Official Title: A Randomized, Sponsor-Open, Investigator-Blind, Subject-Blind, Placebo-Controlled, Single Ascending Dose, to Investigate the Safety, Tolerability and Pharmacokinetics of RO7062931 Following Subcutaneously Administration in Healthy Chinese Volunteers

NCT Number: NCT03505190

Document Date: Protocol Version 2: 29-November-2017

PROTOCOL

TITLE:	**A RANDOMIZED, SPONSOR-OPEN, INVESTIGATOR–BLIND, SUBJECT-BLIND, PLACEBO-CONTROLLED, SINGLE ASCENDING DOSE, TO INVESTIGATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF RO7062931 FOLLOWING SUBCUTANEOUSLY ADMINISTRATION IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP39432
VERSION:	2
TEST PRODUCT:	RO7062931
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 9 January 2017 Version 2: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted] ([redacted])	Company Signatory	29-Nov-2017 12:43:38

PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, SPONSOR-OPEN, INVESTIGATOR–BLIND, SUBJECT-BLIND, PLACEBO-CONTROLLED, SINGLE ASCENDING DOSE, TO INVESTIGATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF RO7062931 FOLLOWING SUBCUTANEOUSLY ADMINISTRATION IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP39432
VERSION NUMBER:	2
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 2:
RATIONALE

Protocol YP39432 has been amended to incorporate the following changes:

Substantial changes

- One cohort with a projected dose of 3.0 mg/kg and an optional cohort with a projected dose of 4.0 mg/kg have been added, in response to newly available pharmacokinetic data in the ongoing global study BP39405 (Sections 3.1.1, 3.2.1, 6.1 and Figure 1). [redacted] Both doses were considered to be safe and well tolerated in participants enrolled in study BP39405. This change will align this protocol with the ongoing global study.
- A dose escalation stopping rule has been added to Section 3.1.2.2 'Dose Escalation Stopping Criteria' in response to feedback from the pre-IND meeting with the Chinese Center for Drug Evaluation (CDE).
- The follow up period has been extended in all clinical studies with RO7062931 to proactively collect long term safety data. The follow up period for this protocol has been extended to include a follow up visit on Study Day 85, which is consistent with four times the estimated liver tissue half-life of RO7062931 (Section 4.6.2.3 and Appendix 1 and 2). This change is not triggered by any new safety data.
- Additional specification of normal ranges for liver and renal function tests, which are two of the organs where toxicities were observed in the pre-clinical toxicology studies, as follows:
  - The entry safety criteria have been set within the normal ranges for liver and renal function tests (Section 4.2.3).
  - Addition of renal safety variable 'calculated creatinine clearance' (Section 4.6.1.5).
- Information from the addendum to the Investigator's Brochure has been incorporated, including new toxicology data (Section 1.2.1) and new information on drug color (Section 4.4.1.1).
- Additional details for the grading of pre-defined injection site reaction symptoms have been added (Section 5.3.5.1 and Appendix 4).

Clarification of study procedures

- The dose escalation/review meetings will take place after receipt of Day 29 safety data to simplify study conduct and data evaluation (Section 3.1.2).
- A cut-off value has been assigned for follicle-stimulating hormone in Inclusion Criterion 4 (Section 4.2.2).
- Exclusion Criteria 3, 4, 5, 6, 7 and 8 have been updated since tests/assessments are done both at *S*creening and at Day –1 (Section 4.2.3).

- Concomitant therapy and food has been modified to remove duplications and provide clarity (Section 4.5).
- Correction of inconsistencies in the method for measurement of blood pressure and pulse rate (Section 4.6.1.3).
- Urine microscopy is performed on all urine samples for this study, irrespective of the dipstick result (Section 4.6.1.5).
- Those healthy volunteers who have completed the study dose, or who discontinue from the study early, will be encouraged to attend the clinic for long term follow up (Section 4.6.2.3).
- To accommodate sites in the preparation of the study drug, if the sites prefer, they could randomize and prepare the study drug the day before dosing. Stability of the prepared study drug allows for this. Therefore randomization will also be allowed on Day −1 (Appendix 1).
- Due to the long follow up period the following visit windows will be applicable to the follow up visits, to allow flexibility to the study participants and sites with scheduling: Day 15 ± 1 Day, Day 29 ± 2 Days, Day 85 ± 1 week (Appendix 1).
- Blood PK sampling on Day 15 and Day 29 have been deleted (Appendix 1).
- Modification of text to update the SAE reporting tool (Section 5.4.2.2).

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

Protocol Synopsis

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

1.2.1 Previous Non-Clinical Studies

RO7062931 has shown potent antiviral activity through the inhibition [redacted], [redacted] in cellular assays. RO7062931 is [redacted] active in vitro against [redacted]. In mice infected with a recombinant adeno-associated virus (AAV) carrying a replicable HBV genome (AAV-HBV), administration of RO7062931 reduced [redacted] to below level of quantification.

……

The pivotal non-clinical safety package ~~(5-week SC dosing + 9-week recovery periods)~~ in accordance with Good Laboratory Practice (GLP) compliant regulations, was conducted in rats and cynomolgus monkeys (non-human primates [NHP]) *for systemic toxicity (5-week SC dosing + 9-week recovery periods), and in rats (fertility and definitive EFD studies) and rabbits (preliminary EFD study) for reproductive and developmental toxicity*. The *local tolerance assessment,* safety pharmacology core battery and in vivo micronucleus test were integrated in repeat-dose *systemic toxicity* studies. Overall, RO7062931 shows the expected effects [redacted]

[redacted]

[redacted]

....

[redacted]

1.2.2 Previous Clinical Studies

~~No clinical studies with RO7062931 have been performed to date.~~ Study BP39405, the first-in-human (FIH) study with RO7062931, ~~is~~ *was* ~~planned to be~~ initiated in January 2017. *In this ongoing study, as of 8 November, 2017, 60 healthy subjects (including 15 Asian healthy subjects) had received a single dose of RO7062931 or placebo at various dose levels from 0.1, 0.3, 1.0, 2.0, 3.0 to 4.0 mg/kg. As of 8th November 2017, two HBV patients had been randomized in Part 2a of the study.*

[redacted]

[redacted]

1.3.2 Benefit–Risk Assessment

~~No prior~~ *Limited* clinical experience with RO7062931 currently exists. The evaluation of the potential risks of drug administration and the specific tests, observations, and precautions required for this clinical study with RO7062931 will be based on information from non-clinical toxicology and safety pharmacology studies as well as available data from the FIH study BP39405.

3.1.1 Overview of Study Design

This study is randomized, Sponsor-open, Investigator-blind and subject-blind. Up to ~~four~~ *five* ascending dose-levels (cohorts) will be explored within the dose-range shown to be safe and well-tolerated in Study BP39405. The planned doses for the first ~~three~~ *four* cohorts will be 0.3 mg/kg, 1.0 mg/kg, 2.0 mg/kg *and 3.0 mg/kg*, respectively (see Figure 1). The planned dose-levels may be modified and an additional (optional, *4.0 mg/kg*) cohort enrolled based on emerging results from ongoing preclinical and clinical studies (including this study). ~~The dose level for the optional Cohort 4 will be determined based on all available safety and PK data from Cohorts 1-3, as well as data collected from Study BP39405, however without exceeding a 3 fold increase of the dose administered in Cohort 3.~~

It is planned to enroll 10 HVs in each cohort; eight HVs will receive RO7062931 and two will receive placebo. Sentinel dosing will be employed in each cohort, where two subjects will be dosed on Day 1, of which at least one HV will receive RO7062931 in order to monitor *for potential* acute ~~injection~~ reactions. The remaining 8 subjects will be dosed on the following day (24 hours after the initial administrations) following satisfactory safety assessment of the first two HVs by the Investigator. The sentinel dosing requirements may be modified based on the data from Study BP39405.

Figure 1. Study Design

Figure 1 now reflects the addition of one cohort and specification of the dose for the optional cohort.

The total duration of the study for each HV will be up to ~~8~~ *16* weeks divided as follows:

- Screening: Up to 4 weeks;
- In-Clinic period: Days -1 to 3;
- Safety Follow-up: up to at least Day ~~29~~ *85*

3.1.2 Dose 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 3.1.2.1). The actual doses may be modified based on emerging data from this study, and emerging results from ongoing preclinical studies and Study BP39405.

Escalation to the next dose cohort will be based primarily on the review of safety and tolerability information (including adverse events, electrocardiograms [ECGs], vital signs, clinical laboratory test results) collected ~~at least~~ *up to* 28 days post-dose *(Day 29 ± 2 Days)* and, all available PK data collected at least 7 days post-dose in a

minimum of 8 subjects (receiving active drug or placebo) within the previous cohort. The decision to escalate the dose will be made by mutual agreement between the Sponsor and the Investigator.

3.1.2.2 Dose Escalation Stopping Criteria

Additionally, planned dose-escalation may be stopped by mutual agreement between the [redacted]

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

Any serious adverse event considered related to study drug will lead to an immediate halt of study drug dosing, dose escalation and enrollment of new subjects until a thorough investigation has been conducted by the Sponsor's Clinical Team and the Principal Investigator. The sponsor or designee will notify all investigators and IRBs/EC regarding the outcome of such investigation, and the study will only continue if agreed by the IRBs/EC.

Due to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor (see Section 4.7).

3.2.1 Rationale for Dosage Selection

The anticipated dose levels for this study are 0.3 mg/kg, 1.0 mg/kg, *2.0 mg/kg and 3.0* mg/kg for Cohorts 1~~-34 but may change based on data from the FIH study (BP39405)~~. In addition, based on the PK and safety evaluation of the top dose cohort *and the available data from FIH Study BP39405*, an optional ~~fourth~~ *fifth* cohort *(4.0 mg/kg)* may be enrolled~~ to receive a higher dose~~. All dose levels in this study will be within the dose range which has been demonstrated to be safe and well tolerated in the BP39405 study. [redacted]

~~When this study initiates, it is anticipated that the d~~*D*ata from the *ongoing* BP39405 study *have shown that single doses of RO7062931 from 0.1 to 4.0 mg/kg were considered safe and well tolerated in healthy humans (Section 1.2.2)*.~~will provide more information about the safety and projected efficacious dose in humans.~~ The planned starting dose of 0.3 mg/kg is higher than ~~that proposed~~*was used* for the first EIH study, BP39405~~ and may be modified to a lower dose based on data from the global study.~~ The 0.3 mg/kg dose is chosen to minimize additional testing in Chinese HVs of doses that may not provide information. This starting dose would have a safety margin >10-fold to the most sensitive species evaluated in GLP toxicology studies.

[redacted]. The starting-dose of 0.3 mg/kg in HVs is expected to yield plasma concentrations of RO7062931 below or near that required [redacted]. Widening the dose range from a low

starting-dose not expected to exhibit liver saturation up through higher doses shown or anticipated to be safe in humans (i.e., 0.3-~~2~~*24*.0 mg/kg or higher), is believed to increase the chances of identifying the [redacted], which would greatly inform the dosing regimen for subsequent studies in Chinese CHB patients. [redacted] It has been shown in preclinical rat and monkey studies that once the specific receptor-mediated uptake in the liver is saturated, RO7062931 is taken up more readily into other organs. Minimizing this non-specific organ uptake by dosing [redacted] is thought to result in a better risk/benefit profile in CHB patients.

4.2.2 Inclusion Criteria

4. 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~~*These include those who have undergone surgical sterilization (removal of ovaries and/or uterus) or are* post-menopausal ~~state~~ (≥12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH] *≥ LLN (Local Lab)*, or amenorrhea for at least 24 months if on hormone replacement therapy [HRT]).~~, and has not undergone surgical sterilization (removal of ovaries and/or uterus)~~.

4.2.3 Exclusion Criteria

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 *at Screening*.
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 *S*creening *or Day -1*.
6. Confirmed (e.g., two consecutive triplicate measurements) average resting pulse rate > 90 or < 45 beats per minute (bpm) at Screening *or Day -1*.
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 *S*creening *or Day -1*).

8. ECG morphology at screening *or Day -1* 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 c*linically 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 *S*creening ~~and~~ *or* on Day-1. *Abnormal renal function including serum creatinine* > ULN (Local Lab) or calculated creatinine clearance < 70 mL/min (using the Cockcroft Gault formula).

4.4.1.1 RO7062931 and Placebo

RO7062931 and placebo investigational medicinal products (IMPs) to be used in the study will be provided by Roche.

[redacted] As the formulation contains no preservatives, it should be diluted under appropriate aseptic conditions. An in-line filter must be used prior to administration (see Pharmacy Manual for further details).

4.5 CONCOMITANT THERAPY AND FOOD

~~The following restrictions for HVs 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 study drug administration (with the exception of HRT, which is allowed throughout the study). Paracetamol (up to 1 g per day) will be allowed.~~
- ~~However, in the event that a HV requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor.~~

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

~~It is unlikely that food will have an impact on the PK of RO7062931, however, RO7062931 should be administered in a fasted state. (It is unlikely that food will have an impact on the PK of RO7062931, however, RO7062931 should be administered in a fasted state [i.e., 2 hours before, or, 2 hours after a meal]).~~

4.5.1 Permitted Therapy

~~Concomitant therapy includes any mediation, e.g., prescription drugs, OTC drugs, approved dietary and herbal supplements, nutritional supplements used by a HV from 30 days prior to screening until the follow up visit (with some restrictions as given above, see Section 4.5).~~

Patients will be permitted to use the following therapies during the study:

- *Hormone-replacement therapy*
- *Paracetamol (up to 1 g per day)*
- *Medications used to treat an AE may only be prescribed after consultation with the Sponsor (with the exception of paracetamol), unless there is a medical need to ensure the well-being of the subject that should not be delayed. All therapy and/or medication administered to manage AEs should be recorded on the AE electronic case report form (eCRF).*

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 due to no foreseen RO7062931 drug-drug interactions, however the restrictions described in Section 4.5 apply.~~

Use of 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 exceptions of therapies listed in Section 4.5.1. However, in the event that a HV requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor.

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

4.5.3 Prohibited Food

There are no prohibited foods.

It is unlikely that food will have an impact on the PK of RO7062931, however, RO7062931 should be administered in a fasted state (i.e., 2 hours before, or, 2 hours after a meal).

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 Schedule of Assessments tables (see Appendix 1 and Appendix 2). Blood pressure and pulse rate will be performed in triplicate (can be as short as 20 seconds to 1-minute interval between measurements)

and recorded in eCRF. ~~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 pulse 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).~~

4.6.1.5 Laboratory Assessments

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. 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, alkaline phosphatase (ALP), blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT) (at Screening only), creatine phosphokinase (at Screening only), total protein, albumin, creatinine *and calculated creatinine clearance using Cockcroft Gault formula*, glomerular filtration rate (GFR) calculated, uric acid, cystatin c, fasting glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (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. *All urine samples will also be 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 ~~microscopy and~~ culture. If there is an explanation for the positive dipstick result, e.g., menses, it should be recorded~~, and there is no need to perform microscopy~~.

Urine color may be evaluated from urinalysis or urine PK samples if considered necessary. ~~Urinary sediment (casts, cells).~~

4.6.1.8 Other Assessments

The following urinary kidney biomarkers will be analyzed from urine samples: α1-microglobulin, β2-microglobulin, and KIM-1. *Each biomarker will be normalized to urine creatinine.*

4.6.2.3 Follow-Up Assessments and Study Completion

HVs who complete the study, or who discontinue from the study early, *will be encouraged to attend the clinic for long term follow up as per the SOA in Appendix 1.* ~~will be asked to return to the clinic after the dose of study drug for a follow up visit.~~

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 related to the SC study drug injection should be captured as a diagnosis (e.g., “injection 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 4.* If a subject 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.

5.4.1 Emergency Medical Contacts

To ensure the safety of study subjects, access to the Medical monitors is available 24 hours a day, 7 days a week. ~~Medical monitors contact details are listed in the “Protocol Administrative and Contact Information & List of Investigators”.~~ *Medical monitors' contact details will be available on a separate list generated by the study management team.*

5.4.2.2 Events That Occur after Study Drug Initiation

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 Serious Adverse Event 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.

6.1 DETERMINATION OF SAMPLE SIZE

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, as comparisons of these parameters across doses will be used in part [redacted].

Up to ~~40~~ *50* HVs will be included in this study. Up to ~~4~~ *5* cohorts of 10 HVs (8 on active and 2 on placebo per dose level) are planned with the ~~fourth~~ *fifth* and last cohort being optional and based on the analysis of emerging PK and safety data from this study and available data from study BP39405.

Appendix 1 Schedule of Assessments – Main table

The table has been updated to include follow up visit Day 85, visit window and deletion of the blood PK sampling on Day 15 and Day 29. The possibility for randomization has also been added on Day -1.

Appendix 2 Schedule of Assessments –Detailed table

The table has been updated to include: follow up visit Day 85; the time windows Day 15 $\pm$ 1day, Day 29 $\pm$ 2days, Day 85 $\pm$ 1week. Columns for drug-induced antibodies, ADA, urine kidney biomarkers and blood liver biomarkers and rows for 'Screening' and 'Day $-$1' are added for clarification.

Appendix 4 Toxicity Table for Grading Injection Reactions

A new appendix has been added with a table for grading injection reactions.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, SPONSOR-OPEN, INVESTIGATOR–BLIND, SUBJECT-BLIND, PLACEBO-CONTROLLED, SINGLE ASCENDING DOSE, TO INVESTIGATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF RO7062931 FOLLOWING SUBCUTANEOUSLY ADMINISTRATION IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP39432
VERSION:	2
TEST PRODUCT:	RO7062931
PHASE:	I
INDICATION:	NA
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES

Primary Objective:

The primary objective of this study is:

- To assess the safety and tolerability of RO7062931 compared to placebo after single-ascending doses in healthy Chinese volunteers.

Secondary Objectives:

The secondary objective for this study is:

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

STUDY DESIGN

Description of Study

This study is randomized, Sponsor-open, Investigator-blind and subject-blind. *U*p to *five* ascending dose-levels (cohorts) *will be explored within the dose-range* shown to be safe and well-tolerated *in S*tudy BP39405. The planned doses for the first *four* cohorts will be 0.3 mg/kg, 1.0 mg/kg, 2.0 mg/kg and *3.0 mg/kg*, respectively *(see Figure 1)*. The planned dose-levels may be modified and an additional (optional, *4.0 mg/kg*) cohort enrolled based on emerging results from ongoing preclinical and clinical studies (including this study).

It is planned to enroll 10 healthy volunteers (HVs) in each cohort; eight HVs will receive RO7062931 and two will receive placebo. Sentinel dosing will be employed in each cohort, where two subjects will be dosed on Day 1, *of which at least one HV will receive RO7062931* in order to monitor for potential acute reactions. The remaining 8 subjects will be dosed *on the following day (*24 hours after the initial administrations*)* following satisfactory safety assessment of the first two HVs by the Investigator. The sentinel dosing requirements may be modified based on the data from Study BP39405.

NUMBER OF PATIENTS

Up to 50 HVs will be included in this study. Up to *5* cohorts of 10 HVs (*8 on active and 2 on placebo per dose level*) are planned *with the fifth and last cohort being optional and based on the analysis of emerging PK and safety data from this study and available data from Study BP39405.*

TARGET POPULATION

Chinese healthy male and post-menopausal or surgically sterile female HVs of 18 to 60 years of age.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

Healthy volunteers must meet the below criteria for study entry.

1. Chinese healthy male and female (of non-childbearing potential) volunteers. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, concomitant drug use (including hormonal supplements), a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.
2. 18 to 60 years of age, inclusive.
3. A Body Mass Index (BMI) between 19 to 27 kg/m2 inclusive and a body weight of at least 45 kg.
4. Women should be of non-childbearing potential. *These include those who have undergone surgical sterilization (removal of ovaries and/or uterus) or are* post-menopausal (≥ 12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH] ⩾ *LLN (Local Lab)*, or amenorrhea for at least 24 months if on hormone replacement therapy [HRT]).

   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 up to 105 days after the last RO7062931 dose to avoid exposing the embryo to the study drug. 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 HV. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
5. Able to participate and willing to give written informed consent and to comply with the study restrictions.
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.

Exclusion criteria:

Healthy volunteers who meet any of the below criteria will be excluded from study entry.

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 *at Screening*.
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 *S*creening *or Day -1*.
6. Confirmed (e.g., two consecutive triplicate measurements) average resting pulse rate > 90 or < 45 beats per minute (bpm) at *S*creening *or Day -1*.
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 *S*creening *or Day -1*).
8. ECG morphology at *S*creening *or Day -1* 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 c*linically 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 *S*creening *or* on Day -1. *Abnormal renal function including serum creatinine* > ULN (Local Lab) or calculated creatinine clearance <70 *mL/min (using the Cockcroft Gault formula).*
12. Participation in an investigational drug or device study within 90 days prior to *S*creening 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 *S*creening.
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 subject in this study.
15. Any major illness within the one month preceding the *S*creening visit, or any febrile illness within the two weeks preceding the *S*creening visit.
16. Alcohol consumption of more than 2 standard drinks per day on average; 1 standard drink equals 10 grams of alcohol, and/or drug abuse within one year of randomization.
17. Hypersensitivity to the excipients of the study drug.
18. HVs under judicial supervision, guardianship or curatorship.

LENGTH OF STUDY

The total duration of the study for each HV will be up to *16* weeks, divided as follows:

Screening: Up to 4 weeks;

In Clinic period: *Days –1 to 3;*

Safety Follow--up: up to at least Day *85*

END OF STUDY

The end of the study is defined as the date the last subject's (HV's) last observation (LSLO) occurs. LSLO is expected to occur at the safety follow-up visit of the last HV enrolled.

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 *(see Section 5.1.3)*.
- 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, pulse rate and temperature *(Section 4.6.1.3)*.

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 and Appendix 2)*. 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/F (apparent clearance) and

  V_z/F (apparent 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.

OTHER OUTCOME MEASURES

- Kidney biomarkers including urine α1-microglobulin, β2-microglobulin and KIM-1.
- Liver biomarkers including, miRNA122 and GLDH.
- Assessments for inflammatory markers (complement, C-Reactive Protein [CRP], erythrocyte sedimentation rate [ESR], gamma globulin and the following inflammatory biomarkers [interleukin (IL)-6, IL-8, IL12, mast cell protease (MCP1), tumor necrosis factor (TNF)α]), drug-induced autoantibodies and anti-drug antibodies (ADA).

INVESTIGATIONAL MEDICINAL PRODUCT(S)

The investigational medicinal products (IMPs) in this study are RO7062931 and placebo, and will be provided by the Sponsor.

All *RO7062931 doses and placebo* 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*. Subcutaneous doses will be administered at an appropriate site (*for example the abdomen or upper thigh*).

PROCEDURES

A Schedule of Assessments (SoA) is provided.

STATISTICAL METHODS

All HVs on placebo will be pooled as one treatment group.

SAFETY ANALYSES

All HVs who *have* receive*d* one dose of *the* study *medication, whether prematurely withdrawn from the study or not,* will be included in the safety analysis. The safety data*,* includ*ing* adverse events*,* injection site reactions *(*ISRs), reason for withdrawal from *study,* laboratory *data,* ECG*, concomitant medications,* vital signs and *physical examination results will be listed and summarized descriptively by treatment and dose level. All placebo patients will be pooled as one treatment group. 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.

PHARMACOKINETIC ANALYSES

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

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 including means, geometric means, standard deviations (SD), coefficients of variation (CV), medians and ranges. *Note: the geometric mean and associated CV% will be used to describe* C_{max}*,* AUC_{inf}*,* AUC_{last}*. 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 data from this study may be pooled with data from other studies to develop a population PK model.

The Power model method will be used to aid assessment of dose-proportionality, *as a departure from dose-proportionality could be an indication* [redacted]. For *each of* the PK parameters, AUC and C_{max}, a regression model will be fitted where the log transformed PK parameter is fitted as the response variable and log-transformed dose, treated as a continuous data, fitted as a fixed effect. The estimate of the regression coefficient for log dose and the intercept and associated 90% Confidence Intervals for each will be presented.

Urinary PK parameters will also be used [redacted]. In addition to the summaries described above for the urinary PK parameters, a two-parameter logistic regression model can be used to model the relationship between the dose and the probability of observing drug concentration in the urine. *Where p is the probability of observing concentration in the urine at a given dose,* α *is the log of the odds for p at the reference dose (i.e., equals to 0.3 mg/kg, the starting dose of SAD) and* β *is the change in log odds for an* $e^{1\text{-}fold}$ *increase in dose (detailed discussion can be found in Neuenschwander et al 2008).*

These analyses will be carried out initially at the end of the second cohort and at the end of each subsequent cohort[redacted].

OTHER ANALYSES

The *immunogenicity analyses, if applicable, will include subjects with a pre-dose* and *one post-dose ADA assessment, with subjects grouped according to treatment received.*

The kidney *and liver* biomarker*s (see Section 4.6.1.8) 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. A*t minimum, any data *that is* collected *as detailed in Section 4.6.1.7, and is* available at the time of database closure will be *listed and* summarized *using descriptive statistics. Data* may *also* be explored graphically.

SAMPLE SIZE JUSTIFICATION

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, as comparisons of these parameters across doses will be used in part [redacted].

Up to 50 HVs will be included in this study. Up to 5 cohorts of 10 HVs (8 on active and 2 on placebo per dose level) are planned with the fifth and last cohort being optional and based on the analysis of emerging PK and safety data from study BP39405.

CONCOMITANT MEDICATIONS

Restrictions apply to healthy volunteers regarding prescribed or over-the-counter (OTC) medication, vitamins, fish oils, protein powders, including herbal remedies, taken within 2 weeks prior to 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.

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

In the event that a HV requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor.

Medications used to treat an AE may only be prescribed after consultation with the Sponsor (with the exception of paracetamol), unless there is a medical need to ensure the well-being of the subject that should not be delayed.

It is unlikely that food will have an impact on the PK of RO7062931, however, RO7062931 should be administered in a fasted state (i.e., 2 hours before, or, 2 hours after a meal).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAV	Adeno-associated virus
AAV-HBV	Adeno-associated virus carrying a replicable hepatitis B virus genome
ADAs	Anti-drug antibodies
AE	Adverse events
A_e	Cumulative amount of drug excreted in urine over a 24-hour period
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
[redacted]	[redacted]
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
cccDNA	Covalently closed circular DNA
CHB	Chronic hepatitis B virus
CL	Clearance
CL/F	Apparent clearance
CNS	Central nervous system
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
dsDNA	Double stranded DNA
EC	Ethics Committee
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
ESF	Eligibility Screening Form

Abbreviation	Definition
ESR	Erythrocyte sedimentation rate
EU	European Commission
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLDH	Glutamate-dehydrogenase
GLP	Good Laboratory Practice
HAV	Hepatitis A virus
HBeAg	HBV envelop antigen
HBV	Hepatitis B virus
β-HCG	beta-human chorionic gonadotropin
HCV	Hepatitis C
HDL	High density lipoproteins
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
HV	Healthy volunteer
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRR	*Injection Related Reactions*
ISRs	Injection site reactions
k	Terminal elimination rate constant
KIM-1	Kidney injury molecule-1
LDH	Lactate dehydrogenase
LDL	Low density lipoproteins
LH	Luteinizing hormone
LLN	*Lower limit of normal*
LNA	Locked nucleic acid

Abbreviation	Definition
LSLO	Last study subject, last observation
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP	Mast cell protease
miRNA	Micro RNA
msec	Milliseconds
MTD	Maximum tolerated dose
NGAL	Neutrophil gelatinase-associated lipocalin
NHP	Non-human primate
NOAEL	No-observed-adverse-event level
OTC	Over-the-counter
PD	Pharmacodynamic
PEG-IFN	Pegylated IFN
PK	Pharmacokinetic
PT	Prothrombin time
QRS	QRS complex
QT	QT interval
RBC	Red blood cell
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SoA	Schedule of assessments
ssDNA	Single stranded DNA
SSO	Single stranded oligodeoxyribonucleotide
TNF	Tumor necrosis factor
ULN	Upper limit of normal
V	Volume
V_Z/F	Apparent volume of distribution
WBC	White blood cell

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, among which around 38% of the patient population reside in China (WHO 2015). 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 chronic hepatitis B virus (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 the 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). 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 a N-Acetylgalactosamine (GalNAc)-targeted locked nucleic acid (LNA)-containing single stranded oligodeoxyribonucleotide (SSO), complementary to HBV genome-derived mRNA species, 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 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], [redacted]. RO7062931 is [redacted] active in vitro against [redacted]. In mice infected with a recombinant adeno-associated virus (AAV) carrying a replicable HBV genome (AAV-HBV), administration of RO7062931 reduced [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

1.2.2 Previous Clinical Studies

Study BP39405, the first-in-human (FIH) study with RO7062931, *was* initiated in January 2017. *In this ongoing study, as of 8 November, 2017, 60 healthy subjects (including 15 Asian healthy subjects) had received a single dose of RO7062931 or placebo at various dose levels from 0.1, 0.3, 1.0, 2.0, 3.0 to 4.0 mg/kg. As of 8th November 2017, two HBV patients had been randomized in Part 2a of the study.*

[redacted]

[redacted]

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Study BP39405 is the first clinical study with 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 (Part 2). Study YP39432 will assess the safety, tolerability and PK of single

doses of RO7062931 in healthy Chinese volunteers, This initial evaluation will be important to inform future clinical studies in Chinese subjects.

This study will be conducted in healthy Chinese volunteers and results from this study will be compared with the global study, BP39405, to determine if there may be any detectable differences between Caucasian and Asian healthy volunteers in safety, tolerability and pharmacokinetics. For the healthy volunteers, no therapeutic benefit is anticipated. However, data from these healthy volunteers is expected to provide a clearer and more consistent assessment of safety and PK to allow better design of therapeutic studies in HBV patients.

1.3.2 Benefit–Risk Assessment

Limited clinical experience with RO7062931 currently exists. The evaluation of the potential risks of drug administration and the specific tests, observations, and precautions required for this clinical study with RO7062931 will be based on information from non-clinical toxicology and safety pharmacology studies as well as available data from the FIH study BP39405. Safety and tolerability will be carefully assessed, and HVs will be closely monitored. All dose levels to be included in this study will be within the dose-range which has been demonstrated to be safe and well-tolerated in the FIH study (BP39405). The study will be done under a controlled setting, with tight clinical and laboratory monitoring to minimize potential risks to the participants. Dose-escalation

decisions will be made based on the safety/tolerability and PK observations from the previous cohorts and the ongoing study BP39405.

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 doses in healthy Chinese volunteers.

2.2 SECONDARY OBJECTIVES

The secondary objective for this study is:

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

3. STUDY DESIGN

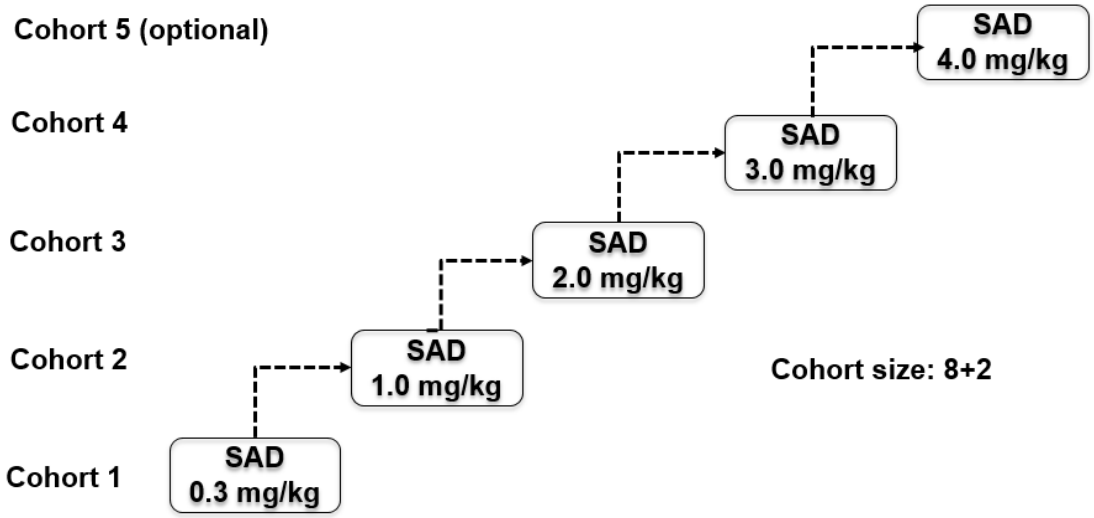
3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This study is randomized, Sponsor-open, Investigator-blind and subject-blind. Up to *five* ascending dose-levels (cohorts) will be explored within the dose-range shown to be safe and well-tolerated in Study BP39405. The planned doses for the first $four$ cohorts will be 0.3 mg/kg, 1.0 mg/kg, 2.0 mg/kg $and\ 3.0\ mg/kg$, respectively (see Figure 1). The planned dose-levels may be modified and an additional (optional, $4.0\ mg/kg$) cohort enrolled based on emerging results from ongoing preclinical and clinical studies (including this study).

It is planned to enroll 10 HVs in each cohort; eight HVs will receive RO7062931 and two will receive placebo. Sentinel dosing will be employed in each cohort, where two subjects will be dosed on Day 1, of which at least one HV will receive RO7062931 in order to monitor $for\ potential$ acute reactions. The remaining 8 subjects will be dosed on the following day (24 hours after the initial administrations) following satisfactory safety assessment of the first two HVs by the Investigator. The sentinel dosing requirements may be modified based on the data from Study BP39405.

Figure 1 Study Design



The total duration of the study for each HV will be up to *16* weeks divided as follows:

- Screening: Up to 4 weeks;
- In-Clinic period: Days -1 to 3;
- Safety Follow-up: up to at least Day *85*

3.1.2 Dose- 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 3.1.2.1). The actual doses may be modified based on emerging data from this study, and emerging results from ongoing preclinical studies and Study BP39405.

Escalation to the next dose cohort will be based primarily on the review of safety and tolerability information (including adverse events, electrocardiograms [ECGs], vital signs, clinical laboratory test results) collected *up to* 28 days post-dose *(Day 29 ± 2 Days)* and, all available PK data collected at least 7 days post-dose in a minimum of 8 subjects (receiving active drug or placebo) within the previous cohort. The decision to escalate the dose will be made by mutual agreement between the Sponsor and the Investigator.

3.1.2.1 Dose-Escalation Decision Criteria

This study uses a dose-escalation schedule that may be modified if:

- 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 3.1.2.2 below) but may exceed the dose level of 4.0 mg/kg (see Section 3.2.1) only if anticipated to be safe and necessary to generate additional PK data in support of dosing regimens for use in patients.

3.1.2.2 Dose-Escalation Stopping Criteria

Dose-escalation will not be implemented as planned if one of the criteria below 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 HVs receiving RO7062931 experience the following:

- Severe or clinically significant (as defined by the Investigator) RO7062931-related adverse events of the same character, or
- Clinically significant 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 (in 4 HVs) 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 should be halted.

Additionally, planned dose-escalation may be stopped by mutual agreement between the Sponsor and Investigator, [redacted]

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

Any serious adverse event considered related to study drug will lead to an immediate halt of study drug dosing, dose escalation and enrollment of new subjects until a thorough investigation has been conducted by the Sponsor's Clinical Team and the Principal Investigator. The sponsor or designee will notify all investigators and IRBs/EC regarding the outcome of such investigation, and the study will only continue if agreed by the IRBs/EC.

Due to the exploratory nature of this clinical study, its conduct can be discontinued at any time at the discretion of the Sponsor (see Section 4.7).

3.1.3 Communication Strategy

After each HV receives RO7062931 (or placebo), the Investigator(s) must confirm to the Sponsor that the HV 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). The Investigator(s) will provide a safety assessment feedback of the first two sentinel dosing HVs of each cohort prior to dosing the remaining HVs enrolled in the 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 has been completed, the Sponsor will organize a teleconference with the Investigator to discuss the safety and tolerability of RO7062931 and to discuss eventual next cohort(s) or continuation. During these teleconferences, adverse events (with severity assessed as given in Table 1) 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 Investigator(s) 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.

3.1.4 End of Study

The end of the study is defined as the date the last subject's (HV's) last observation (LSLO) occurs. LSLO is expected to occur at the safety follow-up visit of the last HV enrolled.

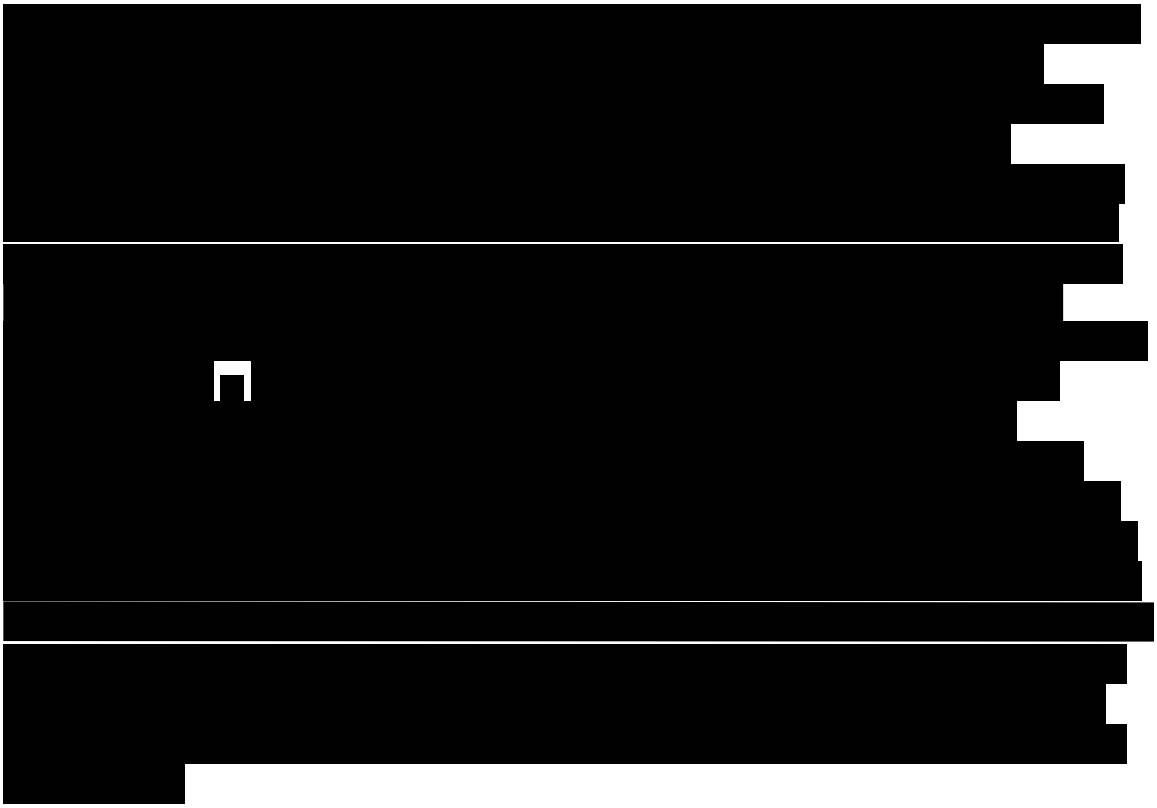
3.2 RATIONALE FOR STUDY DESIGN

Safety and PK of single RO7062931 doses will be characterized in HVs to determine the best liver-targeted dose to be evaluated in future studies in Chinese patients with CHB.

3.2.1 Rationale for Dosage Selection

The anticipated dose levels for this study are 0.3 mg/kg, 1.0 mg/kg, *2.0 mg/kg and 3.0* mg/kg for Cohorts 1-*4*. In addition, based on the PK and safety evaluation of the top dose cohort *and the available data from FIH Study BP39405*, an optional *fifth* cohort *(4.0 mg/kg)* may be enrolled. All dose levels in this study will be within the dose range which has been demonstrated to be safe and well tolerated in the BP39405 study. Doses up to 4.0 mg/kg are anticipated to be safe in humans [redacted]

*D*ata from the *ongoing* BP39405 study *have shown that single doses of RO7062931 from 0.1 to 4.0 mg/kg were considered safe and well tolerated in healthy humans (Section 1.2.2).* The planned starting dose of 0.3 mg/kg is higher than was used for the first EIH study, BP39405. The 0.3 mg/kg dose is chosen to minimize additional testing in Chinese HVs of doses that may not provide information. This starting dose would have a safety margin > 10-fold to the most sensitive species evaluated in GLP toxicology studies.



3.2.2 Rationale for Study Population

Chinese healthy male and post-menopausal or surgically sterile female HVs of 18 to 60 years of age, inclusive, have been selected for this study, for the following reasons:

- A dedicated study in HVs is expected to provide a more consistent and robust assessment of safety, PK parameters and pharmacological effect in the absence of potentially confounding disease and medications.
- Unexpected adverse events or toxicities are usually better identified and easier to treat in HVs without co-morbid diseases or concomitant medications. At the dose and regimen selected, HVs have lower risk of developing clinically significant sequelae from potential temporary adverse events.
- The rate of incidental or sporadic findings that may interfere with the assessment of basic safety parameters or with meeting study objectives is likely to be lower in healthy individuals than in patients.

- The doses to be explored in this study, will have already been declared as safe and well tolerated in the BP39405 study.

3.2.3 Rationale for Control Group

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

3.2.4 Rationale for Biomarker Assessments

Complementary liver biomarkers, attempting to further characterize potential hepatic effects may include microRNA-122 (miRNA-122) and glutamate dehydrogenase (GLDH). According to Hornby et al 2014, miRNA-122, a liver-enriched miRNA, has demonstrated its use both in animal and human studies as a sensitive and specific biomarker of drug induced liver injury (DILI) and may be elevated earlier than ALT. In addition, it has also been used as a marker of viral hepatitis; Zhang et al 2010 reported that plasma miRNA-122 levels change in patients infected with HBV showing a disease–severity relationship and a strong correlation with plasma ALT activity.

In the pre-clinical studies (monkey and rat GLP studies) with RO7062931, increased levels of α1-microglobulin, kidney injury molecule (KIM)-1, neutrophil gelatinase-associated lipocalin (NGAL) and β2-microglobulin were observed. In a first-in-human study, the treatment with the LNA antisense oligonucleotide SPC5001 (Poelgeest et al 2015) was associated with acute renal tubular toxicity at the highest dose tested. Therefore, urine kidney biomarkers α1-microglobulin, β2-microglobulin and KIM-1 will be included in this study to evaluate potential acute kidney effects.

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

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 5.1.3).
- 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, pulse rate and temperature (see Section 4.6.1.3).

3.3.2 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 and Appendix 2). 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/F (apparent clearance) and

  V_z/F (apparent 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.

3.3.3 Other outcome measures

- Kidney biomarkers including urine α1-microglobulin, β2-microglobulin and KIM-1.
- Liver biomarkers including, miRNA122 and GLDH.
- Assessments for inflammatory markers (complement, C-Reactive Protein [CRP], erythrocyte sedimentation rate [ESR], gamma globulin and the following inflammatory biomarkers [interleukin (IL)-6, IL-8, IL12, mast cell protease (MCP1), tumor necrosis factor (TNF)α]), drug induced autoantibodies and anti-drug antibodies (ADA).

4. MATERIALS AND METHODS

4.1 CENTER

An additional site(s) may be included for back-up purposes and may be activated if needed. Administrative and Contact Information, and List of Investigators are provided separately.

4.2 STUDY POPULATION

Healthy volunteers 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

HVs will be identified for potential recruitment using pre-screening enrollment logs, Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) approved newspaper/radio advertisements and mailing lists prior to consenting to take place on this study.

4.2.2 Inclusion Criteria

HVs must meet the following criteria for study entry:

1. Chinese healthy male and female (of non-childbearing potential) volunteers. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, concomitant drug use (including hormonal supplements), a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.
2. 18 to 60 years of age, inclusive.
3. A Body Mass Index (BMI) between 19 to 27 kg/m^2 inclusive and a body weight of at least 45 kg.
4. Women should be of non-childbearing potential. *These include those who have undergone surgical sterilization (removal of ovaries and/or uterus) or are* post-menopausal ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause, confirmed by follicle-stimulating hormone [FSH] $\geqslant$ *LLN (Local Lab)*, or amenorrhea for at least 24 months if on hormone replacement therapy [HRT]).

   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 up to 105 days after the last RO7062931 dose to avoid exposing the embryo to the study drug. 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 HV. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5. Able to participate and willing to give written informed consent and to comply with the study restrictions.
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.

4.2.3 Exclusion Criteria

HVs who meet any of the following criteria will be excluded from study entry:

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 *at Screening*.
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 *S*creening *or Day -1*.
6. Confirmed (e.g., two consecutive triplicate measurements) average resting pulse rate > 90 or < 45 beats per minute (bpm) at Screening *or Day -1.*
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 *S*creening *or Day -1*).
8. ECG morphology at *S*creening *or Day -1* 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 c*linically 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 *S*creening *or* on Day-1. *Abnormal renal function including serum creatinine* > ULN (Local Lab) or calculated creatinine clearance < 70 *mL/min (using the Cockcroft Gault formula).*

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 subject 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 3) and/or drug abuse within one year of randomization.
17. Hypersensitivity to the excipients of the study drug.
18. HVs under judicial supervision, guardianship or curatorship.

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study is Sponsor-open, Investigator-blinded and 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. Additionally, the site pharmacist and the study drug administrator 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 Contract Research Organisations (CROs) and any Sponsor staff in direct contact with the Investigators and the study sites, who will remain blinded.

Ten HVs will be randomized to active drug or placebo 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 HVs, one will receive active drug, and the other will receive placebo. The remaining 8 HVs 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 to a subject will be performed in isolation of other subjects.

To allow informed recommendations or decisions regarding the dose selection, an integrated assessment of the safety, tolerability and available PK data will be made prior to each dose decision (see Sections 3.1.2 to 3.1.3). 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.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 RO7062931 and Placebo

RO7062931 and placebo investigational medicinal products (IMPs) to be used in the study will be provided by Roche.

The drug substance RO7062931 is *colorless to yellow, brownish yellow or greenish yellow sterile liquid for injection* provided in single-use vials. As the formulation contains no preservatives, it should be diluted under appropriate aseptic conditions. An in-line filter must be used prior to administration (see Pharmacy Manual for further details).

Placebo vials are manufactured containing the same inactive ingredients (sodium chloride, sodium dihydrogen phosphate and disodium hydrogen phosphate) but no active substance.

The packaging and labeling of the study medication 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 (2-8°C, protected from light. For further details see the product 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.

For further details, see the RO7062931 Investigator's Brochure and Pharmacy Manual.

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. All RO7062931 doses *and placebo* 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.

4.4.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO7062931 and placebo) 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 HV to whom the study drug was dispensed (for example, HV's initials and date of birth).
- 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.

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Patients will be permitted to use the following therapies during the study:

- *Hormone-replacement therapy*
- *Paracetamol (up to 1 g per day)*
- *Medications used to treat an AE may only be prescribed after consultation with the Sponsor (with the exception of paracetamol), unless there is a medical need to ensure the well-being of the subject that should not be delayed. All therapy and/or medication administered to manage AEs should be recorded on the AE electronic case report form (eCRF).*

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

4.5.2 Prohibited Therapy

Use of 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 exceptions of therapies listed in Section 4.5.1. However, in the event that a HV requires additional medication during the course of the trial, this may be allowed after consultation with the Investigator and Sponsor.

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

4.5.3 Prohibited Food

There are no prohibited foods.

It is unlikely that food will have an impact on the PK of RO7062931, however, RO7062931 should be administered in a fasted state (i.e., 2 hours before, or, 2 hours after a meal).

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 and Appendix 2. 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, 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, herbal or homeopathic remedies, nutritional supplements) used by the study subject within 30 days prior to the Screening visit.

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'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 *S*creening 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 Schedule of Assessments tables (see Appendix 1 and Appendix 2). Blood pressure and pulse rate will be performed in triplicate (can be as short as 20 seconds to 1-minute interval between measurements) *and recorded in eCRF*. 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 pulse 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.

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 the Schedule of Assessments tables; Appendix 1 and Appendix 2), 12-lead ECGs will be obtained in triplicate, i.e., three consecutive interpretable 12-lead ECGs within a 2-5-minutes, and recorded in eCRF. 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 (if the schedule of assessment allows) ECG recordings within 3 hours after meals.
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

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the Schedule of Assessments (Appendix 1).

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 HV 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. 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, alkaline phosphatase (ALP), blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT) (at Screening only), creatine phosphokinase (at Screening only), total protein, albumin, creatinine *and calculated creatinine clearance using Cockcroft Gault formula*, glomerular filtration rate (GFR) calculated, uric acid, cystatin c, fasting glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (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. *All urine samples will also be 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: HIV-1 Antibody, HIV-2 Antibody, hepatitis A virus (HAV IgM Antibody), HBV (surface antigen, HBsAg), hepatitis C virus (HCV RNA or HCV antibody).
- 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.
- 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.

4.6.1.6 Pharmacokinetic Assessments

PK samples are mandatory. Blood and urine samples will be collected to evaluate the PK of RO7062931 and metabolites, if applicable, from all HV cohorts, as specified in the Schedule of Assessments (see Appendix 1 and Appendix 2). 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. The volume of each urine sample at each interval will be measured by the site staff and recorded in eCRF. 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 eCRF. RO7062931 levels will be analyzed by using validated assays.

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

[redacted] PK parameters will be estimated using standard non-compartmental methods for RO7062931/ metabolites.

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. Details on sampling procedures, sample storage and shipment are given in the lab manual.

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).

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.

4.6.1.7 Assessments for Inflammatory Markers, Drug-Induced 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. Based on 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. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

The timing of sampling and parameter may change based on emerging results and after agreement with the Sponsor and the Investigator.

The following separate assessments will take place in this study:

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

Inflammatory Markers

Blood samples for assessing inflammatory markers will be obtained for all HVs at pre-specified time-points (see the Schedule of Assessments; Appendix 1 and Appendix 2). In addition, in case an immune-driven adverse event/ an adverse event suggestive of immunological involvement occurs, an unscheduled sample will be collected as close to the onset of the adverse event as possible. Blood samples (both planned and unscheduled) will be taken to assess: complement, C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), gamma globulin and the following inflammatory biomarkers (interleukin [IL]-6, IL-8, IL12, mast cell protease [MCP1], tumor necrosis factor [TNF]α).

Drug-Induced Auto-antibodies

Blood samples for assessing drug-induced autoantibodies will be obtained for all study subjects before dosing, at baseline (see the Schedule of Assessments; Appendix 1 and Appendix 2). In addition, in case an autoimmune driven adverse event/ an adverse event suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected as close to the onset of the adverse event as is possible. The panel of autoantibodies to be assessed will be: anti-nuclear antibodies, anti-double-stranded DNA (dsDNA) antibodies, anti-histone antibodies, anti-single stranded DNA (ssDNA) antibodies, anti-neutrophil cytoplasmic antibody, anti-cardiolipin antibodies, rheumatoid factor.

ADA Assessment

Blood samples will be collected from all subjects at each time-point as specified in the Schedule of Assessments tables (Appendix 1 and Appendix 2). All ADA blood samples should 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 adverse event / an adverse event suggestive of immunological, anti-drug involvement or in case of an atypical PK result. If required, the residual of the ADA samples taken during the study (any time-point) can be used for additional analysis (including assay validations and immunogenicity analyses).

Unless otherwise indicated for the above samples, the collected samples will be stored for up to 5 years for the protocol assessments. Samples will be destroyed no later than 5 years after the date of final closure of the clinical database, unless regulatory authorities require specimens to be maintained for a longer time period.

4.6.1.8 Other Assessments

The following urinary kidney biomarkers will be analyzed from urine samples: α1-microglobulin, β2-microglobulin, and KIM-1. *Each biomarker will be normalized to urine creatinine.*

The following liver biomarkers will be analyzed from blood samples: miRNA122 and GLDH.

The timing of sampling and parameter may change based on emerging results and after agreement with the Sponsor and the Investigator.

Based on 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.

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Predosing 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 HVs and for HVs who are not subsequently enrolled will be maintained at the study site.

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

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

If a HV 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 28 days of the screening period. If the HV fails a second time, they will be classed as a screen failure and cannot be re-screened. Re-screening is allowed for HV who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized within 28 days after the start of screening period. In order to re-screen such a HV, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated if done more than 28 days before randomization.

4.6.2.2 Assessments during Drug administration

Under no circumstances will HVs who enroll in this study and have received RO7062931 or placebo as specified, be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as listed in the Schedule of Assessments (Appendix 1 and Appendix 2).

4.6.2.3 Follow-Up Assessments and Study Completion

HVs who complete the study, or who discontinue from the study early, *will be encouraged to attend the clinic for long term follow up as per the SOA in Appendix 1.*

Blood sample for PK and safety lab assessment will be collected in the event of early termination. Adverse events should be followed as outlined in Section 5.5.

4.7 HEALTHY VOLUNTEER, STUDY, AND SITE DISCONTINUATION

4.7.1 Healthy Volunteer Discontinuation

The Investigator has the right to withdraw a HV from the study at any time. In addition, HVs have the right to voluntarily 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*:*

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

Healthy volunteers who discontinue early for non-safety reasons may be replaced.

The decision to replace a subject will be made by a mutual agreement between the Sponsor and Investigator.

4.7.1.1 Withdrawal from Study

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

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

When a HV voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the HV specifically requests for these to be discarded or local laws require their immediate destruction.

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 HVs.
- Clinically significant changes in safety parameters considered to be related to RO7062931 and not considered acceptable by the Investigator and/or Sponsor.
- HV 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 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 5.3.5.8.
- 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 subject 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 5.3.5.9).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the HV'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 HV 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 (e.g., NCI CTCAE criteria; see Section 5.3.3); 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 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 subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Severe injection site reactions.
- Renal adverse events defined as serum creatinine 1.5 × upper limit of normal (ULN) or increase of ≥ 50% from baseline.

5.2 SAFETY PLAN

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

The Investigator has the right to withdraw a HV 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.

ALT elevations of 2-3 times the baseline value that are self-limited, are likely to reflect drug toxicity. Progressive increases, or ALT elevations associated with increases in bilirubin and alkaline phosphatase, should be treated as adverse events.

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.

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 HV or noted by study personnel, will be recorded in the HV'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 study drug administration (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 Healthy Volunteer 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 1 provides guidance for assessing adverse event severity in the study.

Table 1 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).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the HV, 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 HV 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.

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 related to the SC study drug injection should be captured as a diagnosis (e.g., “injection 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 4.* If a subject 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 HV 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 subject 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 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 Values

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

- Accompanied by clinical symptoms
- Results in a 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 Abnormal Liver Function Tests

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. 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.

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).

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 subject 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 subject 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 Preexisting Medical Conditions

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

A 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 Hospitalization or Prolonged Hospitalization

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

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

- Planned in-clinic stay required by the protocol for the study.

The following hospital 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.

5.3.5.10 Overdoses

Study drug 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 subjects, 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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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 Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

5.4.2.2 Events That Occur after Study Drug Initiation

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 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 Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Healthy Volunteers

Female subjects of childbearing potential will not be allowed to take part 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. 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 study subject, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Healthy Volunteer

Male subjects 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 HV 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 HV 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 (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 HV or female partner of a male HV 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).

5.5 FOLLOW-UP OF SUBJECTS 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 HV is lost to follow-up, or the HV 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 subject's medical records 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 subjects 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 administration, 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's Brochure

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

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, as comparisons of these parameters across doses will be used in part [redacted].

Up to 50 HVs will be included in this study. Up to 5 cohorts of 10 HVs (8 on active and 2 on placebo per dose level) are planned with the $fifth$ and last cohort being optional and based on the analysis of emerging PK and safety data from this study and available data from study BP39405.

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 HVs 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 by treatment and dose level. All HVs on placebo will be pooled as one treatment group.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All HVs who have received 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

HVs will be excluded from the PK 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 PK 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.

6.3.3 Immunogenicity Analysis Population

The immunogenicity analyses, if applicable, will include subjects with a pre-dose and one post-dose ADA assessment, with subjects grouped according to treatment received.

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

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Descriptive statistics will be generated for demographics, including sex, self-reported race, ethnicity, age.

Data for study drug administration and concomitant medication will be listed. The number of subjects who were randomized, completed treatment period, discontinued study and completed the study (including follow-up period) will be summarized by treatment and dose level. All placebo patients will be pooled as one treatment group.

6.5 SAFETY ANALYSES

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

The safety data, including adverse events, injection site reactions (ISRs), reason for withdrawal from study, laboratory data, ECG, concomitant medications, vital signs and physical examination results will be listed and summarized descriptively by treatment and dose level. All placebo patients will be pooled as one treatment group. 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.

Adverse events 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 reported 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 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 including means, geometric means, standard deviations (SD), coefficients of variation (CV), medians and ranges. Note: the geometric mean and associated CV% will be used to describe C_{max}, AUC_{inf}, AUC_{last}. 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 data from this study may be pooled with data from other studies to develop a population PK model.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.7 OTHER ANALYSES

6.7.1 Liver and Kidney Biomarker Data

The kidney and liver biomarkers (see Section 4.6.1.8) 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.

6.8 INFLAMMATORY MARKERS, DRUG-INDUCED AUTOANTIBODIES AND ADA DATA

At minimum, any data that is collected as detailed in Section 4.6.1.7 , and is available at the time of database closure will be listed and summarized using descriptive statistics. Data may also be explored graphically.

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 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 online 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 HV enrolled, an eCRF must be completed and electronically signed by the principal Investigator or authorized delegate from the study staff. If a HV withdraws from the study, the reason must be noted on the eCRF. If a HV 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 subject 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 subjects' 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, subject-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,

subject 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, 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 such as a Child's Assent or Caregiver's Informed Consent 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 subject 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 subject to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Subjects 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 subject 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 subject. All signed and dated Consent Forms must remain in each subject'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 subject, 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 subject 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 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 subject names are not included in data sets that are transmitted to any Sponsor location.

Subject 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 subject's personal physician or other appropriate medical personnel responsible for the subject'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., $LSLO$).

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 subject data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

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

Committee for Medicinal Products for Human Use (CHMP). Assessment Report: Kynamro Solution for injection 189 mg. European Medicines Agency (EMA) 2013.

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 2009;50:227-242.

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167–185.

Investigator's Brochure RO7062931.

Hornby RJ, Lewis PS, Dear J, et al. MicroRNAs as potential circulating biomarkers of drug-induced liver injury: key current and future issues for translation to humans. Expert Rev Clin Pharmacol. 2014;7(3):349-362.

Lucifora J, Xia Y, Reisinger F. Specific and non-hepatotoxic degradation of nuclear hepatitis B virus cccDNA. Science. 2014; 343(6176):1221-1228.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27(13):2420-2439.

Poelgeest EP, Hodges MR, Moerland M, et al. Antisense-mediated reduction of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9): a first-in-human randomized, placebo-controlled trial. Br J Clin Pharmaco.l 2015; 80(6):1350-1361.

World Health Organization (WHO). New Hepatitis B treatment guidelines released in China. 2015;
http://www.wpro.who.int/china/mediacentre/releases/2015/20150515/en/

WHO Fact Sheet N°204, updated July 2016.
(http://www.who.int/mediacentre/factsheets/fs204/en/index.html)

Zhang Y, Jia Y, Zheng R, et al. Plasma microRNA-122 as a biomarker for viral-, alcohol-, and chemical-related hepatic diseases. Clin Chem. 2010;1(12):1830-1838.

Appendix 1 Schedule of Assessments – Main table

Protocol Activity	Screening	Period 1								Follow Up		
Scheduled Time	Day -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 15	Day 29	Day 85[e]
Visit Window										(± 1 day)	(± 2 days)	(± 7 days)
Informed Consent	X											
Inclusion + Exclusion Criteria	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			
Drug-induced antibodies[i]			x[d]							X	X	X
ADA[f]			x[d]							X	X	X
Urine kidney biomarkers			x[d]	X	X				X		X	X
Blood liver biomarkers		X		X					X	X	X	X
Pregnancy Test[b]	X	X									X	X
FSH[c]	X											
Substance Use	X	X										
Admission		X										
Discharge					X							
Ambulatory Visit	X					X	X	X	X	X	X	X
Randomisation		X	X									
Medication			X									
Blood PK Sample[a]			12	3	X	X	X	X	X			
Urine PK Sample[j]			4	X								
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Treatments	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 1 Schedule of Assessments – Main table (cont.)

a) Timing of PK sampling may change based on PK results from the FIH (BP39405) study, blood sample for PK and safety laboratory assessments will be collected in the event of a SAE or at early termination.

b) Blood for 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.

d) Pre-dose.

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

f) For ADA samples will be stored and will only be analyzed in case an immune driven AE/AE suggestive of inflammatory 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) In case an autoimmune driven AE/AE suggestive of autoimmunological involvement occurs, an unscheduled sample will be collected and analysed.

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

Appendix 2 Schedule of Assessments – Detailed table

Period	Day	Scheduled Time (h)	Administration of Study Medication	Vital Signs	ECG-12 lead	Inflammatory markers	Drug-induced antibodies	ADA	Urine kidney biomarkers	Blood liver biomarkers	Blood PK Sample	Urine PK Sample[a]
Screening	Day -28 to -2			X	X							
Period 1	Day -1			X	X					X		
	Day 1	Predose		X	X	X	X	X	X		X	
		0	X									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 (± 1 day)			X	X		X	X		X		
	Day 29 (± 2 days)			X	X		X	X	X	X		
	Day 85 (± 7 days)			X	X		X	X	X	X		

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

Appendix 3
Alcohol Unit Calculation - Examples

From Australian Department of Health (Population Health Division)

http://www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/standard

Appendix 3
Alcohol Unit Calculation - Examples (cont.)

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

* Ready-to-Drink

Appendix 4
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*