers (HVs; Part 1); and safety, tolerability, PK, and pharmacodynamic (PD) effects of subcutaneously administered multiple doses to CHB patients *for a short duration of treatment (Part 2a and Part 2b) and for an extended duration of treatment (Part 2c).* In this protocol, both healthy volunteers and patients are referred to as study subjects.

[redacted]

[redacted]

[redacted]

Parts *2a/2b* will involve patients with CHB infection who have responded to standard treatment with NUC inhibitors of HBV reverse transcriptase. [redacted] However, the results from Parts *2a/2b* will provide essential information for selecting doses for future clinical trials and for supporting the development of a new treatment for chronic HBV infection.

Part 2c of the study will assess the efficacy and safety of RO7062931 when administered with Standard of Care (SoC; NUC with/without PEG-IFN) for up to 48 weeks. Preliminary data from Part 2a/2b have demonstrated proof of mechanism (PoM) and RO7062931 administration in CHB patients is associated with a good safety and tolerability profile following 4 weeks of treatment. Considering steady state exposure of RO7062931 in liver with QW dosing is anticipated to take about 13 weeks, longer treatment duration is needed to evaluate the maximum effect on HBsAg levels, at steady state and beyond.

1.3.2 Benefit–Risk Assessment

Before initiation of this first-in-human study, no prior clinical experience with RO7062931 *existed*. The evaluation of the potential risks of treatment and the specific tests, observations, and precautions required for clinical studies with RO7062931 *were* based on information from non-clinical toxicology and safety pharmacology studies as well as prior experience with other oligonucleotide therapeutics. Safety and tolerability will be carefully assessed, and study subjects (referring to both healthy volunteers and patients in the protocol) will be closely monitored. The RO7062931 Investigator Brochure, Section 6 summarizes the key risk management activities to consider when administering this novel compound to study subjects.

Based on the exposure multiple to the predicted human efficacious dose calculations, and the non-clinical toxicology data, the selected starting-dose of 0.1 mg/kg is considered to be safe (see Section 3.2.1). Equivalent human exposures anticipated from the target dose range between 0.1 and 4 mg/kg of RO7062931 proposed within this study and evaluated under a controlled setting, should provide a better understanding of clinical safety and tolerability to guide future clinical studies. The risks for an individual study subject due to ascending doses of RO7062931 or study-related procedures are considered to be minimal.

The good safety and tolerability observed to date in CHB patients, the preliminary encouraging dose dependent declines in HBsAg levels, and the favorable results from pre-clinical chronic toxicity studies, support an evaluation of RO7062931 treatment at a dose level of up to 4mg/kg/week and for up to 48 weeks treatment duration when administered with standard of care (SoC) therapies. Consistent with current guidelines (FDA 2018), non-clinical combination studies of RO7062931 with approved SoC therapies (i.e. NUC or PEG-IFN) were not conducted, as available nonclinical data does not suggest a potential for serious synergistic toxicity.

For further information please refer to the latest RO7062931 Investigator Brochure.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is:

- To assess the safety and tolerability of RO7062931 compared to placebo after single-ascending subcutaneous (SC) doses in HVs.
- To assess the safety and tolerability of RO7062931 compared to placebo after multiple SC doses in CHB patients.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

For Part 1:

- To assess plasma and urine PK of RO7062931, and if applicable metabolite(s), after single-ascending SC doses.

For Part 2:

- To assess the plasma and urine PK of RO7062931 and if applicable metabolite(s), after multiple SC doses.
- To study HBsAg dynamics after SC administration of RO7062931.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

– PD exploratory objectives:
  - For Part 2: to explore the effect of multiple doses of RO7062931 on viral and anti-viral parameters other than quantitative HBsAg during and after the end of treatment in CHB patients.
  - To explore the effects of RO7062931 doses on further exploratory biomarkers

– PK exploratory objective:
  - [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

The study will be conducted in two parts, of which Part 1 will be in healthy volunteers and Part 2 will be in CHB patients (see Figure 1). Both parts of the study are randomized. Part 1 will evaluate the safety, tolerability and PK of RO7062931, and if applicable metabolite(s), following SC administration of single doses in healthy volunteers. Part 2 will evaluate the safety, tolerability PK and PD (viral dynamics) following administration of multiple SC doses of RO7062931 in CHB patients *over a short treatment duration (Figure 1) and extended treatment durations (Figure 2)* (see Section 4.6).

Figure 1 Study Design*: Parts 1, 2a, and 2b Short Treatment Durations*

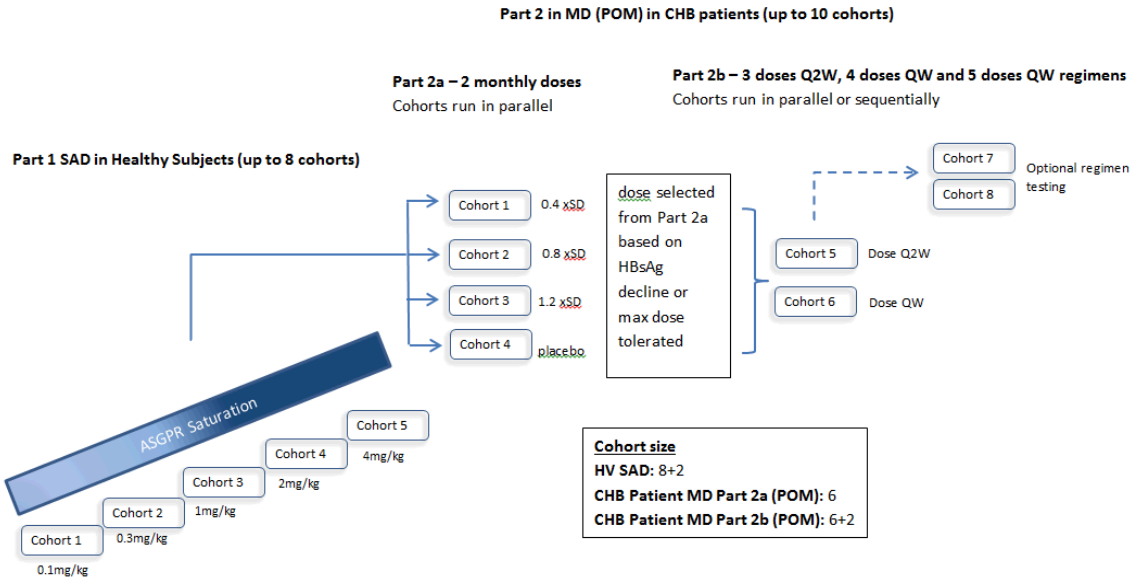
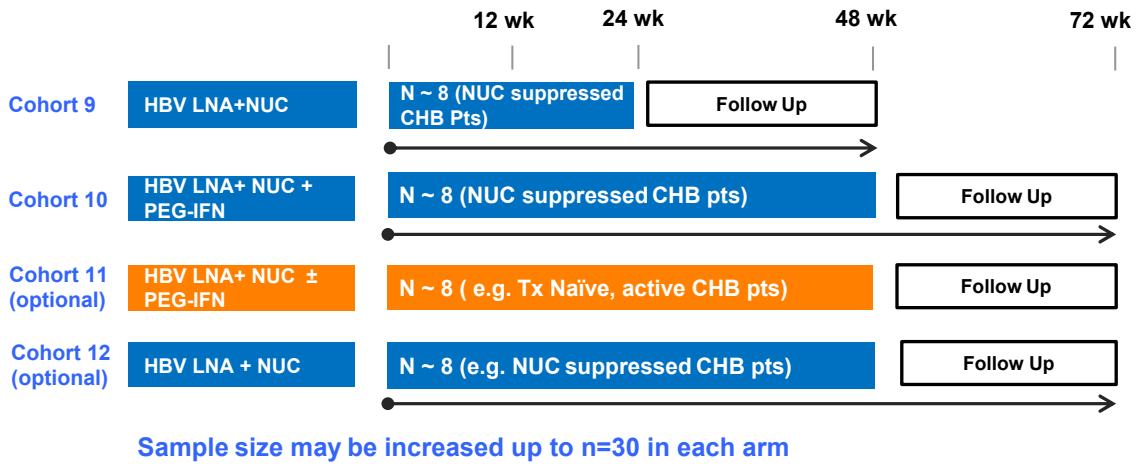


Figure 2 Study Design: Part 2c - Extended Treatment Durations



The total duration of the study for each HV in Part 1 will be ≥ 16 weeks.

- Part 1 (1 dose)
  - Screening: Up to 28 days;
  - In Clinic period: Days – 1 to 3;
  - Safety Follow-up: up to at least Day 85.

The total duration of the study for each patient in Part 2 will be ≥ 24 weeks*, except for Part 2c where the total duration may be ≥ 52 weeks.*

- Part 2a (2 doses, Q1M)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days – 1 to 2 and Days 29 to 30;
  - Safety Follow-up: up to at least Day 113.
- Part 2b (3 doses, Q2W)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days – 1 to 2 and Days 29 to 30;
  - Safety Follow-up: Up to at least Day 113.
- Part 2b (4 doses, QW)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days –1 to 2 and Days 22 to 23;
  - Safety Follow-up: Up to at least Day 106.

- Part 2b (5 doses, QW)
  - Screening: Up to 56 days;
  - In Clinic period (optional): Days −1 to 2 and Days 29 to 30;
  - Safety Follow-up: Up to at least Day 113.
- *Part 2c (QW)*
  - *Screening: Up to 28 days;*
  - *Treatment period: Up to 48 weeks;*
  - *Follow-up period: Up to 24 weeks.*

3.1.1.1 Part 1: Single-Ascending Dose (SAD) in Healthy Volunteers

Part 1 is a randomized, Sponsor-open, Investigator-blinded, subject-blinded placebo-controlled, adaptive SAD study with an adaptive dose-escalation schedule. The first cohort will receive a single dose of 0.1 mg/kg RO7062931 or placebo using a 4:1 randomization scheme. [redacted]. However, at this dose, AEs are expected to be mild and within this protocol higher doses may be evaluated if this dose is found to be safe and well tolerated. [redacted] The use of a Bayesian analysis, specifically a continual reassessment method (CRM) analysis will be explored as a tool to help to guide the selection of these additional doses and is explained in further detail in the exploratory analysis (Section 6.8). There will be ongoing assessment of available safety, tolerability, and PK data prior to initiation of the next dose and cohort.

Eight HVs receiving RO7062931 and two receiving placebo are planned to be enrolled in each cohort of Part 1. The HVs will be admitted to the clinic on Day −1 and discharged on Day 3, following the morning assessments. Ambulatory visits will be performed as indicated in the SoA tables (see Appendix 1 to Appendix 2).The HVs of each cohort will receive sentinel dosing, where two subjects will be dosed on Day 1, at least one of which will receive RO7062931 to monitor acute reactions and the remaining 8 subjects can be dosed on the following day (24 hours afterwards) following satisfactory safety assessments of the first two subjects by the Investigator. Following the single dose of all HVs in a cohort, safety will be monitored for at least 28 days prior to escalation to the next dose cohort.

3.1.1.2 Part 2a/2b: Proof-of-Mechanism in CHB Infected Patients

Part 2a/b is a multi-center randomized, Sponsor-open, Investigator-blinded, subject-blinded, placebo-controlled, adaptive, parallel multiple-dose study in chronically HBV infected patients, with the aim to study the safety, tolerability, PK of RO7062931(and if applicable metabolite[s]), and the relationship between RO7062931 dose, dose regimen and viral dynamic response.

[redacted]

In Part 2a, CHB patients will receive two monthly doses (Q1M) of RO7062931. Part 2a is planned to consist of 4 parallel cohorts of 3 RO7062931 dose levels and one placebo.

[redacted] In addition to safety, PK will be evaluated in the first two patients of each dose cohort prior to subsequent randomization to confirm that RO7062931 exposure is comparable as found for the HVs. Cohort doses may be adjusted across the patient cohorts if plasma PK appears to significantly differ from the HVs. Each cohort in Part 2a will consist of 6 patients.

In Part 2b, a dose identified from the dose-response analysis of Part 2a (based on either HBsAg decline or maximum dose evaluated and well tolerated) will be tested in different dosing regimens administered weekly (QW) or bi-weekly (Q2W). The total dose of 400 mg per day will not be exceeded. The selection of dosing regimens will be guided by the analysis of safety, PK and PD data of all previous cohorts in Part 2.

In Part 2b, each patient will be randomized to active or placebo in each dose cohort/level in a 3:1 ratio. Each cohort in Part 2b will be comprised of 8 patients, six patients will receive RO7062931 and two will receive placebo. CHB patients will be followed up weekly for the first 28 days and then monthly up to at least 84 days after the last dose of RO7062931.

There will be two optional overnight stay periods for the patients: between Day −1 and Day 2, and between Day 29 and Day 30 (exception: between Day 22 and Day 23 for the cohort with 4 doses given QW). If the Investigator agrees, the patients can leave the clinic after completing the last evening assessment and return the following morning prior to the first scheduled assessment. In Part 2b, where drug administration is given on days other than Day 1 and Day 29 (or Day 22 for the cohort with 4 doses given QW), the patients will be administered the drug in the clinic as an ambulatory visit.

Visits and assessments will be performed as indicated in the SoA tables (see Appendix 3 to *Appendix 14*).

All doses in Part *2* will be lower than, or equal to, the doses studied and considered to be well-tolerated in Part 1. Subsequent doses and regimens for Part 2b*/2c* will be selected on the basis of the analysis of Part 2a data. Part 2b will be initiated once Part 2a data have been analyzed. *The* total dose will not exceed 400 mg per day.

Due to the adaptive nature of this study, the actual number of dose levels and the number of study subjects/cohorts at each dose may be modified depending on emerging data. Planned doses may be adjusted (increased, decreased, or repeated) or dosing may be discontinued. After safety and PK data review (see Section 3.1.4), study subjects may be requested to return to the site for additional safety or PK assessments, upon agreement between subjects, Investigators and the Sponsor.

3.1.1.3 *Part 2c: Extended Duration of RO7062931 Therapy in CHB Infected Patients*

Part 2c *is an adaptive, open-label, non-controlled, multi-arm, multi-center, study to evaluate the efficacy and safety of RO7062931 following subcutaneous administration on top of SoC therapies (a NUC with/without PEG-IFN) in NUC-suppressed or treatment- naïve CHB patients (Figure 2). Both HBeAg positive and negative patients will be enrolled.*

- *Cohort 9 will enroll NUC-suppressed CHB patients. Patients will receive RO7062931 on top of a NUC for up to 24 weeks. RO7062931 will be administered at a dose determined from study Parts 2a and 2b.*

- *Cohort 10 will enroll NUC-suppressed CHB patients. Patients will receive RO7062931 on top of a NUC plus PEG-IFN for up to 48 weeks. RO7062931 will be administered at a dose determined from study Parts 2a and 2b.*

- *Cohort 11 and 12 (optional cohorts) may enroll treatment-naïve immune-active CHB patients and/or different treatment combinations or treatment duration.*

All cohorts will initially enroll approximately 8 CHB patients per cohort. Initially the enrollment will occur sequentially (Cohort 9 will be followed by Cohort 10, see Section 4.3). At the end of treatment (either 24 or 48 weeks depending on cohort), all study treatment (RO7062931 and PEG-IFN) will be discontinued and all patients will be followed up for at least 24 weeks post-treatment follow up.

Based on emerging and accumulated PK, PD, efficacy and safety data from this study or other related studies, the initial cohorts may be expanded to enroll a total of 30 CHB patients. Enrollment of the expanded cohorts may be either sequential or parallel.

3.1.2 Dose-Review/Escalation Decisions

Dose-escalation/review meetings will be conducted by the Investigator, the Medical Monitor, and the Sponsor Clinical Team prior to each RO7062931 dose-escalation (see Section 3.1.4). The study will have an adaptive dosing design and the actual doses may be modified based on emerging safety, tolerability, PK and PD data, but with dose-escalation ratios not higher than currently projected (i.e., with more conservative escalations at higher dose levels). The decision to escalate to the next dose level, or add an additional cohort at a previously studied dose, will be made following the review of the following data from the completed cohort:

For Part 1

- All available safety information, including AEs, ECGs, vital signs, clinical laboratory test results collected up to Day 29 visit.
- All available PK data collected over ≥ 1 week post-dose to characterize the RO7062931, and if available, its metabolite(s) and predict exposure in the following cohort(s).

For Part*s 2a/2b*

- All available safety information, including AEs, ECGs, vital signs, clinical laboratory test results collected up to Day 57 visit (exception: Day 50 for the cohort with 4 doses given QW).
- Adequate data over the first week in Part 2a to characterize the RO7062931 PK and predict exposure in cohorts with different regimens or doses used in Part 2b.
- HBsAg levels at least by two weeks after the last dose.

For Part 2c

- *Commencement of optional cohorts, or expansion of existing cohorts, will be determined based on accumulated safety, tolerability, PK, and PD data from this study.*

3.1.2.1 Part 1 Dose- Escalation Decision Criteria

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

[redacted]

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

Single doses will not be escalated if the dose-escalation stopping criteria are met (see Section 3.1.3.1) but may exceed the proposed maximum dose level of 4 mg/kg only if anticipated to be safe and necessary to generate additional PK or PD data in support of dosing regimens for use in Part 2 of the study.

3.1.3 Dose-Escalation Stopping Criteria

3.1.3.1 Part 1

Dose-escalation in Part 1 will not be implemented as planned in healthy volunteers dosed with RO7062931, and dosing for a treatment arm/cohort in Part 2 will be discontinued, if one of the below criteria is fulfilled, unless it is obvious that the occurrence is not considered to be related to RO7062931.

Dose-escalation will be stopped if at a dose level, more than 2 of 8 healthy volunteers receiving RO7062931 in Part 1 or, within a treatment arm/cohort in Part 2, more than 2 of 6 patients experience:

- Severe or clinically significant (as defined by the Investigator) RO7062931-related AEs of the same character, or
- *S*ignificant RO7062931-related laboratory abnormality of the same character, or
- Clinically significant RO7062931-related changes in vital signs or ECGs of the same character (e.g., QTcF > 500 msec, or > 60 msec longer than the pre-dose baseline, within the first 48 hours post-dose).
- Within two consecutive dose cohorts, four occurrences of any of the above conditions in HVs receiving active drug.

Other findings (regardless of the incidence rates) that at the joint discretion of the Sponsor and the Investigator indicate that dose-escalation (in Part 1) or dosing (in Part 2) should be halted (see Section 4.7).

3.1.3.2 Part 2

In Part 2, in case a cohort is stopped, alternative regimens within a previously tolerated dose/monthly-exposure range could be further investigated or a regimen repeated in the subsequent cohorts by mutual agreement between the Sponsor and Investigator, in order to increase the amount of data within the tolerated dose/monthly-exposure range. Due to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor.

3.1.4 Communication Strategy

After each subject receives RO7062931 (or placebo), the Investigator(s) must confirm to the Sponsor that the subject (HV or patient) has been dosed and provide a brief summary of the status of the subject in terms of safety and tolerability to RO7062931/placebo (this will be communicated by email and/or telephone). In Part 1 of the study, the Investigator(s) will provide a safety assessment feedback of the first two sentinel dosing HVs of each cohort.

In case of a safety concern, the Investigator will contact the Sponsor immediately to discuss study subject status and action taken/to be taken. In addition, after each cohort in Part 1 has been completed and after completion of Part 2a and Part 2b, the Sponsor will organize a teleconference with the investigators to discuss the safety and tolerability of RO7062931 and to discuss eventual next cohort(s) or continuation (Part 2a and Part 2b). The next recommended dose-level (supported by nCRM, if appropriate, for Parts 1 and 2b) will be discussed by Sponsor and investigators. During these teleconferences, adverse events (with severity assessed as given in Section 5.3.3, Table 2) in addition to available safety laboratory results, vital signs, ECGs, will be discussed along with the results of the available PK data, and any other available data that may assist the dose-escalation decision process. The decision of these meetings will be documented in writing.

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

3.1.5 End of Study

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

3.2 RATIONALE FOR STUDY DESIGN

A two-part study design has been chosen to characterize RO7062931 in this clinical trial. In Part 1, safety and PK of single RO7062931 doses will be characterized in healthy volunteers to determine the best liver-targeted dose to be evaluated in CHB patients. In Part 2, safety, PK, HBsAg decline and other possible PD effects will be assessed following multiple RO7062931 doses in CHB patients and data will be obtained to further refine the dose and dosing regimen. *Part 2c will evaluate the efficacy and safety of RO7062931 when administered with SoC for up to 48 weeks.*

3.2.1 Rationale for Dosage Selection

A starting dose of 0.1 mg RO7062931 per kg has been selected for this first study in humans. [redacted] Therefore, the starting-dose of 0.1 mg/kg represents the lower end of the predicted therapeutic dose range in humans and would be expected to have little or no measureable pharmacodynamic effect if evaluated in CHB patients.

A two-pronged approach to the calculation of safety multiples was taken, in that calculations were based, respectively, on plasma and liver levels. By applying the PK model for scaling to human PK, the expected $AUC_{0\text{-}24h}$ in plasma, and liver concentration at 168 hours post-dose, were derived and compared to the corresponding values obtained at the NOAEL in the GLP toxicity studies. [redacted]

For the calculations of safety margins, the anticipated efficacious dose level was conservatively [redacted], which is the upper part of the predicted range. While liver exposure is more relevant to the nature of the prevailing preclinical target organ (the liver), plasma exposure is expected to be more relevant to the other potential AEs (e.g., renal). [redacted]

3.2.2 Rationale for Study Population

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

Part ~~2~~*2a/2b* will be conducted in nucleoside/nucleotide suppressed CHB infected patients. Only in this patient population can the pharmacodynamic effects of RO7062931 in humans be tested. The PK and safety of RO7062931 will also be evaluated in this population. The results will provide essential information for supporting the future development, such as dose-selection for a Phase II study in CHB patients.

Part 2c of the study will be conducted in NUC-suppressed or potentially treatment-naïve immune-active CHB patients, and will include both HBeAg positive and HBeAg negative patients. These patient populations are considered appropriate for trials of novel CHB therapeutics regimen, as highlighted in current guidelines (FDA 2018).

3.2.3 Rationale for Control Group

This phase I study is designed to be adequate and well-controlled. In Part 1, randomization to RO7062931 or placebo will occur in a 4:1 ratio within each of the up to 8 cohorts planned. This is considered sufficient to allow for comparisons of safety and tolerability of active to placebo both within and across cohorts.

In Part 2a, randomization to 3 doses of active or placebo will occur in a 1:1:1:1 ratio. In Part 2b, randomization to active or placebo will be 3:1 (within cohorts). The assessment of dynamic changes of HBsAg in CHB patients, will allow estimating the effect of RO7062931 over placebo. The control patients will also allow for the comparisons of safety of active with placebo.

It is not considered necessary to include controls within the cohorts of Part 2c. Part 2a and 2b have shown that placebo controls have negligible change in HBsAg levels over time. This information can be leveraged in Part 2c for interpretation of HBsAg dynamics. The safety data from Part 2c will be compared qualitatively against Part 2a and Part 2b placebo data and against well-established historical safety profiles of SoC therapies.

3.2.4 Rationale for Biomarker Assessments

RO7062931 is a GalNAc-targeted LNA-containing single stranded oligodeoxyribonucleotide, complementary to HBV genome-derived mRNA species. With this, a rapid reduction of viral parameters like HBsAg, HBeAg, but also the corresponding mRNAs, is expected. Structural and functional differences between viral genotypes can influence the severity and response to treatment of hepatitis B virus infection (Kramvis et al, 2005). Blood samples to monitor decline of viral parameters in correlation with administered dose and to establish the viral genotype will be taken at time-points, as indicated in the Schedule of Assessments tables (see Appendix 1 to *Appendix 14*).

Based on nonclinical data (and class effect [Kynamro Solution for injection 189 mg, CHMP-EMA Assessment Report 2013]) RO7062931 is considered of to be low risk for acute reactions; however, cytokines and complement activation will be measured and sentinel dosing will be implemented.

[redacted]

[redacted]

[redacted]

3.2.5 Rationale for Resistance Monitoring

Blood samples to monitor the potential for resistance emergence will be taken at time-points as indicated in the Schedule of Assessments (see Appendix 1 to *Appendix 14* and Section 4.6.1.5.4).

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events, including adverse events of special interest (see Section 5.3.1).
- Incidence of laboratory abnormalities based on hematology, blood chemistry, coagulation and urinalysis test results (see Section 4.6.1.5).
- ECGs (see Section 4.6.1.4).

- Vital signs, including blood pressure, heart rate and temperature (see Section 4.6.1.3).

3.3.2 Pharmacokinetic (PK) and Pharmacodynamic (PD) Outcome Measures

3.3.2.1 Pharmacokinetic Outcome Measures

The PK evaluations for this study are as follows:

Blood and urine samples will be collected to evaluate the RO7062931 and if applicable metabolite(s) PK, as specified in the Schedule of Assessment tables (see Appendix 1 to *Appendix 14*). Plasma and urine concentrations will be measured by specific validated methods.

The following plasma and urine PK parameters will be calculated for RO7062931 (and its metabolites, as appropriate), when possible, using non-compartmental methods:

- C_{max}: maximum plasma concentration.
- t_{max}: time to reach the maximum plasma concentration.
- $AUC_{0\text{-}inf}$: area under the plasma concentration-time curve from time zero to infinity.
- $AUC_{0\text{-}last}$: area under the plasma concentration-time curve from time zero until the last quantifiable time-point.
- Additional PK parameters may be calculated from available data including:
  - k (terminal elimination rate constant),
  - $t_{1/2}$ (terminal elimination half-life),
  - CL (total clearance)
  - V_{ss} (volume of distribution).
- Urine PK parameters may be calculated with available data including:
  - A_e - cumulative amount of drug excreted in urine over a 24hour period or over defined time periods linked to the pools of urine collected.
- In Part 2: sparse sampling for tenofovir (including tenofovir alafenamide, if approved for HBV and applicable), entecavir, adefovir and telbivudine will be made to determine patient compliance.

3.3.2.2 Pharmacodynamic Outcome Measures (Part 2 only)

In Part 2, blood samples for quantitative and qualitative determination of viral dynamic response measurements of, but not limited to, HBsAg, HBV DNA, *HBV RNA,* HBeAg, *HBcrAg*, anti-HBe, anti-HBc*,* and, anti-HBs and HBsAg/anti-HBs complex, will be collected at the time-points indicated in the Schedule of Assessment tables (see Appendix 3 to *Appendix 14*) and as detailed in Section 4.6.1.5.4.

The PD outcome measure to support the secondary objective is the change in quantitative HBsAg over time. Derived endpoints of quantitative HBsAg will include:

- Quantitative HBsAg *(qHBsAg)* (log10) and its change from baseline
- Maximum change from baseline in quantitative HBsAg across all time-points
- Rate of decrease for HBsAg at each time-point
- *Proportion of patients with undetectable qHBsAg (< 0.05 IU/mL)*

All other PD outcome measures are considered exploratory (see Section 3.3.3).

3.3.3 Exploratory Outcome Measures

Exploratory PD outcome measures:

These will include but may not be limited to HBeAg, qualitative HBsAg, anti-HBs, anti-HBe, and maintenance of HBV DNA levels less than 90IU/mL *(for Part 2c (for Part 2c lower limit of quantification [LLOQ]).*

Viral resistance monitoring will be performed in any patient who experiences viral breakthrough. Please see Section 4.6.1.5.4.

[redacted]

Exploratory safety outcome measures

[redacted]

Exploratory PK outcome measure:

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 CENTER

This is a multi-center study. Additional sites may be opened if necessary. Administrative and Contact Information, and List of Investigators are provided separately.

4.2 STUDY POPULATION

In this study, the target population consists of male and female HVs/ patients diagnosed with chronic hepatitis B infection, between the age of 18 and 65, inclusive. Study subjects must satisfy all inclusion and exclusion criteria to be enrolled into the study. Under no circumstances are subjects who enroll in this study permitted to be re-randomized to another cohort of this study.

Study subjects who drop out of the study for non-safety reasons may be replaced to ensure sufficient data to characterize the safety, tolerability, and PK and/or to make dose-escalation decisions. Study subjects who withdraw from the study due to poor tolerability or for study drug-related adverse events will not be replaced.

4.2.1 Recruitment Procedures

Study subjects will be identified for potential recruitment using sites' database, pre-screening enrollment logs, IEC/IRB approved newspaper/radio/television/Social Network Service/campus poster advertisements, mailing lists and other distributable documents, prior to consenting to take place on this study.

4.2.2 Inclusion Criteria

Study subjects must meet the below criteria for study entry.

4.2.2.1 Part 1 - Healthy volunteers only:

1. Able to participate and willing to give written informed consent and to comply with the study restrictions.
2. Healthy male and female (of non-childbearing potential) subjects. Health status is defined by absence of any active or chronic disease following a detailed medical and surgical history, concomitant drug use (including hormonal supplements), a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.
3. 18 to 65 years of age, inclusive.
4. A Body Mass Index (BMI) between 18 to 30 kg/m^2 inclusive and a body weight of at least 50 kg.

5. Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH], or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

   All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

   With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and up to 105 days after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the healthy volunteer. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

4.2.2.2 *Part 2a and Part 2b* - CHB patients only:

1. Ability and willingness of patient to provide written informed consent.
2. Adult male and female (of non-childbearing potential) patients, aged 18-65 years (inclusive).
3. A BMI between 18 to 32 kg/m^2 inclusive.
4. Chronic hepatitis B infection.
5. Positive test for HBsAg for more than 6 months prior to randomization.
6. HBsAg titer $\geq 10^3$ IU/mL at screening.
7. On entecavir, tenofovir, adefovir or telbivudine treatment for at least 6 months prior to randomization and will remain on stable treatment during the study.
8. HBV DNA $\leq$ 90 IU/mL for at least the preceding 6 months.
9. Screening laboratory values (hematology, chemistry, urinalysis) obtained up to 56 days prior to first study treatment within normal ranges, with the exception of otherwise specified criteria or judged to be not clinically significant by Principal Investigator (PI) and Medical Monitor.
10. Alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP) at screening $\leq 1.5 \times$ upper limit of normal (ULN); normal values for total bilirubin and prothrombin time (PT)/International Normalized Ratio (INR)/activated partial thromboplastin time (aPTT) tests at screening (except for patients with Gilbert's syndrome TB $\leq$ 47 μmol/L [2.75 mg/dL]).

11. 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 3, recommended cut-off for fibroscan 8.5 kPa).
12. Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH], or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

    All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

    With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and up to 105 days after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2.2.3 *Part 2c - CHB patients only:*

1. *Ability and willingness of patients to provide written informed consent.*
2. *Adult male and female patients, 18 to 65 years of age, inclusive.*
3. *A BMI between 18 to 32 kg/m^2 inclusive.*
4. *CHB infection (HBsAg-positive for ≥ 6 months).*
5. *For cohorts only enrolling NUC-suppressed CHB patients, patients must meet the following criteria:*
    a. *Patients treated with a single NUC (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate) for ≥12 months. Patients must be on the same NUC therapy for at least 3 months before screening.*
    b. *HBV DNA <LLOQ at screening and in preceding 6 months (at least one measurement >30 days prior to screening).*
    c. *ALT ≤ 2 x ULN for >6 months prior to screening and confirmed at screening. Total bilirubin within normal range at screening, except for patients with Gilbert's syndrome (TB ≤ 47 µmol/L [2.75 mg/dL]).*
6. *For cohorts only enrolling treatment-naïve and immune-active patients (e.g., Cohort 11), patients must meet the following criteria:*
    a. *HBV DNA at screening ≥2 x 10^4 IU/mL for HBeAg positive patients, or ≥2 x 10^3 IU/mL for HBeAg negative patients.*

b. *Elevated serum ALT >2 ULN to ⩽5 ULN, 2 values within 6 months, at least one of which is at screening and both results must be at least 14 days apart. Total bilirubin within normal range at screening, except for patients with Gilbert's syndrome (TB ≤ 47 µmol/L [2.75 mg/dL]).*

7. *Screening laboratory values (hematology, chemistry, urinalysis) obtained up to 28 days prior to first study treatment within normal ranges, with the exception of otherwise specified criteria or judged to be not clinically significant by PI and Medical Monitor.*
8. *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 3, recommended cut-off for fibroscan 8.5 kPa).*
9. *Women should be of non-childbearing potential. A woman is considered to be of childbearing potential if she is post-menarcheal but has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by FSH, or amenorrhea for at least 24 months if on hormone replacement therapy), and has not undergone surgical sterilization (removal of ovaries and/or uterus).*

   All males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

   With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus spermicide during the treatment period and up to 6 months after the last dose to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2.3 Exclusion Criteria

Study subjects who meet any of the below criteria will be excluded from study entry.

4.2.3.1 Part 1 - Healthy volunteers only:

1. Women who are lactating.
2. Any suspicion or history of alcohol and/or other substance abuse or dependence in the past 6 months.
3. Positive urine drug and alcohol screen (barbiturates, benzodiazepines, methadone, amphetamines, methamphetamines, opiates, cocaine, cannabinoids and alcohol), or positive cotinine test at Screening or Day −1.

4. Positive result on hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) 1 and 2.
5. Confirmed (e.g., two consecutive triplicate measurements) average systolic blood pressure (SBP) > 140 or < 90 mmHg, and diastolic blood pressure (DBP) > 90 or < 45 mmHg at Screening.
6. Confirmed (e.g., two consecutive triplicate measurements) average resting pulse rate (PR) > 90 or < 45 beats per minute (bpm) at Screening.
7. A personal history of unexplained blackouts or faints, or known risk factors for Torsade de Pointes (e.g., hypokalemia, heart failure). Clinically significant abnormal ECG, including arrhythmias or marked QT abnormalities (QTcF < 300 msec or > 450 msec at Screening).
8. ECG morphology at screening that renders measurement of QT interval imprecise (e.g., neuromuscular artifact that cannot be readily eliminated, indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves, arrhythmias, etc.).
9. Screening or baseline ECG evidence of atrial fibrillation, atrial flutter, complete right or left bundle branch block, Wolff-Parkinson-White syndrome, or cardiac pacemaker.
10. Personal or family history of congenital long QT syndrome or sudden death.
11. Any out of range findings in liver function tests *(LFTs)*, INR and renal function tests or any clinically significant abnormalities (as judged by the Investigator) in the physical examination and in the remaining laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis) at Screening and on Day-1.
12. Participation in an investigational drug or device study within 90 days prior to screening or 5 times the half-life of the investigational drug (whichever is longer).
13. Donation of blood over 500 mL within three months prior to screening.
14. Concomitant disease or condition (including allergic reactions against any drug, or multiple allergies) that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the healthy volunteers in this study.
15. Any major illness within the one month preceding the Screening visit, or any febrile illness within the two weeks preceding the screening visit.
16. Alcohol consumption of more than 2 standard drinks per day on average; 1 standard drink equals 10 grams of alcohol (for further guidance please see *Appendix 15*).
17. Hypersensitivity to the excipients of the study drug.
18. Healthy volunteers under judicial supervision, guardianship or curatorship.

4.2.3.2 *Part 2a and Part 2b* - CHB patients only:

1. Women who are lactating.
2. History or other evidence of bleeding from esophageal varices.

3. Decompensated liver disease (e.g., Child-Pugh Class B or C clinical classification [see *Appendix 16*] or clinical evidence such as ascites or varices).
4. 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, non-alcoholic steatohepatitis, etc.).
5. Documented history or other evidence of metabolic liver disease within one year of randomization.
6. Positive test for hepatitis A (IgM anti-HAV), hepatitis C, or HIV.
7. Documented history of infection with hepatitis D virus.
8. 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 Herpes simplex virus (HSV) I or HSV II.
9. History of or suspicion of hepatocellular carcinoma or alpha fetoprotein (AFP) $\geq$ 13 ng/mL at Screening.
10. 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).
11. History of clinically significant and not adequately controlled cardiovascular, endocrine, gastrointestinal, renal, ocular, pulmonary, or neurological disease.
12. Evidence of an active or suspected cancer or a history of malignancy other than adequately treated basal cell carcinoma.
13. History of having received (in the last 6 months) or currently receiving any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic corticosteroids).
14. History of organ transplantation.
15. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
16. Significant acute infection (e.g., influenza, local infection) or any other clinically significant illness within 2 weeks of randomization.
17. Clinically relevant ECG abnormalities on screening ECG including arrhythmias or marked QT abnormalities (QTcF $<$ 300 msec or $>$ 450 msec) at Screening.
18. Any of the following laboratory parameters at screening:
    a) White blood cells (WBC) $<$ 3,000 cells/ mm^3
    b) Neutrophil count $<$ 1500 cells/mm^3
    c) Platelet count $<$ 140,000 cells/mm^3
    d) aPTT $>$ 40 seconds, INR $>$ 1.2
    e) Hemoglobin (Hgb) $<$ 12 g/dL in females or $<$ 13 g/dL in males.

19. Abnormal renal function including serum creatinine > ULN or calculated creatinine clearance < 70 mL/min (using the Cockcroft Gault formula).
20. Participation in an investigational drug or device study within 30 days prior to randomization.
21. Donation or loss of blood over 500 mL within 3 months prior to starting study medication.
22. Administration of any blood product within 3 months of randomization.
23. History or evidence of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink equals 10 grams of alcohol, for further guidance please see *Appendix 15*) and/or drug abuse within one year of randomization; positive test result for drugs of abuse at Screening.
24. Patients under judicial supervision, guardianship or curatorship.
25. Medical or social conditions that would potentially interfere with the patient's ability to comply with the study visit schedule or the study assessments.

4.2.3.3 *Part 2c - CHB patients only:*

1. *Women who are lactating.*
2. *History or other evidence of bleeding from esophageal varices.*
3. *Evidence of liver cirrhosis or decompensated liver disease such as ascites, esophageal or gastric varices, splenomegaly, nodular liver, jaundice, hepatic encephalopathy, portal hypertension.*
4. *One or more of the following laboratory abnormalities at screening:*
   a) *Total serum bilirubin > ULN (exception Gilbert's disease).*
   b) *INR >1.1 ULN.*
   c) *Serum albumin <3.5 g/dL (<35g/L).*
   d) *AFP >13 ng/mL (if >ULN, hepatic imaging must exclude hepatocellular carcinoma [HCC]).*
   e) *Positive results for anti-mitochondrial antibodies (AMA >1:80), anti-nuclear antibody (ANA) (>1:80), anti–smooth muscle antibody (ASMA >1:40), anti-thyroperoxidase antibodies (a-TPO), anti-thyroglobulin, or anti-platelet antibodies*
   f) *Thyroid stimulating hormone (TSH) within normal ranges.*
   g) *Platelet count <100,000 cells/mm^3.*
   h) *Hemoglobin <12 g/dL (females) or <13 g/dL (males).*
   i) *White blood cell count <2500 cells/mm^3.*
   j) *Neutrophil count <1500 celsl/mm^3 (<1200 cell/mm^3 if considered a physiological variant in a patient of African descent).*

5. *History or other evidence of a medical condition associated with chronic liver disease other than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposure, thalassemia, nonalcoholic steatohepatitis, etc.).*
6. *History of thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests TSH.*
7. *Documented history or other evidence of metabolic liver disease within one year of randomization.*
8. *Positive test for hepatitis A (IgM anti-HAV), hepatitis C (quantitative anti-HCV), hepatitis D (total anti-HDV), hepatitis E (IgM and IgE anti-HEV), or human immunodeficiency virus (anti-HIV1/anti-HIV2).*
9. *Expected to need systemic antiviral therapy other than that provided by the study at any time during their participation in the study, with the exception or oral therapy for HSV I or HSV II.*
10. *History of significant gastrointestinal disease (including but not limited to gastric ulcers).*
11. *History of clinically significant cardiovascular, endocrine, renal, ocular, pulmonary, psychiatric, or neurological disease.*
12. *Evidence of an active or suspected cancer or a history of malignancy other than adequately treated basal cell carcinoma.*
13. *History of organ transplantation.*
14. *Participation in an investigational drug or device study within 30 days prior to screening or previous treatment with an investigational agent for HBV (6 months prior to screening).*
15. *Taking any drugs or nutrients listed in prohibited medications and prohibited food sections.*
16. *Significant acute infection (e.g., influenza, local infection) or any other clinically significant illness within 2 weeks of randomization.*
17. *ECG at screening with clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia's formula) ≥450 msec for males and ≥470 msec for females.*
18. *Abnormal renal function including serum creatinine >ULN or calculated creatinine clearance <70 mL/min (using the Cockcroft Gault formula).*
19. *Donation or loss of blood over 500 mL within 3 months prior to randomization.*
20. *Administration of any blood product within 3 months prior to randomization.*
21. *History of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1 standard drink = 10 grams of alcohol) and/or drug abuse within one year of randomization; positive test result for drugs of abuse or alcohol breath test at screening.*
22. *Subjects under judicial supervision, guardianship, or curatorship.*

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

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Part 1, Part 2a, and Part 2b are Sponsor-open, Investigator-blinded, subject-blinded. This means that the study subjects will be blinded, the Investigator(s), site staff observing the subjects will be blinded and the Sponsor will be unblinded. *Part 2c is open-label.*

In Part 1, the site pharmacist and the study drug administrator will be unblinded. For Part*s 2a and 2b*, the site Pharmacist will be unblinded. Members of the Sponsor's study team who do not have direct contact with the Investigator or study site staff will be unblinded. This does not include any CROs and any sponsor staff in direct contact with the investigators and the study sites, who will remain blinded. *Part 2c of the study is a non-randomized, non-controlled, open-label study; therefore site staff observing the patients, patients, and the Sponsor will be unblinded.*

Part 1

Ten healthy volunteers will be randomized to active or placebo treatment in each dose cohort/level in a 4:1 ratio. The randomization numbers 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 enrolled. For each dose cohort, the randomization will be designed such that of the first 2 subjects, one will receive active drug, and the other will receive placebo. The remaining 8 subjects in the cohort will be randomized such that 7 receive active drug and 1 receives placebo. The treatment allocation will be managed by the unblinded Pharmacist and will be based on the randomization assignment list. An unblinded study drug administrator will administer the drug to the subject. Drug administration of a subject will be performed in isolation of other subjects.

To allow informed recommendations or decisions regarding the dose selection in Part 1, an integrated assessment of the safety, tolerability and available pharmacokinetics and/or pharmacodynamics will be made prior to each dose decision. If required, unblinded data (individual as well as at group level) may also be presented to the Drug Safety Committee or other experts of the Sponsor.

Part 2a

Patients will be randomized to placebo or one of three active dose levels of RO7062931 in a 1:1:1:1 ratio. The randomization numbers will be generated by an IxRS (Interactive voice/web response system) according to specifications provided by the sponsor to the external randomization vendor. The Sponsor may postpone or stop enrolment of certain patient subgroups, in order to evaluate pharmacodynamic parameters in different patient subgroups. Each cohort/arm will consist of 6 patients. These cohorts will be run in parallel. The treatment allocation will be managed by the unblinded

Pharmacist and will be based on the IxRS randomization assignment. The unblinded pharmacist will fix tape to the syringes to mask any potential color difference between syringes while still allowing visualization of dose volumes.

The PK data from the first 8 patients of Part 2a (assuming 2 patients per cohort/arm), who have been randomized and have received their first dose will be reviewed by the project Clinical Pharmacologist prior to randomization of any further patients to ensure the exposure for patients is in the same range as for healthy volunteers. Should the ranges look different, dose levels for subsequent patients may be adjusted.

Part 2b

Similar to Part 1, each patient will be randomized to active treatment or placebo in each dose cohort/level in a 3:1 ratio. The randomization numbers will be generated by an IxRS (Interactive voice/web response system) according to specifications provided by the sponsor to the external randomization vendor. The Sponsor may postpone or stop enrolment of or only enroll certain patient subgroups, in order to evaluate pharmacodynamic parameters in different patient subgroups. Each cohort will be comprised of 8 patients, six patients will receive RO7062931 and two will receive placebo. The first two cohorts will be run in parallel; therefore, patients will also be randomized to a cohort. Any subsequent cohorts may be sequential or parallel. The treatment allocation will be managed by the unblinded Pharmacist and will be based on the IxRS randomization assignment. The method of tape masking as described for Part 2a will be used in Part 2b to protect the blind.

Part 2c

For Part 2c, the IxRS will be used to register patients to the open-label cohorts. Additionally, IxRS will be used to dispense RO7062931 and PEG-IFN for patients. The Sponsor may postpone or stop enrolment of, or only enroll certain patient subgroups, in order to evaluate pharmacodynamic parameters in different patient subgroups. The initial 8 patients of cohort 9 will be enrolled prior to the enrollment of the initial 8 patients in cohort 10. Either or both of these cohorts may be expanded up to a maximum of 30 patients in total. Assignment of patients at this expansion stage may be sequential or in parallel. Enrolment of subsequent cohorts 11 and 12 may be sequential or parallel.

The treatment allocation will be managed by the Pharmacist and will be based on the IxRS assignment.

The Principal Investigator(s) will receive a set of sealed treatment codes for Part 1. These may have the form of sealed envelopes or scratch codes. If the identity of the test medication needs to be known in order to manage the study subject's condition (in the case of a serious adverse event), the treatment code for that study subject may be broken. For Part*s 2a and 2b*, the Investigator(s) will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly before the code is broken, if possible. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

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. As per health authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (see Section 5.1) that are considered by the Investigator to be related to study drug.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 RO7062931 and Placebo

RO7062931 and placebo (IMP) to be used in the study will be provided by Roche.

[redacted]

[redacted]

4.4.1.2 *Standard of Care (NUC and PEG-IFN)*

As NUCs (entecavir, tenofovir alafenamide or tenofovir disoproxil fumarate) are to be used as background SoC therapies, they are classed as non-investigational medicinal product (NIMP). Please see local prescribing information for additional information.

As PEG-IFN is not licensed for use in CHB patients receiving NUC therapy, it is thus classed as an IMP.

PEG-IFN is a clear and colourless to light yellow sterile liquid provided in prefilled syringes for single use. Each prefilled syringe of 0.5 mL solution contains 180 µg peginterferon alfa-2a.

The list of excipients is as follows: sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid, and water for injections.

The packaging and labeling of PEG-IFN will be in accordance with Roche standard and local regulations. Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage. Study drug should be stored under the recommended storage conditions (2 to 8°C, protected from light). For further details, see the packaging label.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

4.4.2 Dosage, Administration and Compliance

4.4.2.1 RO7062931 and Placebo

The qualified individual responsible for dispensing the study drug will be unblinded and will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed, study subject number and initials on the study drug vial label and on the Drug Accountability Record. This individual will also record the study drug (e.g., batch number) received by each subject during the study.

SC doses will be administered at an appropriate site, for example the abdomen or upper thigh. For multiple doses, the administration site should be rotated so that the nature of any injection site reactions may be better understood (for details on dosing and dose regimen, see Section 3). All RO7062931 doses will be administered at the study clinic in

the morning by investigational staff and should be administered in the fasted state either two hours before or two hours after a morning meal. After SC administration of study drug, the Part 2 patients should remain at the site at least until the post-dose assessments are completed. The drug should be administered concomitantly with the nucleosides/nucleotides taken by the patient.

For Part 2c:
All RO7062931 administrations will be via the SC route utilizing sterile technique.RO7062931 doses will be administered SC once weekly for up to 24 weeks in Cohort 9 and for up to 48 weeks in Cohort 10. All RO7062931 doses will be administered at the study clinic in the morning by investigational staff and should be administered in the fasted state either two hours before or two hours after a morning meal.

For cohorts involving PEG-IFN, RO7062931 and PEG-IFN SC doses should be administered at different sites (e.g. left thigh and right thigh), and the administration sites should be rotated on a weekly basis between doses. This will allow to better characterize and minimize the risk of injection site reactions. For convenience, consider SC treatment administrations in the same morning as the NUC administration and PEG-IFN SC administration should be at least 1 hour after RO7062931 SC administration.

PEG-IFN administration
All PEG-IFN administrations will be administered via the SC route utilizing sterile technique. PEG-IFN at a dose of 180 µg will be administered once weekly for up to 48 weeks. PEG-IFN will be administered weekly at study clinic.

Specific guidelines for adjusting the doses of PEG-IFN for adverse event management are provided in Section 5.2.1.3. If PEG-IFN is interrupted or discontinued permanently, patients should continue treatment with RO7062931 and NUC until the end of the treatment period.

For further information on the PEG-IFN, please refer to the latest PEG-IFN Investigator Brochure.

NUC administration
NUC will be administered per local label or as per prescribing information and should be taken in the morning of RO7062931 or RO7062931 and PEG-IFN administration. NUC administration during the study, including the follow-up period, should be captured in the site documentation and eCRF. This information should include information about any missing doses during treatment and follow-up period.

For further information on the NUCs used in this study, please follow local prescribing information.

4.4.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (RO7062931*,* placebo, *and PEG-IFN*) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, to confirm the shipment condition and content. Any damaged shipments will be replaced.

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the study subject to whom the study drug was dispensed (for example, subject initials and date of birth).
- The date(s) and quantity of the study drug returned by the study subject.
- All records and drug supplies must be available for inspection by the Roche Monitor at every monitoring visit.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity [e.g., batch number] of investigational product[s] destroyed
- Quantity of investigational product[s] destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person [or company] who destroyed investigational product[s].

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4.4 Post-Trial Access to RO7062931

Currently, the Sponsor does not have any plans to provide RO7062931 to study subjects after conclusion of the study.

4.4.5 *Post-Trial Access to NUC/PEG-IFN*

NUC or PEG-IFN are marketed drugs and commercially available. No post-study medication or drug reimbursement is provided as part of this protocol. The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition.

4.5 CONCOMITANT THERAPY AND FOOD

There are no concomitant treatment restrictions at this time as no drug-drug interactions are foreseen for RO7062931. In Part 1, there are some restrictions for healthy volunteers that should be maintained.

- Any prescribed or over-the-counter (OTC) medication, vitamins, fish oils, protein powders, including herbal remedies, taken within 2 weeks prior to first study drug administration with the exception of hormone replacement therapy (HRT) which is allowed throughout the study. Paracetamol (up to 1 g per day) will be allowed.
- However, in the event that a healthy volunteer requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor.
- *Herbal therapy or substances (e.g. tea)/supplements/traditional Chinese medicines, as well as OTC drugs, may affect patient laboratory values. Abnormal values may lead to screening failures or patient withdrawal from study treatment. As such, patients at screening should be carefully questioned regarding such practices/habits and should be advised to refrain from them, if deemed necessary.*

It is unlikely that food will have an impact on the PK of RO7062931, however, for study subjects taking nucleosides/nucleotides food restrictions may apply. Therefore, it is suggested that both RO7062931 and the nucleosides/nucleotides be taken in the fasted state (2 hours before, or, 2 hours after a meal) during each clinic visit where RO7062931 is administered. Taking RO7062931 in a fasted state will apply to healthy volunteers and patients.

4.5.1 Permitted Therapy

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements used by a patient from 30 days prior to screening until the follow-up visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

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

4.5.2 Prohibited Therapy

As a general rule, no concomitant medication will be prohibited. All concomitant medications need be discussed with the Sponsor prior to enrolling study subjects.

For patients in Part 2c who take NUC or PEG-IFN during the study, please follow the prescribing information or the PEG-IFN Investigator Brochure, to guide as to whether concomitant medications are permitted or prohibited.

In case of doubt, the Sponsor may be contacted regarding potential prohibited concomitant medications, which may be allowed if the rationale is discussed, agreed and documented between the Investigator and Sponsor Medical Monitor.

4.5.3 Prohibited Food

There are no prohibited foods for either healthy volunteers or patients.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the Schedule of Assessments tables as outlined in Appendix 1 to *Appendix 14*. At time-points when several assessments coincide, the following sequence should be followed with the PK blood sample to be taken first at the nominal time-point:

- Urine collection
- Vital signs
- ECGs
- PK, viral dynamic, safety blood sampling
- Study drug administration

4.6.1.1 Medical History and Demographic Data

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

For the CHB patients, 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 nucleos(t)ide analogue resistance (if any), previous evaluations of cirrhosis, dates/outcomes of liver biopsies (if any).

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

4.6.1.2 Physical Examinations

A complete physical examination should be performed at baseline and include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

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

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in healthy volunteer/patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Body weight will be recorded at screening and during the study. Height will be recorded at the Screening visit only. BMI will be calculated at Screening.

4.6.1.3 Vital Signs

Vital signs will be obtained after the subject has been resting in a supine position for at least 10 minutes.

Blood pressure (BP; systolic and diastolic), pulse rate and body temperature (tympanic) will be recorded at the time-points specified in the SoA tables (see Appendix 1 to *Appendix 14*). Blood pressure and pulse rate will be performed in triplicate (can be as short as 20 seconds to 1-minute interval between measurements). The mean of three consecutive replicates will be used as the value for the defined time-point. Vital signs should be measured prior to blood draw. When possible, the same arm should be used for all blood pressure measurements.

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

4.6.1.4 Electrocardiograms

ECGs will be collected after the study subject has been in a supine position for at least 10 minutes prior to each ECG evaluation. At the specified time-points (see SoA tables, see Appendix 1 to *Appendix 14*), 12-lead ECGs will be obtained in triplicate, i.e., three consecutive interpretable 12-lead ECGs within a 3-5-minute interval, and recorded in the case report form (CRF). Triplicate recordings should be taken for any unscheduled ECG.

All ECG recordings must be performed using a standard digital high-quality, high-fidelity ECG machine equipped with computer-based interval measurements. Automated ECG intervals (PR [PQ], QRS, QT, QTcF [to be derived in eCRF]) and heart rate (HR) will be captured or calculated, and the changes in T-wave and U-wave morphology will be documented. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper or electronic ECG tracings must be appropriately kept by the study center and must fulfill all applicable archiving requirements. The ECG intervals and interpretation will be recorded on the eCRF or may be sent electronically. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

The following are requirements for ECG assessments:

1. Digital ECG recordings, storage and analysis.
2. Three useful recordings must be collected without artefacts, per time-point.
3. Body position should also be consistently maintained for each ECG performed. In particular, changes in HR should be avoided. The absence of any environmental distractions (television, radio, conversation) during the pre-ECG rest and the ECG recording in the clinic must be emphasized.
4. Avoid ECG recordings within 3 hours after meals (it is accepted that this is not possible after the light breakfast which is administered prior to dosing in the fed period for the relevant cohort).
5. Strictly match timing and conditions of ECG recording to baseline. Conditions to be standardized include food intake, activity level, stressors, and room temperature.
6. If possible, the same machine, brand and model, should be used for the same study subject throughout the study.
7. ECGs should be 12-lead, recorded at 25 mm/sec for at least 10 seconds.
8. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.
9. ECG machines should have periodic calibration and service records (minimum once a year).

10. If any QT/QTc values > 500 msec or increases from pre-dose on Day 1 QTc > 60 msec (as provided by the machine), the site should repeat the ECG within the next 5 minutes and notify the Sponsor. If confirmed, ECG recordings should be repeated at least hourly until two successive ECGs show QTc values below the threshold value that triggered the repeated measurement.

4.6.1.5 Laboratory Assessments

All laboratory assessments will be performed at one or more central laboratories. The subsections below provide additional details specific to the type of assessments being conducted. Applicable reference ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts.

Residual laboratory samples may be used to repeat laboratory tests in the event of a problem with the original sample as outlined in the SoA. Additionally, the residual samples may be used for exploratory HBV biomarker analyses to further understand disease biology and treatment impact. This may include, but is not limited to, analysis of viral and host response factors (DNA and/or non-DNA) to infection and treatment, development/validation of HBV assays, and immunogenicity analyses.

The collected samples will be destroyed no later than 5 years after the final closure of the clinical database, unless specified otherwise in the subsections below or unless regulatory authorities require specimens to be maintained for a longer time period. For patients who consented to optional RBR sample collection and analyses, any unused residual samples will be used for RBR specimen storage (see Section 4.6.1.5.7).

4.6.1.5.1 Safety Laboratory Assessments

Laboratory safety tests shall be collected at time-points specified in the Schedule of Assessments (see Appendix 1 to *Appendix 14*). Handling of residual samples is described in Section 4.6.1.5.

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 study subject safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

Additional blood and urine safety samples will also be collected at the time of a serious adverse event.

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

The following blood and urine samples will be collected:

- Hematology: leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).
- Blood chemistry: ALT, AST, total and indirect bilirubin, ALP, blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT) (at Screening only), *glutamate dehydrogenase (GLDH),* creatine phosphokinase (at Screening only), total protein, albumin, creatinine *and calculated creatinine clearance (using the Cockcroft Gault formula),* glomerular filtration rate (GFR) calculated *(MDRD4 method),* uric acid, cystatin c, fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, sodium, chloride, potassium, calcium, magnesium, phosphate and bicarbonate.
- Coagulation: prothrombin time (PT), International Normalized Ratio (INR), activated partial thromboplastin time (aPTT)
- Urinalysis: A mid-stream, clean catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocytes, specific gravity and pH. Urine will be also sent to the laboratory to perform microscopy to examine urine sediment for casts and cells. If there is a clinically significant positive dipstick result, (i.e., confirmed by a positive repeated sample), urine will be sent to the laboratory for culture. If there is an explanation for the positive dipstick result, e.g., menses, it should be recorded. Urine color may be evaluated from urinalysis or urine PK samples if considered necessary.
- Viral serology: Human immunodeficiency virus (HIV-1 Antibody, HIV-2 Antibody), hepatitis A virus (HAV IgM Antibody), hepatitis B virus (surface antigen, HBsAg), hepatitis C virus *(quantitative HCV antibody), hepatitis D (total HDV antibody) (Part 2c), and hepatitis E virus (IgM and IgG HEV antibodies) (Part 2c).*
- *Auto-antibodies at Screening: AMA, ANA, ASMA, a-TPO, anti-thyroglobulin, and anti-platelet antibodies (Part 2c).*
- Pregnancy test

  For all women enrolled in the study: Blood sample for determining beta-human chorionic gonadotropin (β-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.
- Alpha fetoprotein: At Screening only for HBV patients.
- *Thyroid function test: TSH (Part 2c).*

- Hormones: FSH (females only to confirm post-menopausal status, performed at Screening only).
- Drugs of abuse (urine): Cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates.
- Alcohol breath or blood test will be performed.

4.6.1.5.2 Pharmacokinetic Assessments

Blood and urine samples will be collected to evaluate the PK of RO7062931 and metabolites as specified in the SoA (see Appendix 1 to *Appendix 14*). When the PK assessment is scheduled for the same nominal time as another scheduled assessment, the PK blood samples should be taken as close as possible to the scheduled time.

Blood and urine samples will be collected from all healthy volunteer cohorts in Part 1 and from CHB patients in Part 2. The volume of each urine sample at each interval will be measured by the site staff and recorded in CRF. The actual date and time of each blood sample collection, the start and end date and time for each urine sample collection will be recorded in CRF.

Sparse sampling for tenofovir (including tenofovir alafenamide, if approved for HBV and applicable), entecavir, adefovir and telbivudine will be collected *for Parts 2a and 2b and entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate for Part 2c.*

A decision to stop PK sampling earlier or to collect more samples than currently proposed scheduled times will be based on the PK profile of the study drug. Timing of PK sampling may change based on emerging PK results after agreement with the Sponsor and the Investigator.

PK parameters will be estimated using standard non-compartmental methods for RO7062931.

PK samples will be stored for up to 2 years for the protocol assessments, unless otherwise indicated. Samples will be destroyed no later than 2 years after the date of final closure of the clinical database, unless regulatory authorities require specimens to be maintained for a longer time period. If required, the residual of the PK samples taken during the study (any time-point) can be used for additional analysis (including assay validations and immunogenicity analyses).

Additional PK samples will also be collected at the time of a serious adverse event.

Samples for laboratory tests as specified above will be sent to one or several central laboratories or to the Sponsor for analysis. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

4.6.1.5.3 Assessments for Inflammatory Markers, Autoantibodies and Anti-Drug Antibodies (ADA)

Samples for laboratory tests as specified below will be sent to one or several central laboratories or to the Sponsor for analysis. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

Handling of residual samples is described in Section 4.6.1.5.

The following separate assessments will take place in this study:

- For inflammatory markers
- For development of autoantibodies
- For development of anti-drug antibodies (ADAs)

Inflammatory Markers

Blood samples for assessing inflammatory markers will be obtained for all study subjects at pre-specified time-points (see SoA, Appendix 1 to *Appendix 14*). In addition, in case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected as close to the onset of the AE as possible. Blood samples (both planned and unscheduled) will be taken to assess: complement, CRP, ESR, gamma globulin and other inflammatory biomarkers (such as, but not limited to, IL-6, IL-8, IL12, MCP1, TNFα).

For patients in Part 2c, a baseline (Day 1, pre-dose) sample for inflammatory markers will be assessed. In case an immune AE/AE suggestive of immunological involvement occurs, the samples collected at the other time-points as well as an unscheduled sample collected as close to the onset of the AE as possible will be assessed.

Auto-antibodies

Blood samples for assessing autoantibodies will be obtained for all study subjects before dosing, at baseline (also see SoA, Appendix 1 to *Appendix 14*). In addition, in case *of* an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected as close to the onset of the AE as is possible. The panel of autoantibodies to be assessed will be: anti-nuclear antibodies, anti-ds-DNA antibodies, anti-histone antibodies, anti-ssDNA antibodies, anti-neutrophil cytoplasmic antibody, anti-cardiolipin antibodies, *and* rheumatoid factor.

ADA Assessment
Blood samples will be collected from all subjects at each time-point as specified in the SoA tables (see Appendix 1 to *Appendix 14*). All ADA blood samples *will* be collected prior to dosing of investigational drug.

4.6.1.5.4 Pharmacodynamic Assessments

During the course of the study, PD sampling time-points may be modified on the basis of emerging data to ensure the pharmacodynamics of RO7062931 can be adequately characterized.

Blood samples for pharmacodynamics assessments will be collected as indicated in the SoA tables (see Appendix 1 to *Appendix 14*). Samples for laboratory tests as specified below will be sent to one or several central laboratories or to the Sponsor for analysis. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

In Part 2c, based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for PD evaluation may be stopped at any time if the data from the samples collected does not produce useful information.

Handling of residual samples is described in Section 4.6.1.5.

HBV-Specific Viral Assessments
HBV-specific viral assessments will be performed only in patients in Part 2 of the study; also see viral dynamic outcome measures in Section 3.3.2.2. Monitoring of viral resistance will be performed in any patient that experiences breakthrough.

Commercially available assays will be used for the assessment of viral parameters when available and applicable. For the parameters that do not have suitable commercial assays, validated research type assays will be used.

Blood samples for viral dynamic data and viral genotyping will be collected.

Viral Resistance Monitoring

Blood samples will be collected at baseline (BL; Day 1 pre-dose) and throughout the study, as detailed in the SoA, to monitor for the development of drug resistance. Sequencing of the complete HBV genome will be performed for all viral resistance monitoring samples at BL if viral load is ≥ 1000 copies/mL. For patients whose BL sample contains < 1000 copies/mL and therefore, a BL sequence cannot be established, an archived sample should be provided with a reasonable effort if available in order to get a BL sequence. If a patient experiences an increase in serum HBV DNA level of more than 1log10 (10-fold) over nadir (viral breakthrough) during the treatment period or follow-up period of the study, an ad hoc (unscheduled) blood sample will be taken to confirm the breakthrough. Samples from confirmed viral breakthrough and subsequent follow-up visits will be sent for population sequencing. Other sequencing analyses (e.g., ultra deep sequencing) and phenotypic analysis may be performed in addition.

Virological breakthrough should be reported as an adverse event.

4.6.1.5.5 Clinical Genotyping

A blood sample will be taken pre-dose on Day 1 for DNA extraction from all subjects. If, however, the genetic blood sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study. [redacted]

The sample collected for DNA extraction may be used for whole exome and/or whole genome sequencing and other genetic analysis and may be sent to one or more laboratories for analysis. These assessments will be performed if safety or scientific rationales develop.

Handling of residual samples is described in Section 4.6.1.5.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.6.1.5.6 Other Assessments

A number of exploratory safety urinary kidney biomarkers will be analyzed from urine samples including but not limited to: α1-microglobulin, β2-microglobulin, and KIM-1.

[redacted]

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

Samples as specified above will be sent to one or several central laboratories or to the Sponsor for analysis. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

Handling of residual samples is described in Section 4.6.1.5.

4.6.1.5.7 Optional Samples for Research Biosample Repository

Overview of the Research Biosample Repository

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

Unused residual samples from the assessments described in Section 4.6.1.5.1 through to Section 4.6.1.5.6 will be retained as well as specimens will be collected from patients who give specific consent to participate in this optional Research Biosample Repository. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression.
- To increase knowledge and understanding of disease biology.
- To study drug 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.

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

Sample Collection
The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Leftover serum and plasma samples to assess protein biomarkers including, but not limited to proteomics.

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood for DNA extraction to assess for biomarkers, including but not limited to the following: single nucleotide polymorphisms (SNPs).

The samples collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and in Section 8.4).

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

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

Data derived from RBR specimen analysis on individual study subject 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. Patients 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 patients unless required by law.

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

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

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

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

Withdrawal from the Research Biosample Repository
Study subjects who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a study subject wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the study subject's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The study subject will be provided with instructions on how to withdraw consent after the trial is closed. A study subject's withdrawal from Study BP39405 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a study subject's withdrawal from the RBR does not constitute withdrawal from Study BP39405. Data already generated before time of withdrawal of consent to RBR will still be used.

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

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study‑specific screening tests or evaluations. Informed Consent Forms for enrolled study subjects and for study subjects who are not subsequently enrolled will be maintained at the study site.

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

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

For Part 2, documented liver biopsy or Fibroscan® or equivalent test results demonstrating chronic HBV infection with absence of cirrhosis and bridging fibrosis must be available within the 6 months. If no results are available, a Fibroscan® will be performed during screening.

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 *Part 2c and* 56 days for Part*s 2a and 2b)*. If the subject fails a second time, they will be classed as a screen failure and cannot be re-screened. Re-screening is allowed for subjects who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized within 28 days after the start of *the* screening period *for Part 1 and Part 2c or within 56 days after the start of the screening period for Part 2a and 2b*. In order to re-screen such a subject, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated if done more than 28 days *before randomization* for Part 1 and *Part 2c or more than* 56 days *before randomization* for Part*s 2a and 2b*. There is no need to repeat alpha-fetoprotein test if done for the study in central laboratory within 6 months before re-screening.

4.6.2.2 Assessments during Treatment

Under no circumstances will study subjects who enroll in *any part of* 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 SoA tables (see Appendix 1 to *Appendix 14*).

4.6.2.3 Follow-Up Assessments and Study Completion

Study subjects who complete the study or discontinue from the study early will be asked to return to the clinic after the last dose of study drug for a follow-up visit.

All follow up assessments must be performed as per SoA tables (see Appendix 1 to Appendix 14).

Adverse events should be followed as outlined in Section 5.5.

4.7 SUBJECT, STUDY AND SITE DISCONTINUATION

4.7.1 Study Subject Discontinuation

Subjects will be treated until unacceptable toxicities or withdrawal of consent.

The Investigator has the right to discontinue a study subject from RO7062931 or withdraw a study subject from the study at any time. In addition, study subjects have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following*:*

- Study subject withdrawal of consent at any time.
- Any medical condition that the investigator or Sponsor determines may jeopardize the study subject's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the study subject.

- Subject non-compliance.

4.7.1.1 Discontinuation from Study Drug

Study subjects must discontinue study drug if they experience any of the following:

- Pregnancy
- A serious adverse event (SAE) considered by the Investigator to be related to treatment with RO7062931.

Study subjects who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit and may undergo follow-up assessments. The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

Study subjects who discontinue study drug prematurely for safety reasons will not be replaced. Study subjects who discontinue study drug prematurely for non-safety reasons may be replaced. The Sponsor should be informed of subjects' discontinuations from the study or from the study drug.

Part 2: CHB Patients

Individual patients must discontinue RO7062931/placebo if they experience any of the following:

- Safety and tolerability issues, e.g., acute reactions, not tolerable and not manageable with symptomatic treatment.
- Grade 4 ALT (i.e., ≥ 10 × ULN) as defined by the Division of Acquired Immunodeficiency Syndrome (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE grading table) confirmed within 48-72 hours *(not for Part 2c)*.
- Grade 3 ALT (i.e., > 5x *to* < *10* × ULN) combined with total bilirubin > 2 × ULN (of which > 35% is direct bilirubin), or Grade 3 ALT and INR > 1.5.
- Any other confirmed (within 48-72h) Grade 4 laboratory abnormality deemed clinically significant (based on Investigator's assessment).
- Development of liver decompensation (ascites, varices, Child-Pugh Class B or C clinical classification).
- *Grade 3 renal* adverse events defined as creatinine ≥ 50% from baseline *and/or eGFR <60 ml/min/1.73 m²*.
- Development of resistance in a CHB patient is suspected if the patient experiences an increase in serum HBV DNA of > 1 log10 (10-fold) over nadir during the treatment period, i.e., virological breakthrough.
- NUC analogue discontinuation due to safety issues or resistance development.

All prematurely discontinued patients will have assessments performed at the end of treatment with RO7062931/placebo listed in the SoAs tables. If a patient discontinues study drug between study visits, he/she should be called for an unscheduled visit to have these assessments performed.

All patients who discontinued the study treatment prematurely should complete the 4-week follow-up period (starting from the date of the last dose taken) *and continue safety follow up* as per SoAs (see Appendix 1 to *Appendix 14*). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

4.7.1.2 Withdrawal from Study

Every effort should be made to obtain information on study subjects who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Study subjects will not be followed for any reason after consent has been withdrawn.

When a patient voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless patient specifically requests for these to be discarded or local laws require their immediate destruction. A patient's withdrawal from Study BP39405 does not, by itself, constitute withdrawal of specimens donated to the RBR.

Study subjects who withdraw from the study for safety reasons will not be replaced. Study subjects who withdraw from the study for other reasons may be replaced.

4.7.2 Study and Site Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to study subjects.
- Clinically significant changes in safety parameters considered to be related to RO7062931 and not considered acceptable by the Investigator and/or Sponsor.

Study subject enrollment is unsatisfactory.

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

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events (SAEs) and non-serious adverse events of special interest; 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.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- 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.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value 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 drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life-threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death).

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the study subject's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the study subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria (see Table 2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest 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 Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- *Cases of an isolated elevated ALT or AST ≥10 ULN (Section 5.2 and 5.3.5.6).*
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Severe injection site reactions
- *Grade 3 renal* adverse events defined as creatinine ≥50% from baseline *and/or eGFR <60 mL/min/1.73 m²*.

5.2 SAFETY PLAN

Measures will be taken to ensure the safety of the healthy volunteers/patients participating in this trial; in particular, the use of appropriate inclusion and exclusion criteria and close monitoring of the study subjects. HVs/ patients will be monitored by AE monitoring, vital sign monitoring, ECG monitoring, and hematology and clinical chemistry parameters.

The Investigator has the right to withdraw a HV/ patient for safety reasons at any time. Also, the Investigator and Sponsor may terminate a particular cohort or the study as whole at any time if considered warranted for safety reasons. For example, a particular cohort may be terminated in case of safety related drop-outs if the safety events were similar in nature.

5.2.1 Management of Specific Adverse Events

5.2.1.1 *Potential Drug-Induced Liver Injury (DILI)*

Wherever possible, timely confirmation (within 48 to 72 hours) of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs, and discontinuation of all study medications (RO7062931, NUC, or PEG-IFN, where applicable) must be considered.

In this study, potential DILI is defined as follows:

- *For healthy volunteers (Part 1): ALT > 3 × ULN accompanied total bilirubin > 2 × ULN*

- *For CHB patients (Part 2): ALT > 3 × baseline / ULN (whichever is higher) accompanied by total bilirubin >2 × ULN*

AND

- *No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to acute viral hepatitis, cholestasis, pre-existing hepatic disease excluding HCV/HEV or the administration of other drug(s), herbal medications, or substances known to be hepatotoxic.*

5.2.1.2 *Alanine Transaminase (ALT) Elevations*

Abrupt elevation of serum ALT above normal is known to occur spontaneously in patients with CHB during the course of disease, and/or during anti-viral therapy. Transient ALT elevations are not always harmful and may be due to:

- *The underlying disease*

- *Immune clearance of infected hepatocytes*

- *Drug-induced immune-mediated hepatitis*

- *DILI*

Isolated ALT elevations of 2-3 times the baseline value that are self-limited *may* reflect *a desirable* treatment-*related immunologic* response rather than drug toxicity. *However,* progressive increases or ALT elevations associated with increases in bilirubin *without* alkaline phosphatase *increase* should *primarily* be *considered* adverse events*, i.e. potential DILI.*

In the event of ALT elevation > 5x ULN, more frequent monitoring of liver tests should be performed based on medical judgment and other causes of ALT elevations should be investigated. For patients with ALT > 5 × ULN, the following management plan is recommended:

ALT elevations during treatment

- *Isolated ALT elevation with preserved hepatic function (e.g. no significant changes in bilirubin, INR/PT, albumin, and ALP):*
  - *Closely monitor liver function tests (LFTs) (i.e. ALT/AST, bilirubin, albumin, ALP and INR/PT):*
    - *ALT 5 to 10 x ULN: Repeat LFTs every week.*
    - *ALT >10 x ULN: Temporarily interrupt RO7062931 or RO7062931 and PEG-IFN treatment and repeat LFTs twice weekly until ALT level < 5 x ULN. Continue NUC treatment. Consider re-introducing RO7062931 or RO7062931 and PEG-IFN therapy following discussion with medical monitor based on subsequent laboratory results.*
- *ALT flare accompanied by declining liver synthetic and excretory functions (increased bilirubin >2 x ULN, or albumin decline >0.5 g/dL, or INR >1.5) or other signs of hepatic impairment (severe fatigue, nausea, vomiting, right upper quadrant pain):*
  - *RO7062931 or RO7062931 and PEG-IFN will be permanently discontinued, continue NUC treatment.*
  - *Closely monitor liver function tests:*
    - *ALT 5 to 10 x ULN: Repeat LFTs every week.*
    - *ALT >10 x ULN: Repeat LFTs twice weekly until ALT level < 5 x ULN.*
      - *Investigate the participant for potential etiologies of the laboratory changes.*
      - *If alternative reasons/diagnoses cannot explain the laboratory changes, a potential DILI will be considered.*

If ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected (see Section 4.6.1.5.4).

ALT elevations during follow-up

- *Isolated ALT elevation with preserved hepatic function:*
  - *ALT 5 to 10 x ULN: Repeat LFTs every week.*
  - *ALT >10 x ULN: Repeat LFTs twice weekly until ALT level <5 x ULN.*
- *ALT elevation accompanied by declining liver synthetic and excretory functions:*
  - *ALT 5 to 10 x ULN: Repeat LFTs and ALT/AST every week.*
  - *ALT >10 x ULN: Repeat LFTs and ALT/AST twice weekly until ALT level < 5 x ULN.*
  - *Investigate the CHB patient for potential etiologies of the laboratory changes.*
  - *If alternative reasons/diagnoses cannot explain the laboratory changes, a potentially delayed DILI will be suspected and CHB patient will be monitored accordingly.*

In participants who have not discontinued NUC therapy if ALT elevations are associated with increased HBV DNA levels, virological breakthrough will be suspected (see Section 4.6.1.5.4).

The Investigator should aim to exclude development of decompensated liver disease. Patients who develop signs of decompensated liver disease (e.g., ascites, variceal hemorrhage, Child-Pugh Class B or C clinical classification [*Appendix 16*]) should discontinue study treatment (Section 4.7.1.1). Patients who develop flares should be monitored more closely with additional unscheduled visits and laboratory assessments.

At the discretion of the Investigator, study treatment can be discontinued.

5.2.1.3 *Dose Modifications with PEG-IFN*

The intention of Part 2c of the protocol is that patients remain on PEG-IFN until the completion of the allocated treatment period. However, it is possible that some patients will encounter transient or prolonged adverse effects or abnormal laboratory values at some juncture during their participation in the trial leading to potential need for adjustment of the PEG-IFN dosage.

If severe adverse reactions or laboratory abnormalities develop during PEG-IFN therapy, the dose should be modified until the adverse reactions abate. If intolerance persists after dose adjustment, PEG-IFN therapy should be discontinued.

When dose modification of PEG-IFN is required for adverse reactions (clinical and/or laboratory), an initial dose reduction to 135 mcg (adjustment to the corresponding graduation mark for the prefilled syringes) is recommended. Dose reduction to 90 mcg (adjustment to the corresponding graduation mark for the prefilled syringes) may be needed if the adverse reaction persists or recurs. Following improvement of the adverse reaction, re-escalation of the dose may be considered. Table 1 provides guidelines for dose modifications and discontinuation of PEG-IFN for haematological laboratory abnormalities.

Table 1 PEG-IFN Hematological Dose Modifications Guidelines

Laboratory Values	*Recommended Dose*
ANC < 750 cells/mm³	*Reduce to 135 mcg*
ANC < 500 cells/mm³	*Discontinue treatment until ANC values return to more than 1000 cells/mm³. Reinstitute at 90 mcg and monitor ANC.*
Platelets < 50,000 cells/mm³	*Reduce to 90 mcg*
Platelets < 25,000 cells/mm³	*Discontinue treatment*

For patients who discontinue PEG-IFN early due to intolerability or if stopping criteria are met, then NUC and RO7062931 should be continued up to 48 weeks. The reasons for discontinuation of PEG-IFN and length of treatment duration will be recorded in the eCRF.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6. The Investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the last follow-up visit.

After the last follow-up visit, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all study subject evaluation time-points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing adverse event severity in the study *for Part 1 and Parts 2a and 2b*.

Table 2 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

For Part 2c, DAIDS toxicity grading scales (Appendix 18) will be used to assess adverse event severity.

5.3.4 Assessment of Causality of Adverse Events

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

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug.
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the study subject 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 study subjects receiving combination therapy, causality will be assessed individually for each protocol mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Injection-Site Reactions

Adverse events that occur during or after study drug administration and are judged to be local and related to the SC study drug injection should be captured as a diagnosis (e.g., “injection site reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction.") Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF.

Grading of pre-defined injection site reaction symptoms is described in *Appendix 17*. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

Other Adverse Events

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

5.3.5.2 Adverse Events Occurring Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.5 Abnormal Vital Sign Value

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

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

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

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

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

5.3.5.6 *Alanine and Aspartate Transaminases (ALT/AST) Elevations*

For Part 1:

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 *(Hy's Law)*. Therefore, investigators must report as an adverse event 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.

For Part 2:
CHB patients may have elevated baseline ALT levels without an increase in bilirubin. However, the finding of an elevated ALT 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 *or worsening of disease.* Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment- emergent ALT-> 3 × Baseline and >3x ULN value in combination with total bilirubin > 2 × ULN.
- Treatment-emergent ALT > 3 × Baseline and >3x ULN value in combination with clinical jaundice.

**For Part 2c (treatment- naïve and immune-active CHB patients), the threshold of ALT > 3 × ULN baseline will be capped at 10 × ULN.*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of chronic hepatitis B.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

5.3.5.8 Pre-Existing Medical Conditions

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

5.3.5.9 Lack of Efficacy or Worsening of Chronic Hepatitis B Infection

As this is the first study of RO7062931 in humans as well as in CHB patients and these patients are virologically suppressed, the effect on HBsAg is being explored as part of the secondary endpoints in this study. The short duration of treatment RO7062931 is not anticipated to provide the patients with therapeutic benefit, but rather to give evidence on the effect of multiple doses of RO7062931 on HBsAg.

Therefore, lack of RO7062931 efficacy in terms of changes in HBsAg does not qualify for adverse event in Part 2 of this study.

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

Virological breakthrough (Section 4.6.1.5.3), and abnormal liver function tests (as defined in Section 5.3.5.6) should be reported as adverse events. Hepatic flares should be reported as adverse events of special interest (Section 5.1.3).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
  - Planned hospitalization required by the protocol.
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The study subject has not suffered an adverse event.

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

5.3.5.11 Overdoses

Study drug *(including IMP and NIMP)* overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

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

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

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

5.4.1 Emergency Medical Contacts

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

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

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

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 5.1.2 and 5.1.3) that occur after initiation of study drug, investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the SAE Responsible within 24 hours.

In the case of electronic reporting, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Serious Adverse Event / Adverse Event of Special Interest eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the SAE 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.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female subjects of childbearing potential will not be allowed to participate in this study. Although highly unlikely, female subjects will be instructed to immediately inform the Investigator if they become pregnant during the study or within 105 days after the last dose of study drug *(Parts 2a and 2b) or within 6 months after last dose (Part 2c).* A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Study Subjects

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 105 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male study subject exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male study subject 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.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (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 5.4.2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The Investigator must report all medical device complaints to the Sponsor. The Investigator should document as much information as possible on the Medical Device Complaint including the product number and expiration date. If the medical device complaint results in an adverse event, the adverse event must be reported on the Adverse Event eCRF. If the event is serious, the Adverse Event eCRF must be completed and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as after the last follow-up visit).

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

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

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

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

- RO7062931 Investigator Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document. Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

6.1 DETERMINATION OF SAMPLE SIZE

In Part 1 of the study, the adaptive SAD part, the planned sample size of 8 active per cohort was chosen not only to allow adequate assessment of safety and tolerability but also to increase the precision of the estimates of mean PK and urinary parameters, [redacted]

Up to 80 HVs will be included in Part 1 of this study. Up to 8 cohorts of 10 HVs (8 on active and 2 on placebo per dose level) are planned but, based on the analysis of emerging PK and safety data, additional cohorts may be included or subsequent cohorts modified.

For Part*s* ~~2~~*2a and 2b* of the study, the PoM in CHB infected patients, a sample size of no more than 80 patients with CHB has been chosen (6 patients [Part 2a] and 8 patients [Part 2b] per dose cohort). It is anticipated that this sample size will allow characterization of the PK/PD (viral dynamic response) relationship, as well as safety and tolerability, in patients with CHB.

For Part 2c, approximately 16 patients will be enrolled into the initial 2 cohorts (8 patients in each cohort). If utilized, approximately 8 patients will be enrolled to each of the Cohorts 11 and 12. The sample size supports the assessment of response rate of undetectable qHBsAg at Week 24 follow-up in Cohorts 10, 11, and 12.

A sample size of 8 ensures that the associated lower 90% confidence limit is above 10%, if the observed response rate is at least 38% (i.e. at least 3/8), assuming a binomial distribution. This sample size is also considered reasonable to support the safety and tolerability objectives of all cohorts, as well as to allow characterization of the qHBsAg profiles in Cohort 9.The cohorts may be expanded up to 30 subjects if warranted by emerging PD and/or safety data. A sample size of 30 ensures that the associated lower 90% confidence limit is above 20%, if the observed response rate is at least 37% (i.e. at least 11/30).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations and discontinuations from the study will be summarized by treatment and dose level. The number of healthy volunteers or patients who were randomized, discontinued and completed the study will be summarized. Reasons for premature study withdrawal will be listed and summarized by treatment and dose level. Demographic and other baseline characteristics will be summarized with descriptive statistics.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All study subjects who have received at least one dose of the study medication, whether prematurely withdrawn from the study or not, will be included in the safety analysis.

6.3.2 Pharmacokinetic Analysis Population

Study subjects will be excluded from the pharmacokinetic analysis population 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 pharmacokinetic analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Descriptive statistics will be generated for demographics, including sex, self-reported race, ethnicity, age and for Part 2 only: baseline disease characteristics including: HBV history (duration of HBV disease, mode of infection, HBV genotype, previous HBV treatments and outcomes, occurrence of NUC resistance). Baseline viral dynamics: HBsAg, HBV DNA and HBeAg will also be summarized.

Data for study drug administration and concomitant medication will be listed. The number of subjects who were randomized, discontinued treatment period, completed treatment period, discontinued study and completed the study (including follow-up period) will be summarized.

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population.

All study subjects who receive at least one dose of study drug will be included in the safety analysis. The safety data, including AEs, ISRs, reason for withdrawal from study, laboratory data, ECG, concomitant medications, vital signs and physical examination results will be listed and summarized descriptively. Marked abnormalities will be flagged for laboratory data.

As appropriate, listings, summary tables and graphs (study subject plot and/or mean plots) will be provided for safety and tolerability assessments.

6.5.1 Adverse Events

The original terms recorded on the eCRF by the Investigator for adverse events will be standardized by the Sponsor by assigning preferred terms. Adverse events will be summarized by mapped term and appropriate thesaurus level.

AEs will be described by individual listings and frequency tables broken down by body system.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Study subject listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing. Laboratory test values will be presented by listings and descriptive summary statistics.

6.5.2.1 Standard Reference Ranges and Transformation of Data

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

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

6.5.2.2 Definition of Laboratory Abnormalities

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

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

6.5.3 Vital Signs

Vital signs data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.

6.5.4 ECG Data Analysis

ECG data will be as summary descriptive statistics for the actual values and changes from baseline will be tabulated by nominal time for HR, QRS duration, PR and QTcF. For multiple measurements taken at a nominal time-point, the average of these measurements will be used as the value at that nominal time-point in all summaries. In addition, QTcF will be categorized at each time-point as $\leq$450 msec, $>$450-480 msec, $>$480-500 msec and $>$500 msec and summarized. Similarly, a summary will be provided of the QTcF changes from baseline at each time-point categorized as $<$30 msec, 30-60 msec, and $>$60 msec. Changes of the overall ECG interpretation, T-wave and U-wave morphology will be summarized.

6.5.5 Concomitant Medications

The original terms recorded on the study subjects' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.6 PHARMACODYNAMIC ANALYSES

Pharmacodynamic parameters will be presented by listings and descriptive summary statistics separately by Part and/or cohorts.

6.6.1 Viral Dynamic Response Analyses

Summary descriptive statistics will be used to summarize the viral dynamic response outcome measure of quantitative HBsAg (log10), actual and change from baseline in quantitative HBsAg at each time-point by dose group. Rate of decrease in quantitative HBsAg will also be summarized using descriptive statistics.

Plots of quantitative HBsAg (actual and change from baseline) over time will be utilized to compare the longitudinal profiles across doses.

Mean (SD) of HBsAg (actual and change) will be calculated for each dose level and plotted on one plot, different line types and symbols used to differentiate the dose levels, In addition, individual patient data will be plotted over time, one plot for each dose level.

Further exploration may include plots of quantitative HBsAg over time, grouped by baseline characteristics and/or demographics of interest.

All other exploratory viral dynamic responses will be listed by time-points as a minimum.

Further exploration of these exploratory responses for potential treatment effects may include longitudinal graphs and/or summaries.

6.6.2 PK/Viral Dynamic Response Analyses

The relationship between RO7062931 and dose, and metabolite(s) and dose if applicable, and the change of HBsAg at each time-point and rate of decrease will be explored by graphical analysis. The relationship between RO7062931 PK and urinary parameters and HBsAg will also be explored by graphical analysis. Assuming a monotonic relationship between HBsAg decrease and dose/plasma RO7062931, an appropriate exposure/dose-response model may be fitted to the data from Part 2a. This model may be used to guide dose selection for Part 2b*, and will be further developed with data from Parts 2b and 2c*.

6.6.3 *Efficacy Analyses*

The proportion of patients with undetectable qHBsAg and associated 95% binomial confidence intervals will be calculated at 24 week after the end of treatment. Patients with missing HBsAg measures at 24 weeks visit after the end of treatment and thereafter will be treated as non-responders.

6.7 PHARMACOKINETIC ANALYSES

Non-compartmental analysis using WinNonlin software will be used to calculate PK parameters where appropriate. Summary descriptive statistics of plasma PK parameters including C_{max}, T_{max}, AUC_{inf}, AUC_{last}, and $t_{1/2}$ for RO7062931 and any metabolites when available will be presented by cohort/treatment arm including mean, standard deviation (SD), coefficient of variation (CV), medians and ranges. Note: the geometric *or arithmetic* mean and associated CV% will be used to describe C_{max}, AUC_{inf}, AUC_{last} *and* $t_{1/2}$. *Median values* will be used to describe T_{max}. Where appropriate, data may be pooled and analyzed, for example, all single dose data may be pooled. Listings, summary tables and graphs (individual plots and/or mean plots) by treatment group will be provided. Descriptive statistics of urine PK parameters for RO7062931 and any metabolites will be presented, where available. PK and PD data from this study may be used to develop a population PK/PD model.

Where appropriate, listings and summary tables of nucleoside/nucleotide-analogues, tenofovir, tenofovir, alafenamide, entecavir, adefovir, or telbivudine concentrations will be provided based on the sparse sampling throughout the study.

[redacted]

6.8 EXPLORATORY ANALYSES

6.8.1 Liver and Kidney Biomarker Data

The exploratory safety parameters (see Section 4.6.1.5.6), will be explored graphically. Plots will include longitudinal plots for both actual result and change from baseline. Longitudinal plots will include individual subject responses by dose, as well as mean/median plots. Box and whisker plots may also be used to detect outliers.

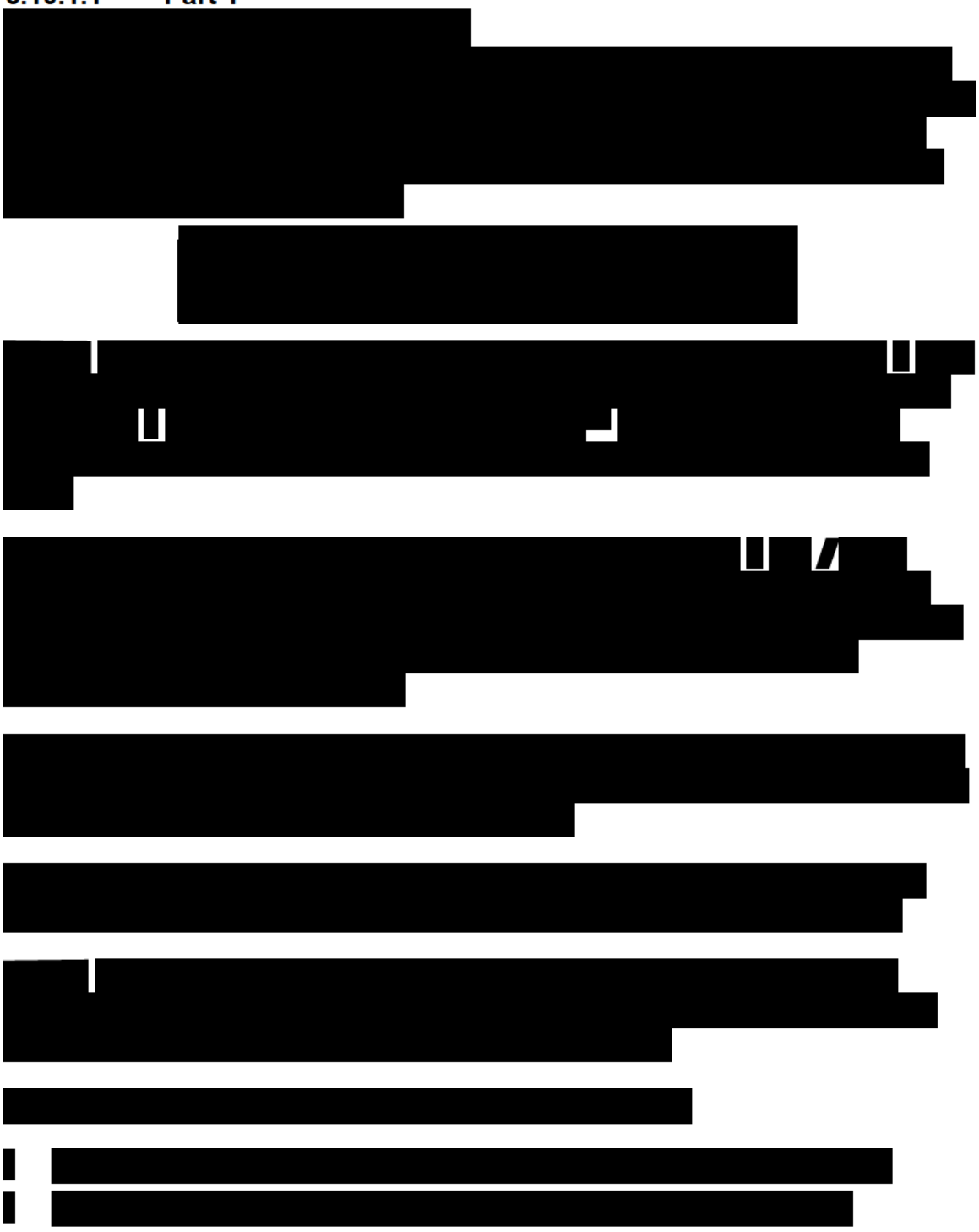
6.9 INFLAMMATORY MARKERS, AUTOANTIBODIES AND ADA DATA

At minimum, any data that is collected as detailed in Section 4.6.1.5.3, and is available at the time of database closure will be listed and summarized using descriptive statistics. Data may also be explored graphically.

6.10 ANALYSIS TO SUPPORT DOSE-SELECTION

Bayesian adaptive methodology will be explored to help guide selection of doses and dosing regimen to be studies in Part 1 and Part 2b of this study. This methodology is exploratory and considered as supporting information only. Clinical judgment will always take precedence in making the final decisions.

6.10.1.1 Part 1



The aim of such a dual endpoint approach would be to estimate an optimal dose level which represents an optimal trade-off between safety and biomarker response.

6.10.1.2 Part 2b Dose Selection: First Two Cohorts

A repeated measures dose-response model will be fitted to the data observed in Part 2a to model the relationship between quantitative HBsAg decline over time. The dose selected to be studied in different dosing regimens in the first two cohorts of Part 2b will be the lowest dose that yields the greatest decline at any time-point. Furthermore, a dual endpoint methodology described above for Part 1, modeling the quantitative HBsAg decline simultaneously with DLE in order to select a dose that maximizes the PD effect (HBsAg decline) whilst controlling on safety (DLE) will also be explored.

The shape of the dose-response observed in Part 2a would determine the function that would be used to parameterize the HBsAg decline. The PD data and the safety data from Part 2a would be used to specify the priors.

6.10.1.3 Part 2b Dose/ Regimen Selection: Exploratory Cohorts

A response-adaptive approach will be explored to help guide the selection of the doses to be studied in the exploratory part of Part 2b using optimization criteria. Criterion that optimizes the dose-response parameters (D-optimality) as well as criterion that optimizes the target dose (TD-optimality) will be explored.

The HBsAg decline at Day 29 will be modelled against cumulative dose using the most appropriate dose-response model. These parameter estimates would then be used as initial parameters for model selection. The efficiency of a set of models, where the doses and dose regimens to be further explored in the exploratory part of Part 2b are varied, will be compared using the R function (optDesign) within the (dose-finding) package (Bornkamp et al 2016).

6.11 *INTERIM ANALYSES*

No interim analysis is planned for Part 1s 2a, and 2b of this study.

In Part 2c, administrative interim analyses will be conducted at Weeks 12 and 24 for the initial 8 enrolled in both Cohorts 9 and 10. Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional administrative interim PD analyses. The decision to conduct additional interim analyses and the timing of the analyses will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the Electronic Data Capture (EDC) system.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the Investigator.

The Sponsor will produce a Data Handling Manual and a Data Management Plan that describes the quality checking to be performed on the data. Central laboratory data and electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an on line EDC system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each study subjects enrolled, an eCRF must be completed and electronically signed by the Principal Investigator or authorized delegate from the study staff. If a study subject withdraws from the study, the reason must be noted on the eCRF. If a study subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor/CRO in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor/CRO and should be handled in accordance with instructions from the Sponsor/CRO.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient 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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after 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 of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms or pregnant partner form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local Health Authority and IRB/EC. 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.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit a Development Safety Update Report (DSUR) once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an Institutional Review Board (IRB). This board must operate in accordance with the current Federal Regulations. The Sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments /modifications are made to the protocol. Roche shall also submit an IND Annual Report to FDA according to local regulatory requirements and timelines.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' 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.

9.3 ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor is responsible for the study management, data management, statistical analysis and medical writing for the clinical study report.

The Sponsor is also responsible for managing CROs, the IxRS vendor and central laboratories used in the study.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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 prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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

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

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

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

9.5 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

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[redacted]

Appendix 1
Schedule of Assessments – Part 1, SAD, Main Table

Period	Screening	Period 1								Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-28 to D-2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 15	Day 29	Day 85[e]
Time Relative (h)	***	***	0	24	48	72	96	120	168	336	672	2016
Visit Window	notime									+/-1	+/-2	+/-7
Assessments												
Informed Consent	X											
Eligibility	X	X										
Demography	X											
Medical History	X											
Physical Examination[h]	X	X							X	X	X	X
Vital Signs	X	X	5	X	X	X	X	X	X	X	X	X
ECG-12 lead	X	X	5	X					X	X	X	X
Hematology[a]	X	X		X					X	X	X	X
Blood Chemistry[a]	X	X		X					X	X	X	X
Urinalysis[a]	X	X		X					X	X	X	X
Serology	X											
Coagulation[a]	X	X		X					X	X	X	X
Inflammatory Markers[g]			3	X					X			
Autoantibodies[j]			X[d]							X	X	X
ADA[f]			X[d]							X	X	X
Urine Kidney Biomarkers			X[d]	X	X				X		X	X
Blood Liver Biomarker		X		X					X	X	X	X
Pregnancy Test[b]	X	X									X	X
FSH[c]	X											
Substance Use	X	X										
Administration of Study Medication			X									
PK Blood Sampling[a]			12	3	X	X	X	X	X			
Urine PK Sample			4[k]	X[k]								
Clinical Genotyping			X[i]									
Admission		X										
Discharge					X							
Ambulatory Visit	X					X	X	X	X	X	X	X
Randomisation			X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 1
Schedule of Assessments – Part 1, SAD, Main Table (cont.)

a) Blood sample for PK and safety lab assessment will be collected in case of a SAE or at times of early termination.

b) Blood beta-human chorionic gonadotropin (β-HCG) for pregnancy test at screening, urine on all other occasions.

c) FSH only for females and to confirm post-menopausal status.

d) Pre-dose.

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

f) ADA samples will be stored and will only be analyzed in case an immune driven AE/AE suggestive of immunological involvement occurs, or in case of an atypical PK result.

g) In case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed.

h) Complete physical examination is required at Screening and Day − 1. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator.

i) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

j) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

k) Urine collection periods [0-4], [4-8], [8-12] and [12-24] hours post-dose.

Appendix 2
Schedule of Assessments – Part 1, SAD, Detailed Table

Period	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	Inflammatory Markers	Autoantibodies	ADA	Urine Kidney Biomarkers	Blood Liver Biomarker	PK Blood Sampling	Urine PK Sample[a]
Screening	D-28 to D-2		X	X							
Period 1	Day -1		X	X					X		
	Day 1	Predose	X	X	X	X	X	X		X	
		0									X
		0.25								X	
		0.5								X	
		1	X	X						X	
		1.5								X	
		2								X	
		3			X					X	
		4	X	X						X	X
		6								X	
		8	X	X						X	X
		12	X	X	X					X	X
		18								X	
	Day 2	24	X	X	X			X	X	X	X
		30								X	
		36								X	
	Day 3	48	X					X		X	
	Day 4	72	X							X	
	Day 5	96	X							X	
	Day 6	120	X							X	
	Day 8	168	X	X	X			X	X	X	
Follow Up Visit	Day 15		X	X		X	X		X		
	Day 29		X	X		X	X	X	X		
	Day 85		X	X		X	X	X	X		

a) Urine collection periods [0-4], [4-8], [8-12] and [12-24] hours post-dose.

Appendix 3
Schedule of Assessments – Part 2a, PoM (2 Doses Q1M), Main Table

Period	Screening	Period 1								Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30		Day 36	Day 43	Day 50	Day 57	Day 85	Day 113[h]
Time Relative (h)	***	***	0	24	168	336	504	672	696	***	840	1008	1176	1344	2016	2688
Visit Window	notime										+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments																
Informed Consent	X															
Eligibility	X	X														
Demography	X															
Medical History	X															
Fibroscan®[a]	X															
Physical Examination[k]	X	X	X		X	X	X	X		X	X	X	X	X	X	X
Vital Signs	X	X	4	X	X	X	X	4	X	X	X	X	X	X	X	X
ECG-12 lead	X	X	4	X	X			4	X	X		X		X	X	X
Hematology[d]	X	X		X	X	X		X[b]		X	X	X		X	X	X
Blood Chemistry[d]	X	X		X	X	X		X[b]		X	X	X		X	X	X
Urinalysis[d]	X	X		X	X	X		X[b]		X	X	X		X	X	X
Serology	X															
Coagulation[d]	X	X		X	X	X		X[b]		X	X	X		X	X	X
Inflammatory Markers[j]			3	X				2	X							
Autoantibodies[m]			X[b]			X		X[b]						X	X	X
ADA[i]			X[b]			X		X[b]						X	X	X
Alpha fetoprotein	X															
RBR DNA			X[b]													
Urine Kidney Biomarkers			X[b]	X	X			X[b]	X	X	X			X	X	X
Blood Liver Biomarker		X		X	X	X		X[b]		X	X			X	X	X
Pregnancy Test[f]	X	X								X				X	X	X
FSH[g]	X															
Substance Use	X	X														
Administration of Study Medication			X					X								
PK Blood Sample[d]			7	X	X	X	X	7	X	X	X	X	X	X	X	X
Urine PK Sample			2													

Appendix 3
Schedule of Assessments – Part 2a, PoM (2 Doses Q1M), Main Table (cont.)

Period	Screening	Period 1								Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30		Day 36	Day 43	Day 50	Day 57	Day 85	Day 113[h]
Time Relative (h)	***	***	0	24	168	336	504	672	696	***	840	1008	1176	1344	2016	2688
Visit Window	notime										+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments																
NUC PK Sample			2					2								
HBsAg Quantitative	X	X		X	X	X	X	X[b]	X	X	X	X	X	X	X	X
HBsAg, HBeAg Qualitative, HBcAg; HBsAg/Anti-HBs Complex; Anti HBe/AntiHBs/Anti HBc*	X		X[b]		X	X	X	X[b]	X	X		X		X	X	X
Viral Genotypes			X[b]													
HBV DNA, HBV TNA, Viral Resistance Monitoring*	X		X[b]		X	X	X	X[b]	X	X		X		X	X	X
Clinical Genotyping			X[l]													
Admission[c]		X						X								
Discharge[c]				X					X							
Ambulatory Visit	X				X	X	X			X	X	X	X	X	X	X
Randomisation		X	X													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) For those patients who do not have a liver biopsy, Fibroscan® or equivalent test within the past 6 months prior to Screening

b) Pre-dose.

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

d) Blood sample for RO7062931 PK and safety lab assessment will also be collected in the event of SAE.

e) Discontinuation visit: in case of early termination, a patient should be called for this visit and assessments should be performed as listed.

f) Blood beta-human chorionic gonadotropin (β-HCG) for pregnancy test at screening, urine on all other occasions.

g) FSH only for females and to confirm post-menopausal status.

h) If necessary, the patients may be asked to return for additional follow-up visits.

Appendix 3
Schedule of Assessments – Part 2a, PoM (2 Doses Q1M), Main Table (cont.)

i) ADA samples will be stored and will only be analyzed in case an auto-immune driven AE/AE suggestive of auto-immunological involvement occurs or in case of an atypical PK result.

j) In case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed.

k) Complete physical examination is required at screening and Day −1. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator.

l) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

m) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

* Keep left over sample for patients participating in the RBR program.

Appendix 4
Schedule of Assessments – Part 2a, PoM (2 Doses Q1M), Detailed Table

Period	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	Inflammatory Markers	Autoantibodies	ADA	Urine Kidney Biomarkers	Blood Liver Biomarker	PK Blood Sample	Urine PK Sample[b]	NUC PK Sample	HBsAg Quantitative	HBsAg, HBeAg Qualitative, HBcAg HBsAg/Anti-HBs Complex Anti HBe/AntiHBs/Anti HBc	HBV DNA, HBV TNA, Viral Resistance Monitoring
Screening	D-56 to D-2		x	x									x	x	x
Period 1	Day -1		x	x					x				x		
	Day 1	Predose	x	x	x	x	x	x		x		x		x	x
		0									x				
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		3			x										
		4	x	x						x	x				
		6								x					
		8	x	x	x					x					
	Day 2	24	x	x	x			x	x	x			x		
	Day 8		x	x				x	x	x			x	x	x
	Day 15		x			x	x		x	x			x	x	x
	Day 22		x							x			x	x	x
	Day 29	Predose	x	x	x	x	x	x	x	x		x	x	x	x
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		4	x	x	x					x					
		6								x					
		8	x	x						x					
	Day 30	24	x	x	x			x		x			x	x	x
Discontinuation			x	x				x	x	x			x	x	x
Follow Up Visit	Day 36		x					x	x	x			x		
	Day 43		x	x						x			x	x	x
	Day 50		x							x			x		
	Day 57		x	x		x	x	x	x	x			x	x	x
	Day 85		x	x		x	x	x	x	x			x	x	x
	Day 113		x	x		x	x	x	x	x			x	x	x

a) One sample to be taken at any point between 2-4 hours post-dose.

b) Urine collection periods [0-4] and [4-8] hours post-dose.

Appendix 5
Schedule of Assessments – Part 2b, PoM (3 Doses Q2W), Main Table

Period	Screening	Period 1								Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30		Day 36	Day 43	Day 50	Day 57	Day 85	Day 113[h]
Time Relative (h)	***	***	0	24	168	336	504	672	696	***	840	1008	1176	1344	2016	2688
Visit Window	notime										+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments																
Informed Consent	X															
Eligibility	X	X														
Demography	X															
Medical History	X															
Fibroscan®[a]	X															
Physical Examination[k]	X	X	X		X	X	X	X		X	X	X	X	X	X	X
Vital Signs	X	X	4	X	X	2	X	4	X	X	X	X	X	X	X	X
ECG-12 lead	X	X	4	X	X	X		4	X	X		X		X	X	X
Hematology[d]	X	X		X	X	X[b]	X	X[b]		X	X	X		X	X	X
Blood Chemistry[d]	X	X		X	X	X[b]	X	X[b]		X	X	X		X	X	X
Urinalysis[d]	X	X		X	X	X[b]	X	X[b]		X	X	X		X	X	X
Serology	X															
Coagulation[d]	X	X		X	X	X[b]	X	X[b]		X	X	X		X	X	X
Inflammatory Markers[j]			3	X		2		2	X							
Autoantibodies[m]			X[b]			X[b]		X[b]						X	X	X
ADA[i]			X[b]			X[b]		X[b]						X	X	X
Alpha fetoprotein	X															
RBR DNA			X[b]													
Urine Kidney Biomarkers			X[b]	X	X	X[b]	X	X[b]	X	X	X			X	X	X
Blood Liver Biomarker		X		X	X	X[b]	X	X[b]		X	X			X	X	X
Pregnancy Test[f]	X	X								X				X	X	X
FSH[g]	X															
Substance Use	X	X														
Administration of Study Medication			X			X		X								
PK Blood Sample[d]			7	X	X	2	X	7	X	X	X	X	X	X	X	X
Urine PK Sample			2													

Appendix 5
Schedule of Assessments – Part 2b, PoM (3 Doses Q2W), Main Table (cont.)

Period	Screening	Period 1								Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30		Day 36	Day 43	Day 50	Day 57	Day 85	Day 113[h]
Time Relative (h)	***	***	0	24	168	336	504	672	696	***	840	1008	1176	1344	2016	2688
Visit Window	notime										+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments																
NUC PK Sample			2					2								
HBsAg Quantitative	X	X		X	X	X[b]	X	X[b]		X	X	X	X	X	X	X
HBsAg, HBeAg Qualitative, HBcAg; HBsAg/Anti-HBs Complex; Anti HBe/AntiHBs/Anti HBc*	X		X[b]		X	X[b]	X	X[b]	X	X		X		X	X	X
Viral Genotypes			X[b]													
HBV DNA, HBV TNA, Viral Resistance Monitoring*	X		X[b]		X	X[b]	X	X[b]	X	X		X		X	X	X
Clinical Genotyping			X[l]													
Admission[c]		X						X								
Discharge[c]				X					X							
Ambulatory Visit	X				X	X	X			X	X	X	X	X	X	X
Randomisation		X	X													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) For those patients who do not have a liver biopsy, Fibroscan® or equivalent test within the past 6 months from Screening.

b) Pre-dose.

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

d) Blood sample for RO7062931 PK and safety lab assessment will also be collected in the event of SAE.

e) Discontinuation visit: in case of early termination, a patient should be called for this visit and assessments should be performed as listed.

f) Blood beta-human chorionic gonadotropin (β-HCG) for pregnancy test at screening, urine on all other occasions.

g) FSH only for females and to confirm post-menopausal status.

h) If necessary, the patients may be asked to return for additional follow-up visits.

Appendix 5
Schedule of Assessments – Part 2b, PoM (3 Doses Q2W), Main Table (cont.)

i) ADA samples will be stored and will only be analyzed in case an auto-immune driven AE/AE suggestive of auto-immunological involvement occurs or in case of an atypical PK result.

j) In case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed.

k) Complete physical examination is required at screening and Day − 1. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator.

l) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

m) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

* Keep left-over sample for patients participating in the RBR program.

Appendix 6
Schedule of Assessments – Part 2b, PoM (3 Doses Q2W), Detailed Table

Period	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	Inflammatory Markers	Autoantibodies	ADA	Urine Kidney Biomarkers	Blood Liver Biomarker	PK Blood Sample	Urine PK Sample[b]	NUC PK Sample	HBsAg Quantitative	HBsAg, HBeAg Qualitative, HBcAg HBsAg/Anti-HBs Complex Anti HBe/AntiHBs/Anti HBc	HBV DNA, HBV TNA, Viral Resistance Monitoring
Screening	D-56 to D-2		x	x									x	x	x
Period 1	Day -1		x	x					x				x		
	Day 1	Predose	x	x	x	x	x	x		x		x		x	x
		0									x				
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		3			x										
		4	x	x						x	x				
		6								x					
		8	x	x	x					x					
	Day 2	24	x	x	x			x	x	x			x		
	Day 8		x	x				x	x	x			x	x	x
	Day 15	Predose	x	x	x	x	x	x	x	x			x	x	x
		2	x		x					x					
	Day 22		x					x	x	x			x	x	x
	Day 29	Predose	x	x	x	x	x	x	x	x		x	x	x	x
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		4	x	x	x					x					
		6								x					
		8	x	x						x					
	Day 30	24	x	x	x			x		x				x	x
Discontinuation			x	x				x	x	x			x	x	x
Follow Up Visit	Day 36		x					x	x	x			x		
	Day 43		x	x						x			x	x	x
	Day 50		x							x			x		
	Day 57		x	x		x	x	x	x	x			x	x	x
	Day 85		x	x		x	x	x	x	x			x	x	x
	Day 113		x	x		x	x	x	x	x			x	x	x

a) One sample to be taken at any point between 2-4 hours post-dose.

b) Urine collection periods [0-4] and [4-8] hours post-dose.

Appendix 7
Schedule of Assessments – Part 2b, PoM (4 Doses QW), Main Table

Period	Screening	Period 1							Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 23		Day 29	Day 36	Day 43	Day 50	Day 78	Day 106[h]
Time Relative (h)	***	***	0	24	168	336	504	528	***	672	840	1008	1176	1848	2520
Visit Window	notime									+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments															
Informed Consent	X														
Eligibility	X	X													
Demography	X														
Medical History	X														
Fibroscan®[a]	X														
Physical Examination[k]	X	X	X		X	X	X		X	X	X	X	X	X	X
Vital Signs	X	X	4	X	2	2	4	X	X	X	X	X	X	X	X
ECG-12 lead	X	X	4	X	X	X	4	X	X		X		X	X	X
Hematology[d]	X	X		X	X[b]	X[b]	X[b]		X	X	X		X	X	X
Blood Chemistry[d]	X	X		X	X[b]	X[b]	X[b]		X	X	X		X	X	X
Urinalysis[d]	X	X		X	X[b]	X[b]	X[b]		X	X	X		X	X	X
Serology	X														
Coagulation[d]	X	X		X	X[b]	X[b]	X[b]		X	X	X		X	X	X
Inflammatory Markers[j]			3	X	2	2	2	X							
Autoantibodies[m]			X[b]			X[b]	X[b]						X	X	X
ADA[i]			X[b]			X[b]	X[b]						X	X	X
Alpha fetoprotein	X														
RBR DNA			X[b]												
Urine Kidney Biomarkers			X[b]	X	X[b]	X[b]	X[b]	X	X	X			X	X	X
Blood Liver Biomarker		X		X	X[b]	X[b]	X[b]		X	X			X	X	X
Pregnancy Test[f]	X	X							X				X	X	X
FSH[g]	X														
Substance Use	X	X													
Administration of Study Medication			X		X	X	X								
PK Blood Sample[d]			7	X	2	2	7	X	X	X	X	X	X	X	X
Urine PK Sample			2				2								

Appendix 7
Schedule of Assessments – Part 2b, PoM (4 Doses QW), Main Table (cont.)

Period	Screening	Period 1							Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 23		Day 29	Day 36	Day 43	Day 50	Day 78	Day 106[h]
Time Relative (h)	***	***	0	24	168	336	504	528	***	672	840	1008	1176	1848	2520
Visit Window	notime									+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments															
NUC PK Sample			2				2								
HBsAg Quantitative	X	X		X	X[b]	X[b]	X[b]		X	X	X	X	X	X	X
HBsAg, HBeAg Qualitative, HBcAg; HBsAg/Anti-HBs Complex; Anti HBe/AntiHBs/Anti HBc[*]	X		X[b]		X[b]	X[b]	X[b]		X		X		X	X	X
Viral Genotypes			X[b]												
HBV DNA, HBV TNA, Viral Resistance Monitoring[*]	X		X[b]		X[b]	X[b]	X[b]		X		X		X	X	X
Clinical Genotyping			X[l]												
Admission[c]		X					X								
Discharge[c]				X				X							
Ambulatory Visit	X				X	X			X	X	X	X	X	X	X
Randomisation		X	X												
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 7
Schedule of Assessments – Part 2b, PoM (4 Doses QW), Main Table (cont.)

a) For those patients who do not have a liver biopsy, Fibroscan® or equivalent test within past 6 months from Screening.

b) Pre-dose.

c) Optional overnight stay in the clinic: On Day -1, Day 1 and Day 22 patients can either stay overnight in the clinic or can be discharged after completion of the 8 hours post-dose assessments and return the next morning for the subsequent assessments, at the Investigator's discretion.

d) Blood sample for PK and safety lab assessment will be collected at the event of SAE.

e) Discontinuation visit: in case of early termination, a patient should be called for this visit and assessments should be performed as listed.

f) Blood beta-human chorionic gonadotropin (ß-HCG) for pregnancy test at Screening, urine on all other occasions.

g) FSH only for females and to confirm post-menopausal status.

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

i) ADA samples will be stored and will only be analyzed in case an immune driven AE/AE suggestive of immunological, anti-drug, involvement occurs or in case of an atypical PK result.

j) In case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed.

k) Complete physical examination, is required at screening and Day -1. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator.

l) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

m) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

* Keep left over sample for patients participating in the RBR program.

Appendix 8
Schedule of Assessments – Part 2b, PoM (4 Doses QW), Detailed Table

Period	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	Inflammatory Markers	Autoantibodies	ADA	Urine Kidney Biomarkers	Blood Liver Biomarker	PK Blood Sample	Urine PK Sample[b]	NUC PK Sample	HBsAg Quantitative	HBsAg, HBeAg Qualitative, HBcAg; HBsAg/Anti-HBs Complex; Anti HBe/AntiHBs/Anti HBc	HBV DNA, HBV TNA, Viral Resistance Monitoring
Screening	D-56 to D-2		x	x									x	x	x
Period 1	Day -1		x	x					x				x		
	Day 1	Predose	x	x	x	x	x	x		x		x		x	x
		0									x				
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		3			x										
		4	x	x						x	x				
		6								x					
		8	x	x	x					x					
	Day 2	24	x	x	x			x	x	x			x		
	Day 8	Predose	x	x	x			x	x	x			x	x	x
		2	x		x					x					
	Day 15	Predose	x	x	x	x	x	x	x	x			x	x	x
		2	x		x					x					
	Day 22	Predose	x	x	x	x	x	x	x	x		x	x	x	x
		0									x				
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		4	x	x	x					x	x				
		6								x					
		8	x	x						x					
	Day 23	24	x	x	x			x		x					
Discontinuation			x	x				x	x	x			x	x	x
Follow Up Visit	Day 29		x					x	x	x			x		
	Day 36		x	x						x			x	x	x
	Day 43		x							x			x		
	Day 50		x	x		x	x	x	x	x			x	x	x
	Day 78		x	x		x	x	x	x	x			x	x	x
	Day 106		x	x		x	x	x	x	x			x	x	x

a) One sample to be taken at any point between 2-4 hours post-dose.

b) Urine collection periods [0-4] and [4-8] hours post-dose.

Appendix 9
Schedule of Assessments – Part 2b, PoM (5 Doses QW), Main Table

Period	Screening	Period 1								Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30		Day 36	Day 43	Day 50	Day 57	Day 85	Day 113[h]
Time Relative (h)	***	***	0	24	168	336	504	672	696	***	840	1008	1176	1344	2016	2688
Visit Window	notime										+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments																
Informed Consent	X															
Eligibility	X	X														
Demography	X															
Medical History	X															
Fibroscan®[a]	X															
Physical Examination[k]	X	X	X		X	X	X	X		X	X	X	X	X	X	X
Vital Signs	X	X	4	X	2	2	2	4	X	X	X	X	X	X	X	X
ECG-12 lead	X	X	4	X	X	X	X	4	X	X		X		X	X	X
Hematology[d]	X	X		X	X[b]	X[b]	X[b]	X[b]		X	X	X		X	X	X
Blood Chemistry[d]	X	X		X	X[b]	X[b]	X[b]	X[b]		X	X	X		X	X	X
Urinalysis[d]	X	X		X	X[b]	X[b]	X[b]	X[b]		X	X	X		X	X	X
Serology	X															
Coagulation[d]	X	X		X	X[b]	X[b]	X[b]	X[b]		X	X	X		X	X	X
Inflammatory Markers[j]			3	X	2	2	2	2	X							
Autoantibodies[m]			X[b]			X[b]		X[b]						X	X	X
ADA[i]			X[b]			X[b]		X[b]						X	X	X
Alpha fetoprotein	X															
RBR DNA			X[b]													
Urine Kidney Biomarkers			X[b]	X	X[b]	X[b]	X[b]	X[b]	X	X	X			X	X	X
Blood Liver Biomarker		X		X	X[b]	X[b]	X[b]	X[b]		X	X			X	X	X
Pregnancy Test[f]	X	X								X				X	X	X
FSH[g]	X															
Substance Use	X	X														
Administration of Study Medication			X		X	X	X	X								
PK Blood Sample[d]			7	X	2	2	2	7	X	X	X	X	X	X	X	X
Urine PK Sample			2													

Appendix 9
Schedule of Assessments – Part 2b, PoM (5 Doses QW), Main Table (cont.)

Period	Screening	Period 1								Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit
Day	D-56 to D-2	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30		Day 36	Day 43	Day 50	Day 57	Day 85	Day 113[h]
Time Relative (h)	***	***	0	24	168	336	504	672	696	***	840	1008	1176	1344	2016	2688
Visit Window	notime										+/-1	+/-1	+/-1	+/-2	+/-7	+/-7
Assessments																
NUC PK Sample			2					2								
HBsAg Quantitative	X	X		X	X[b]	X[b]	X[b]	X[b]		X	X	X	X	X	X	X
HBsAg, HBeAg Qualitative, HBcAg; HBsAg/Anti-HBs Complex; Anti HBe/AntiHBs/Anti HBc[*]	X		X[b]		X[b]	X[b]	X[b]	X[b]		X		X		X	X	X
Viral Genotypes			X[b]													
HBV DNA, HBV TNA, Viral Resistance Monitoring[*]	X		X[b]		X[b]	X[b]	X[b]	X[b]		X		X		X	X	X
Clinical Genotyping			X[l]													
Admission[c]		X						X								
Discharge[c]				X					X							
Ambulatory Visit	X				X	X	X			X	X	X	X	X	X	X
Randomisation		X	X													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 9
Schedule of Assessments – Part 2b, PoM (5 Doses QW), Main Table (cont.)

a) For those patients who do not have a liver biopsy, Fibroscan® or equivalent test within the past 6 months from Screening.

b) Pre-dose.

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

d) Blood sample for RO7062931 PK and safety lab assessment will also be collected in the event of SAE.

e) Discontinuation visit: in case of early termination, a patient should be called for this visit and assessments should be performed as listed.

f) Blood beta-human chorionic gonadotropin (β-HCG) for pregnancy test at screening, urine on all other occasions.

g) FSH only for females and to confirm post-menopausal status.

h) If necessary, the patients may be asked to return for additional follow-up visits.

i) ADA samples will be stored and will only be analyzed in case an auto-immune driven AE/AE suggestive of auto-immunological involvement occurs or in case of an atypical PK result.

j) In case an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed.

k) Complete physical examination, is required at screening and Day −1. At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator.

l) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

m) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

* Keep left over sample for patients participating in the RBR program.

Appendix 10
Schedule of Assessments – Part 2b, PoM (5 Doses QW), Detailed Table

Period	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	Inflammatory Markers	Autoantibodies	ADA	Urine Kidney Biomarkers	Blood Liver Biomarker	PK Blood Sample	Urine PK Sample[b]	NUC PK Sample	HBsAg Quantitative	HBsAg, HBeAg Qualitative, HBcAg HBsAg/Anti-HBs Complex Anti HBe/AntiHBs/Anti HBc	HBV DNA, HBV TNA, Viral Resistance Monitoring
Screening	D-56 to D-2		x	x									x	x	x
Period 1	Day -1		x	x					x				x		
	Day 1	Predose	x	x	x	x	x	x		x		x		x	x
		0									x				
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		3			x										
		4	x	x						x	x				
		6								x					
		8	x	x	x					x					
	Day 2	24	x	x	x			x	x	x			x		
	Day 8	Predose	x	x	x			x	x	x			x	x	x
		2	x		x					x					
	Day 15	Predose	x	x	x	x	x	x	x	x			x	x	x
		2	x		x					x					
	Day 22	Predose	x	x	x			x	x	x			x	x	x
		2	x		x					x					
	Day 29	Predose	x	x	x	x	x	x	x	x		x	x	x	x
		0.5								x					
		1	x	x						x					
		2								x		x[a]			
		4	x	x	x					x					
		6								x					
		8	x	x						x					
	Day 30	24	x	x	x			x		x					
Discontinuation			x	x				x	x	x			x	x	x
Follow Up Visit	Day 36		x					x	x	x			x		
	Day 43		x	x						x			x	x	x
	Day 50		x							x			x		
	Day 57		x	x		x	x	x	x	x			x	x	x
	Day 85		x	x		x	x	x	x	x			x	x	x
	Day 113		x	x		x	x	x	x	x			x	x	x

a) One sample to be taken at any point between 2-4 hours post-dose.

b) Urine collection periods [0-4] and [4-8] hours post-dose.

Appendix 11
Schedule of Assessments – Part 2c, QW Doses for 24 Weeks, Main Table

Period	Screening		Treatment Period									Discont-inuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit[h]
Day	D-28 to D-4	Day -7 to -4	Day 1	week 2	week 4	week 8	week 12	week 13	week 18	week 24	week 25		week 26	week 28	week 30	week 32	week 34	week 36	week 40	week 44	week 48
	notime			+/-3	+/-3	+/-7	+/-7		+/-7	+/-7			+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7
Assessments																					
Informed Consent	X																				
Eligibility	X	X																			
Demography	X																				
Medical History	X																				
Fibroscan®[a]	X																				
Physical Examination[k]	X									X		X									X
Vital Signs[i]	X		X	X	X	X				X		X									X
ECG-12 lead	X									X		X									X
Hematology[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X		X				X			X
Blood Chemistry[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X		X				X			X
Urinalysis[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X		X				X			X
TSH	X																				
Viral Serology[n]	X																				
Coagulation[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X		X				X			X
Inflammatory Markers[j]			X	X	X	X	X			X		X		X							
Autoantibodies (screening)[o]	X																				
Autoantibodies (monitoring)[m]			X[b]			X[b]	X[b]		X[b]	X[b]		X									X
ADA			X[b]		X[b]	X[b]	X[b]		X[b]	X[b]		X									X
Alpha fetoprotein		X																			
RBR DNA			X[b]																		
Pregnancy Test[f]		X										X									X

Appendix 11
Schedule of Assessments – Part 2c, QW Doses for 24 Weeks, Main Table (cont.)

Period	Screening		Treatment Period									Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit[h]
Day	D-28 to D-4	Day -7 to -4	Day 1	week 2	week 4	week 8	week 12	week 13	week 18	week 24	week 25		week 26	week 28	week 30	week 32	week 34	week 36	week 40	week 44	week 48
	notime			+/-3	+/-3	+/-7	+/-7		+/-7	+/-7			+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7
Assessments																					
FSH[g]	x																				
Substance Use		x																			
Medications[c]			x																		
PK Blood Sample[q]			7	x	2	2	7	x	2	7	x	x	x	x	x						
Urine PK Sample[r]			2				2			2											
NUC PK[s]			2																		
HBsAg Quantitative		x	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x	x	x	x	x	x	x	x	x	x	x
HBsAg, HBeAg Qualitative; HBsAg/Anti-HBs Complex; Anti Hbe; AntiHBs		x	x[b]		x[b]	x[b]	x[b]		x[b]	x[b]		x		x		x	x	x	x	x	x
Viral Genotypes			x[b]																		
sequencing		x	x[b]		x[b]	x[b]	x[b]		x[b]	x[b]		x		x		x	x				x
HBV RNA, HBcrAg			x[b]		x[b]	x[b]	x[b]		x[b]	x[b]		x		x		x	x				x
Clinical Genotyping			x[l]																		
Ambulatory Visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomisation			x																		
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous and Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 11
Schedule of Assessments – Part 2c, QW Doses for 24 Weeks, Main Table (cont.)

a) For those patients who do not have a liver biopsy, Fibroscan® or equivalent test within the past 6 months from Screening.

b) Pre-dose.

c) Daily administration of NUC and weekly clinic SC administration of RO7062931

d) Blood sample for RO7062931 PK and safety lab assessment will also be collected in the event of an SAE.

e) Discontinuation visit: in case of early termination, a patient should be called for this visit and assessments should be performed as listed.

f) Blood beta-human chorionic gonadotropin (β-HCG) for pregnancy test at screening, other occasions, at any time a secondary amenorrhea of more than 1 week occurs.

g) FSH only for females and to confirm post-menopausal status.

h) If necessary, the patients may be asked to return for additional follow-up visits.

i) Body weight will be measured at each visit for dosing

j) Baseline sample will be assessed and in case of an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed along with follow-up time-points.

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

l) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

m) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

n) HAV, HCV, HDV, HEV, and HIV.

o) ANA, AMA, ASMA, a-TPO, anti-thyroglobulin, anti-platelet

[redacted]

q) Serial PK samples will be taken at pre-dose and 0.5, 1, 2, 4, 6 and 8 hours post-dose on Day 1 of Weeks 1, 12, 24, and 48.
A Day 2 PK sample (24 hour time point) will be collected in Weeks 1, 12, 24, and 48.
A pre-dose sample will be collected in Weeks 2, 13, and 25 representing 168 hours post the previous dose in Weeks 1, 12, and 24, respectively. An additional sample will be collected in Week 49 at 168 hours post the 48 week dose.
Sparse PK sampling at pre-dose and within a range of 2-4 hours post-dose will be made on Day 1 of Weeks 4, 8, 18, 30, and 36.
One PK sample is required on the follow up visits in Weeks 50, 52, and 54, and one PK sample is required upon discontinuation.

Appendix 11
Schedule of Assessments – Part 2c, QW Doses for 24 Weeks, Main Table (cont.)

r) All voided urine will be collected in two pools from 0-4 hours and 4-8 hours post dose on Day 1 of Weeks 1, 12 and 24.

s) PK samples for NUC analysis on Day 1 of Week 1 pre- NUC dose and 2-4 hours post NUC dose. One sample collected if DNA rebound is detected.

[redacted]

Appendix 12
Schedule of Assessments – Part 2c, QW Doses for 24 Weeks, Detailed Table

Period	Week	Day	Scheduled Time (h)	PK Blood Sample[a]	Urine PK Sample[b]	NUC PK Sample[c]	[redacted]
Screening		-7 to -4					
Treatment Period	1	1	Predose	x		x	
			0.5	x	x		
			1	x			
			2	x		x	
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	2	7	Predose	x			
	4	1	Predose	x			
			2	x			
			4				
	8	1	Predose	x			
			2	x			
			4				
	12	1	Predose	x			
			0.5	x	x		
			1	x			
			2	x			
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	13	7	Predose	x			
	18	1	Predose	x			
			2	x			
			4				
	24	1	Predose	x			
			0.5	x	x		
			1	x			
			2	x			
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	25	7	168	x			
Follow up	26	1	NA	x			
Follow up	28	1	NA	x			
Follow up	30	1	NA	x			
Discontinuation				x			
DNA Rebound						x	

Appendix 12
Schedule of Assessments – Part 2c, QW Doses for 24 Weeks, Detailed Table (cont.)

a) Serial PK samples will be taken at pre-dose and 0.5, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Weeks 1, 12 and 24.
A day 2 PK sample (24-hour time point) will be collected in Weeks 1, 12, and 24.
A pre-dose sample will be collected in Weeks 2 and 13, representing 168 hours post the previous dose in Weeks 1 and 12, respectively. An additional sample will be collected in week 25 at 168 hours post the 24-week dose.
Sparse PK sampling at pre-dose and within a range of 2-4 hours post dose will be made on day 1 of Weeks 4, 8, and 18.
One PK sample is required on the follow up visits in Weeks 26, 28 and 30 and upon discontinuation.

b) All voided urine will be collected in two pools from 0-4 hours and 4-8 hours post dose on day 1 of Weeks 1, 12 and 24.

c) PK samples for NUC analysis on Day 1 of Week 1 pre-NUC dose and 2-4 hours post NUC dose. One sample will be collected if DNA rebound is detected.

[redacted]

Appendix 13
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Main Table

Period	Screening		Treatment Period													
Day	D-28 to D-4	Day -7 to -4	Day 1	week 2	week 4	week 8	week 12	week 13	week 18	week 24	week 25	week 30	Week 36	Week 42	week 48	week 49
	notime			+/-3	+/-3	+/-7	+/-7		+/-7	+/-7		+/-7	+/-7	+/-7	+/-7	
Assessments																
Informed Consent	X															
Eligibility	X	X														
Demography	X															
Medical History	X															
Fibroscan®[a]	X															
Physical Examination[k]	X														X	
Vital Signs[i]	X		X	X	X	X									X	
ECG-12 lead	X														X	
Hematology[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X[b]	X[b]	X[b]	X[b]	
Blood Chemistry[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X[b]	X[b]	X[b]	X[b]	
Urinalysis[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X[b]	X[b]	X[b]	X[b]	
TSH	X															
Viral Serology[n]	X															
Coagulation[d]		X		X[b]	X[b]	X[b]	X[b]		X[b]	X[b]		X[b]	X[b]	X[b]	X[b]	
Inflammatory Markers[j]			X	X	X	X	X			X					X	
Autoantibodies (screening)[o]	X															
Autoantibodies (monitoring)[m]			X[b]			X[b]	X[b]		X[b]	X[b]					X[b]	
ADA			X[b]		X[b]	X[b]	X[b]		X[b]	X[b]		X[b]	X[b]	X[b]	X[b]	
Alpha fetoprotein		X														
RBR DNA			X[b]													
Pregnancy Test[f]		X														

Appendix 13
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Main Table (cont.)

Period	Discont-inuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit[h]
Day		week 50	week 52	week 54	week 56	week 58	week 60	week 64	week 68	week 72
		+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7
Assessments										
Informed Consent										
Eligibility										
Demography										
Medical History										
Fibroscan®[a]										
Physical Examination[k]	X									X
Vital Signs[i]	X									X
ECG-12 lead	X									X
Hematology[d]	X		X				X			X
Blood Chemistry[d]	X		X				X			X
Urinalysis[d]	X		X				X			X
TSH										
Viral Serology[n]										
Coagulation[d]	X		X				X			X
Inflammatory Markers[j]	X		X							
Autoantibodies (screening)[o]										
Autoantibodies (monitoring)[m]	X									X
ADA	X									X
Alpha fetoprotein										
RBR DNA										
Urine Kidney Biomarkers[p]	X		X							
Pregnancy Test[f]	X									X

Appendix 13
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Main Table (cont.)

Period	Screening		Treatment Period													
Day	D-28 to D-4	Day -7 to -4	Day 1	week 2	week 4	week 8	week 12	week 13	week 18	week 24	week 25	week 30	Week 36	Week 42	week 48	week 49
	notime			+/-3	+/-3	+/-7	+/-7		+/-7	+/-7		+/-7	+/-7	+/-7	+/-7	
Assessments																
FSH[g]	x															
Substance Use		x														
Medications[c]									x							
PK Blood Sample[q]			7	x	2	2	7	x	2	7	x	2	2		7	x
Urine PK Sample[r]			2				2			2			2		2	
NUC PK[s]			2													
[redacted]																
HBsAg Quantitative		x	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x
HBsAg, HBeAg Qualitative; HBsAg/Anti-HBs Complex; Anti Hbe; AntiHBs		x	x[b]		x[b]	x[b]	x[b]		x[b]	x[b]					x[b]	
Viral Genotypes			x[b]													
HBV DNA, Viral Resistance sequencing		x	x[b]		x[b]	x[b]	x[b]		x[b]	x[b]					x[b]	
HBV RNA, HBcrAg			x[b]		x[b]	x[b]	x[b]		x[b]	x[b]					x[b]	
Clinical Genotyping			x[l]													
Ambulatory Visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomisation			x													
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 13
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Main Table (cont.)

Period	Discontinuation[e]	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit	Follow Up Visit[h]
Day		week 50	week 52	week 54	week 56	week 58	week 60	week 64	week 68	week 72
		+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7
Assessments										
FSH[g]										
Substance Use										
Medications[c]										
PK Blood Sample[q]	X	X	X	X						
Urine PK Sample[r]										
NUC PK[s]										
HBsAg Quantitative	X	X	X	X	X	X	X	X	X	X
HBsAg, HBeAg Qualitative; HBsAg/Anti-HBs Complex; Anti Hbe; AntiHBs	X		X		X	X	X	X	X	X
Viral Genotypes										
HBV DNA, Viral Resistance sequencing	X		X		X	X				X
HBV RNA, HBcrAg	X		X		X	X				X
Clinical Genotyping										
Ambulatory Visit	X	X	X	X	X	X	X	X	X	X
Randomisation										
Adverse Events	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X

Appendix 13
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Main Table (cont.)

a) For those patients who do not have a liver biopsy, Fibroscan® or equivalent test within the past 6 months from Screening.

b) Pre-dose.

c) Daily administration of NUC and weekly clinic SC administration of RO7062931 or RO7062931 and PEG-IFN

d) Blood sample for RO7062931 PK and safety laboratory assessment will also be collected in the event of an SAE.

e) Discontinuation visit: in case of early termination, a patient should be called for this visit and assessments should be performed as listed.

f) Blood beta-human chorionic gonadotropin (β-HCG) for pregnancy test at screening, other occasions, at any time a secondary amenorrhea of more than 1 week occurs.

g) FSH only for females and to confirm post-menopausal status.

h) If necessary, the patients may be asked to return for additional follow-up visits.

i) Body weight will be measured at each visit for dosing

j) Baseline sample will be assessed and in case of an immune driven AE/AE suggestive of immunological involvement occurs, an unscheduled sample will be collected and analyzed along with follow-up time-points.

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

l) One single whole blood sample to be collected for genetic analysis at any time after randomization. If the sample is not collected at the scheduled time-point, it can be collected at any other time-point. Only one sample will be collected per patient.

m) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analyzed.

n) HAV, HCV, HDV, HEV, and HIV.

o) ANA, AMA, ASMA, a-TPO, anti-thyroglobulin, anti-platelet.

[redacted]

q) Serial PK samples will be taken at pre-dose and 0.5, 1, 2, 4, 6 and 8 hours post-dose on Day 1 of Weeks 1, 12, 24, and 48.
A Day 2 PK sample (24 hour time point) will be collected in Weeks 1, 12, 24, and 48.
A pre-dose sample will be collected in Weeks 2, 13, and 25 representing 168 hours post the previous dose in Weeks 1, 12, and 24, respectively. An additional sample will be collected in Week 49 at 168 hours post the 48 week dose.
Sparse PK sampling at pre-dose and within a range of 2-4 hours post-dose will be made on Day 1 of Weeks 4, 8, 18, 30, and 36.
One PK sample is required on the follow up visits in Weeks 50, 52, and 54, and one PK sample is required upon discontinuation.

Appendix 13
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Main Table (cont.)

r) All voided urine will be collected in two pools from 0-4 hours and 4-8 hours post-dose on Day 1 of Weeks 1, 12, 24, and 48.

s) PK samples for NUC analysis on Day 1 of Week 1 pre-NUC dose and 2-4 hours post-NUC dose. One sample collected if DNA rebound is detected.

[redacted]

[redacted]

* *Keep all left over sample for patients participating in the RBR program.*

Appendix 14
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Detailed Table

Period	Week	Day	Scheduled Time (h)	PK Blood Sample[a]	Urine PK Sample[b]	NUC PK Sample[c]	[redacted]
Screening		-7 to -4					
Treatment Period	1	1	Predose	x		x	
			0.5	x	x		
			1	x			
			2	x		x	
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	2	7	Predose	x			
	4	1	Predose	x			
			2	x			
			4				
	8	1	Predose	x			
			2	x			
			4				
	12	1	Predose	x			
			0.5	x	x		
			1	x			
			2	x			
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	13	7	Predose	x			
	18	1	Predose	x			
			2	x			
			4				
	24	1	Predose	x			
			0.5	x	x		
			1	x			
			2	x			
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	25	1	Predose	x			
	30	1	Predose	x			
			2	x			
			4				
	36	1	Predose	x			
			2	x			
			4				
	48	1	Predose	x			
			0.5	x	x		
			1	x			
			2	x			
			4	x			
			6	x	x		
			8	x			
		2	24	x			
	49	7	168	x			
Follow up	50	1	NA	x			
Follow up	52	1	NA	x			
Follow up	54	1	NA	x			
Discontinuation				x			
DNA Rebound						x	

Appendix 14
Schedule of Assessments – Part 2c, QW Doses for 48 Weeks, Detailed Table (cont.)

a) Serial PK samples will be taken at pre-dose and 0.5, 1, 2, 4, 6 and 8 hours post-dose on Day 1 of Weeks 1, 12, 24, and 48.
A Day 2 PK sample (24-hour time point) will be collected in Weeks 1, 12, 24, and 48.
A pre-dose sample will be collected in Weeks 2, 13, and 25 representing 168 hours post the previous dose in Weeks 1, 12, and 24 respectively. An additional sample will be collected in Week 49 at 168 hours post the 48 week dose.
Sparse PK sampling at pre-dose and within a range of 2-4 hours post-dose will be made on Day 1 of Weeks 4, 8, 18, 30, and 36.
One PK sample is required on the follow up visits in Weeks 50, 52, and 54, and upon discontinuation.

b) All voided urine will be collected in two pools from 0-4 hours and 4-8 hours post-dose on Day 1 of Weeks 1, 12, 24, and 48.

c) PK samples for NUC analysis on Day 1 of Week 1 pre-NUC dose and 2-4 hours post-NUC dose. One sample collected if DNA rebound is detected.

Appendix *15*
Alcohol Unit Calculation - Examples

From Australian Department of Health (Population Health Division)

http://www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/standard

Appendix 15
Alcohol Unit Calculation - Examples (cont.)

Appendix *16*
Child-Pugh Classification of Severity of Liver Disease

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	**2**	**3**
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg per 100 mL)	1 - 2	2 - 3	> 3
Albumin (g per 100 mL)	3.5	2.8 - 3.5	< 2.8
Prothrombin time (sec. prolonged)	1 - 4	4 - 6	> 6

* According to grading of Trey, Burns and Saunders (1966)

1, 2 or 3 points are scored for increasing abnormality of each of the 5 parameters measured.

Grade A: 5 or 6

Grade B: 7 to 9

Grade C: 10 to 15

Appendix *17*
Toxicity Table for Grading Injection Reactions

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

Appendix 18
Division of AIDS (DAIDS) Table for Grading the Severity of Adverse Events (for Part 2c of the Study)

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 July 2017 will be used for assessing adverse event severity (see below table).

For AEs listed in the DAIDS Table, the DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- *Grade 1 indicates a mild event*
- *Grade 2 indicates a moderate event*
- *Grade 3 indicates a severe event*
- *Grade 4 indicates a potentially life-threatening event*
- *Grade 5 indicates death (Note: This grade is not specifically listed on each page of the grading table)*

For AEs not listed on the DAIDS Grading Table, the Functional Table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

Adverse Event Grading (Severity) Scale (For Part 2c)

PARAMETER	*GRADE 1 MILD*	*GRADE 2 MODERATE*	*GRADE 3 SEVERE*	*GRADE 4 POTENTIALLY LIFE-THREATENING*
***Clinical** adverse event **NOT** identified elsewhere in the grading table*	*Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated*	*Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated*	*Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated*	*Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or*

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