Official Title: Open-Label Study to Investigate the Mass Balance and Absolute Bioavailability of a Single Oral Dose of [^{14}C]-Labeled RO7049389 or RO7049389 and an Intravenous Micro-Dose of [^{13}C]-Labeled RO7049389 in Healthy Volunteers

NCT Number: NCT04729309

Document Date: Protocol Version 3: 15-April-2021

PROTOCOL

TITLE:	**OPEN-LABEL STUDY TO INVESTIGATE THE MASS BALANCE AND ABSOLUTE BIOAVAILABILITY OF A SINGLE ORAL DOSE OF [^{14}C]-LABELED RO7049389 OR RO7049389 AND AN INTRAVENOUS MICRO-DOSE OF [^{13}C]-LABELED RO7049389 IN HEALTHY VOLUNTEERS**
PROTOCOL NUMBER:	BP41811
VERSION:	3
EUDRACT NUMBER:	2020-005301-70
TEST PRODUCT:	RO7049389
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 07 December 2020
DATE AMENDED:	Version 2: 10 February 2021 Version 3: See electronic date stamp

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
15-Apr-2021 17:07:22	Company Signatory	[redacted]

CONFIDENTIAL

PROTOCOL ACCEPTANCE FORM

TITLE:	**OPEN-LABEL STUDY TO INVESTIGATE THE MASS BALANCE AND ABSOLUTE BIOAVAILABILITY OF A SINGLE ORAL DOSE OF [^{14}C]-LABELED RO7049389 OR RO7049389 AND AN INTRAVENOUS MICRO-DOSE OF [^{13}C]-LABELED RO7049389 IN HEALTHY VOLUNTEERS**
PROTOCOL NUMBER:	BP41811
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EUDRACT NUMBER:	2020-005301-70
TEST PRODUCT:	RO7049389
SPONSOR:	F. Hoffmann-La Roche Ltd

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

[redacted] BSc, MD, DPM, MFPM (print)

Principal Investigator's Signature

Date

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

PROTOCOL AMENDMENT, VERSION 3
RATIONALE

During the Period 1 of the absolute bioavailability (BA) cohort, infusion pain events occurred in several participants after administration of [^{13}C]-labeled RO7049389. These adverse events (AEs) were identified to be most likely related to high concentration of potassium in the infusion solution of [^{13}C]-labeled RO7049389. Although these AEs were transient and the participants recovered soon after the infusion, Study BP41811 was temporarily halted after the completion of Period 1. The Sponsor amended this study protocol to ensure participant's safety. Changes to the protocol, along with a rationale for each change, are summarized below:

- In Table 3 (Section 1.3), the missing footnote (h) "Follicle stimulating hormone (females only to confirm post-menopausal status, performed at screening only)" has been added.
- Following Medicines and Healthcare products Regulatory Agency (MHRA) guidance relating to the management of COVID-19 vaccine deployment for ongoing non-COVID-19 clinical trials, Section 2.3.1.3 (Assessment Regarding COVID-19 Vaccination) has been added.
- Section 4.1 and Section 4.1.2 have been updated to remove the upper limit of the washout period (21 days) and to allow participants to be discharged after completing Period 1 and re-admitted for Period 2. The longer washout period is not considered to affect either the safety of participants or the integrity of the study. As the study is temporarily halted, the 21-day washout period will not be sufficient for the administration process; this amendment is to provide flexibility to keep the participants who have completed Period 1 to continue with Period 2.
- Since the upper limit of the washout period is removed and the participants are allowed to discharge from the site between the two periods of the absolute BA cohort, requirement for re-assessment of exclusion criteria 7, 8, 15 and 16 before admission/pre-dose of each treatment period have been added (Section 5.2).
- Section 5 and Section 9.1 have been update to remove the sentence "Up to 4 participants of each ethnic group can be replaced." As the participants have been discharged from the site and the washout period will be longer than 21 days, participants who prematurely discontinued from the study may be replaced due to non-safety related issues.
- In Section 6.1.2, a dilution step is added to the [^{13}C]-labeled RO7049389 infusion process, which will reduce the potassium concentration to below 30 mmol/L. The total dose and infusion time of [^{13}C]-labeled RO7049389 remain unchanged, and thus no impact on pharmacokinetics of RO7049389 is expected.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADME	Absorption, metabolism, distribution, and excretion
AE	Adverse event
aPTT	Activated partial thromboplastin time
ARSAC	Administration of Radioactive Substances Advisory Committee
AUC	Area under the curve
AUC_{last}	Area under the concentration–time curve from Time 0 to last measurable concentration
$AUC_{0\text{-}inf}$	Area under the concentration–time curve from Time 0 to infinity
BA	Bioavailability
BID	Twice daily
BP	Blood pressure
bpm	Beats per minute
CL	Clearance
CL/F	Apparent clearance
CLr	Renal clearance
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DIADS	Division of AIDS
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
F	Absolute bioavailability
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GI	Gastrointestinal
HAV	Hepatitis A virus
HBeAg	Hepatitis B surface antigen
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HDV	Total hepatitis D virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
HV	Healthy volunteers
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICRP	International Commission on Radiological Protection
IEC	Independent ethics committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
IV	Intravenous
LC-MS	Liquid chromatography–mass spectrometry
LDL	Low-density lipoproteins
LPLO	Last participant, last observation
LSC	Liquid scintillation counting
MAD	Multiple-ascending doses
MB	Mass balance
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
NSAESI	Non-serious adverse event of special interest
NUC	Nucleos(t)ide analogue
OATP	Organic-anion-transporting polypeptides
OTC	Over-the-counter
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Prothrombin time

QD	Once daily
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RNA	Ribonucleic acid
RR	RR interval
SAD	Single-ascending dose
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
$t_{1/2}$	Apparent terminal half life
t_{max}	Time of maximum concentration observed
ULN	Upper limit of normal
V/F	Apparent volume of distribution
V_{ss}	Volume of distribution at steady-state
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**OPEN-LABEL STUDY TO INVESTIGATE THE MASS BALANCE AND ABSOLUTE BIOAVAILABILITY OF A SINGLE ORAL DOSE OF [^{14}C]-LABELED RO7049389 OR RO7049389 AND AN INTRAVENOUS MICRO-DOSE OF [^{13}C]-LABELED RO7049389 IN HEALTHY VOLUNTEERS**
SHORT TITLE	**Mass balance and absolute bioavailability study of RO7049389 in healthy volunteers**
PROTOCOL NUMBER:	BP41811
VERSION:	3
TEST PRODUCT:	**RO7049389**
PHASE:	I

RATIONALE

[redacted] In order to better understand the disposition of RO7049389, it is important to characterize its metabolic profile and the rate and routes of elimination. To do this, it is necessary to administer a small amount of the drug, which has been radiolabeled in a stable position with carbon 14 [^{14}C]. The intravenously (carbon 13 [^{13}C]) will help differentiate non-absorbed drug and biliary secreted [^{13}C] parent/metabolites in feces. [redacted] Therefore, in the absolute oral bioavailability (BA) cohort of this study, RO7049389 will be administered orally (unlabeled) and intravenously [^{13}C] to allow the quantification of absolute BA [redacted] The results from the study will provide a more comprehensive understanding of the PK of RO7049389 and metabolites and allow for a more complete comparison of the routes of elimination and metabolic pattern of RO7049389 between animals and humans. The risks to the individual participant due to exposure to RO7049389, radiation, or study-related procedures are considered acceptable in this study. [redacted] the doses have been demonstrated to be safe and well tolerated in the Phase 1 study YP39364.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To characterize the mass balance (MB), routes, and rates of elimination of [^{14}C] RO7049389.	• Percentage of dose excreted in urine. • Percentage of dose excreted in feces.
• To determine the absolute oral bioavailability (BA) of RO7049389.	• Absolute oral BA for RO7049389.
• **Secondary**	
• To determine the plasma concentration of RO7049389, its identified three metabolites (RO7121986, RO7255420, and RO7255422), total drug-related radioactivity and related pharmacokinetic (PK) parameters.	• C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$, t_{max}, CL/F, CL, CLr, Ae, V/F and $t_{½}$ of RO7049389 and its identified three metabolites, and total drug-related radioactivity, if appropriate.
• To identify and quantify circulating and excreted metabolites of RO7049389 in plasma, urine, and fecal samples based on radioactive metabolic profiling.	• A metabolic profile for RO7049389 and metabolites, and their structural elucidation, if appropriate. • C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$, t_{max}, CL/F, CLr, Ae, V/F, and $t_{½}$ of other major metabolites related radioactivity, if appropriate.
• To evaluate the safety and tolerability of one or two single-doses of RO7049389 in healthy participants.	• Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG), and physical examination.

OVERALL DESIGN

Study Design

This is an open-label, two-cohort (i.e., a MB cohort and an absolute BA cohort), single-dose study designed to evaluate the MB and absolute BA of RO7049389 in HVs.

Male participants in the MB cohort will receive a 600 mg dose of [^{14}C] RO7049389 as an oral suspension under fasted conditions. Participants will then receive a 100-µg dose of [^{13}C] RO7049389 administered as a 10-minute intravenous (IV) infusion, 2 hours after the oral dose of [^{14}C] RO7049389.

In the absolute BA cohort, each participant will take part in both Period 1 and Period 2. Male or female participants in Period 1 of the absolute BA cohort will receive a 600 mg dose of [^{12}C] RO7049389 administered orally as a clinical formulation under fasted conditions. Participants will then receive a 100-µg dose of [^{13}C] RO7049389 administered as a 10-minute IV infusion, 2 hours after the oral dose of RO7049389.

After a washout period of at least 7 days, in Period 2, male or female participants will receive a 1000 mg dose of [^{12}C] RO7049389 administered orally as a clinical formulation under fasted conditions. Participants will then receive 100 µg of [^{13}C] RO7049389 administered as a 10-minute IV infusion, 2 hours after the oral dose of RO7049389.

Treatment Groups and Duration

The investigational medicinal products (IMPs) required for completion of this study will be [^{12}C] RO7049389 tablet, 200 mg, [^{14}C] RO7049389 oral suspension, 600 mg (NMT 2.2 MBq), and [^{13}C] RO7049389 solution for infusion, 20 µg/mL.

[^{12}C] RO7049389 tablet, 200 mg

An oral dose of RO7049389 600 mg (Period 1) or 1000 mg (Period 2) in the absolute BA cohort will be administered as a clinical formulation in the morning of Day 1 of Period 1 or Period 2, study drug administration will be after an overnight fast of at least 10 hours, followed by another 4 hours of fasting until lunch. Water will be allowed ad libitum until 1 hour prior to dosing and from 1-hour post dosing, at a maximum of three liters a day.

Study drug will be swallowed whole with still water.

[^{14}C] RO7049389 oral suspension, 600 mg (NMT 2.2 MBq)

On the morning of Day 1 for MB cohort, a 20- mL drinking suspension containing 600 mg of RO7049389, providing a maximum of 2.2 MBq of [^{14}C]-labeled RO7049389 (equivalent to 59.3 µCi) will be administered to all eligible participants after an overnight fast of at least 10 hours, followed by another four hours of fasting until lunch. Each participant will receive 190 mL of still water immediately after the dose has been swallowed, followed by a further 50 mL which will be used to rinse out the dosing vessels (50 mL will be used in five separate rinses). Water will be allowed ad libitum until 1 hour prior to dosing and from 1-hour post dosing, at a maximum of three liters a day.

[^{13}C] RO7049389 solution for infusion, 20 µg/mL

On Day 1 of MB cohort, on Day 1 of both Period 1 and Period 2 of absolute BA cohort, a single microdose of [^{13}C]-labeled RO7049389 100 µg will be administered by a 10-minute constant IV infusion. The IV infusion will start 2 hours after administration of the oral dose of RO7049389.

Length of Study

In the MB cohort, the total duration of the study for each participant will be about 8 weeks, divided as follows:

- Screening: Up to 28 days.
- In-clinic period: Day -1 to the day when the discharge criteria are met. This is up to a maximum of 12 days.
- Safety follow-up: One call on Day 29 $\pm$ 3.

In the absolute BA cohort, the total duration of the study for each participant will be $at\ least$ 9 $weeks$, depending on the duration of the washout period, divided as follows:

- Screening: Up to 28 days.
- In-clinic period: Days -1 to 4 for both Periods 1 and 2.
- Washout period: Defined as from Period 1 Day 1 to Period 2 Day 1 and lasts at least 7 days.
- Safety follow-up: One call on Period 2 Day 29 $\pm$ 3.

End of Study

A participant is considered to have completed the study if he/she has completed all parts of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur 28 $\pm$ 3 days after the last dose of RO7049389 is administered.

PARTICIPANT POPULATION

Inclusion Criteria

Informed Consent

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

Age

2. 35 to 65 years (MB cohort) or 18 to 60 years (absolute BA cohort), inclusive, at the time of signing the informed consent.

Type of Participants

3. Caucasian (both MB cohort and absolute BA cohort must have Caucasian parents and grandparents) or East Asian (for the absolute BA cohort only, participants must have Chinese, Korean or Japanese parents and grandparents).
4. Healthy, as judged by the Investigator based on the following definition.

   1. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12 lead ECG, and based on the laboratory safety test results.

Weight

5. Body mass index between 18 to 30 kg/m^2 (inclusive), and a weight range of 50 kg to 100 kg (inclusive) at screening.

Sex

6. Male (both MB cohort and absolute BA cohort) and female (absolute BA cohort only) participants

   The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

   Female Participants

   For women of childbearing potential: agree to use two methods of contraception, with at least one method considered as highly effective during the study and for at least 90 days after the last dose of study drug.

   a. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

b. Contraceptive methods considered as highly effective (failure rate < 1% per year when used consistently and correctly):
   - Combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation
   - Intrauterine device
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion/ligation
   - Vasectomized partner
   - Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study treatment and at least 90 days after the last dose of study drug. In such case, there is no need to use two contraceptive methods. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

Male Participants

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:
- Men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating semen during this same period.

Inclusions for Mass Balance Cohorts Only

7. Must have regular bowel movements (i.e. average stool production of ≥ 1 and ≤ 3 stools per day).

For both study parts, inclusion criterion 4 from the list above will be re-assessed at admission/pre-dose of each treatment period.

Exclusion Criteria

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

Medical Conditions

1. Pregnant (positive pregnancy test) or lactating women, and male participants with partners who are pregnant or lactating.

2. Have a history or symptoms of any clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, oncologic, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study treatment; or of interfering with the interpretation of data.
3. Confirmed (based on the average of three separate resting blood pressure (BP) measurements in a supine position, after at least 5 minutes of rest) systolic BP greater than 140 mmHg or less than 90 mmHg, and diastolic BP greater than 90 mmHg or less than 50 mmHg at screening and Day -1.
4. Personal history or family history of congenital long QT interval (QT) syndrome and/or cardiac sudden death.
5. History of Gilbert syndrome.
6. Participants who have had significant acute infection, e.g., influenza, local infection, acute gastrointestinal (GI) symptoms, or any other clinically significant illness within two weeks of dose administration.
7. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
8. Any clinically significant concomitant diseases or condition that could interfere with the conduct of the study, or in the opinion of the Investigator, would pose an unacceptable risk to the participant in this study.

Prior/Concomitant Therapy

9. Taking any herbal medications or substances, supplements (including vitamins), traditional Chinese medicines, prescription medicine, or over-the-counter medications within 14 days of first dosing or within 5 times the elimination half-life of the medication prior to first dosing, whichever is longer.

   Exceptions are medications listed under Permitted Therapy.
10. History of having received any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids) 6 months prior to the first dose of study drug or the expectation that such treatment will be needed at any time during the study.

Prior/Concurrent Clinical Study Experience

11. Are currently enrolled in or have participated in any other clinical study involving an investigational product or in any other type of medical research within the last 90 days (or within 5 half-lives of the investigational product, whichever is longer).
12. Donation or loss of blood or blood products in excess of 500 mL within three months of screening.

Diagnostic Assessments

13. Clinically relevant ECG abnormalities on screening, Day −1, or Day 1 (pre-dose), e.g.:
    a. QT corrected for heart rate (HR) using the Fridericia's correction factor (QTcF) > 430 msec (males), >450 msec (females), or < 300 msec (males and females).
    b. Notable resting bradycardia (HR < 45 beats per minute [bpm]), or HR > 90 bpm.
    c. Evidence of atrial fibrillation, atrial flutter, complete bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
14. Clinically significant ECG with QRS complex (QRS) and/or T-wave judged by the Investigator to be unfavorable for a consistently accurate QT measurement (e.g., neuromuscular artifact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves).
15. Creatinine clearance (CrCl) ≤ 70 mL/min (using the Cockcroft-Gault formula) at screening (may be repeated for confirmation) *or on Day -1*.
16. Evidence of current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., the virus that causes COVID-19) infection.
17. Positive test at screening of any of the following: hepatitis A virus (HAV immunoglobulin M [IgM] antibody), hepatitis B virus (HBV, HBsAg), hepatitis C virus (HCV ribonucleic acid [RNA]), hepatitis D virus (total HDV antibody), hepatitis E virus (HEV IgM antibody), and human immunodeficiency virus (HIV-1 antibody and HIV-2 antibody, or HIV-1/2 antibody).
18. Any other clinically significant abnormalities in laboratory test results at screening or on Day -1. In the case of uncertain or questionable results, tests performed during screening or Day -1 may be repeated once prior to enrollment to confirm eligibility unless deemed not clinically significant by the Investigator.

Other Exclusions

19. History of any drug or alcohol abuse in the past 2 years.
20. Regular alcohol consumption in males > 21 units per week and in females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
21. A confirmed positive alcohol breath test at screening and on Day −1.
22. Use of > five cigarettes or equivalent nicotine-containing product per day prior to screening.
23. Participants under judicial supervision, guardianship, or curatorship.
24. Medical or social conditions that would potentially interfere with the participant's ability to comply with the study visit schedule or the study assessments.
25. Sensitivity to any of the study treatments, or excipients thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the participation in the study.
26. Participants who do not have suitable veins for multiple venipunctures/cannulation as assessed by the Investigator or delegate at screening.

27. Participants who planned to attempt to have children within 90 days of dosing.

Exclusions for Mass Balance Cohorts Only

28. Regular work with ionizing radiation or radioactive material.
29. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic X-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last five years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study.
30. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton [excluding spinal column]), during work, or during participation in a medical trial in the previous year.
31. History of GI surgery (with the exception of appendectomy unless it was performed within the previous 12 months).
32. Acute diarrhea or constipation in the past seven days prior to admission. Diarrhea will be defined as the passage of liquid feces and/or a stool frequency of greater than three times per day. Constipation will be defined as a failure to open the bowels more frequently than every other day.

For both study parts, exclusion criteria 1, 3, 6, *7, 8,* 9, 12, 13, 14, *15, 16,* 18, 21, 22, 27, and 31 from the list above will be re-assessed at admission/pre-dose of each treatment period.

NUMBER OF PARTICIPANTS

A sample size of 6 healthy male participants for MB cohort was selected for practical purposes. Six participants are customary for this type of study, and should suffice to meet the objectives of the study while limiting the exposure of healthy male participants to radiolabeled study drug.

For the absolute BA cohort, the sample size of 16 participants (8 East Asian HVs and 8 Caucasian HVs) was chosen to estimate the absolute BA of the 600 mg and 1000 mg single-dose with sufficient precision for each ethnic group. The number of either gender of the enrolled participants should not exceed 12 participants of the same gender, nor should they all be in the same ethnic group (Caucasian or East Asian).

Participants prematurely discontinued from the absolute BA cohort of this study may be replaced to ensure adequate numbers of evaluable participants. Participants withdrawn for safety reasons will not be replaced.

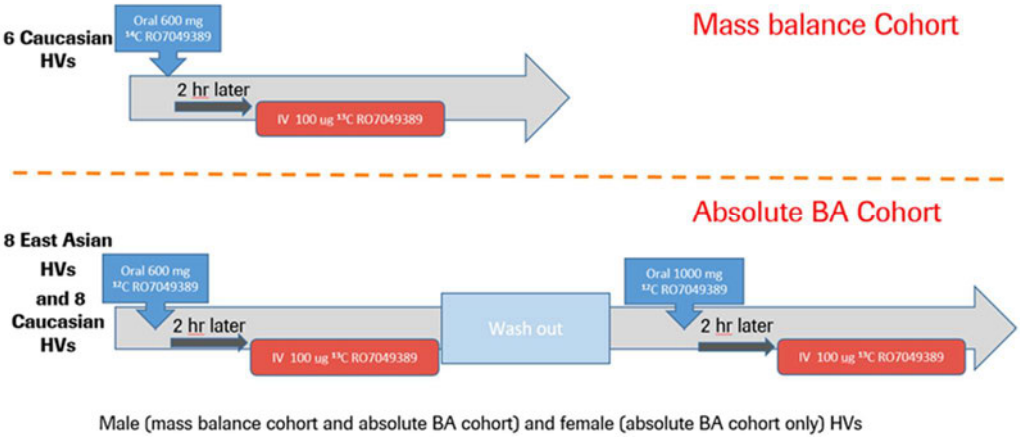
CONCOMITANT MEDICATIONS

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

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design



Male (mass balance cohort and absolute BA cohort) and female (absolute BA cohort only) HVs

1.3 SCHEDULE OF ACTIVITIES

The schedule of activities (SoA) for the mass balance (MB) cohort is provided in Table 1 and Table 2. The SoAs for the absolute bioavailability (BA) cohort is provided in Table 3 and Table 4.

Table 1 Mass Balance Cohort – Main Table

Assessments	Screening	Treatment Period				Follow Up Call	Early termination or Unscheduled visit
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3 to Day of Discharge	Day 29±3	
Time Relative (h)			0	24			
Assessments							
Informed Consent	X						
Eligibility	X	X					
Demography	X						
Vein assessment for venipunctures/cannulation	X						
Medical History	X	X					
Physical Examination[a]	X	X			X[j]		X
Vital Signs[b]	X	X	X		X[j]		X
ECG-12 lead[c]	X	X	X		X[j]		X
Hematology[d]	X	X			X[j]		X
Blood Chemistry[d]	X	X			X[j]		X
Coagulation[d]	X	X			X[j]		X
Urinalysis[d]	X	X			X[j]		X
Viral Serology[e]	X						
SARS-CoV-2[f]	X	X			X		X
Lipids[d]	X	X			X[j]		X
Drug/Alcohol Test	X	X					
Oral Administration of [^{14}C] RO7049389 suspension			X				
IV Administration of [^{13}C] RO7049389 solution			X				
Blood sampling for PK, radioactivity counting and metabolic profiling[g]			X	X	X		X[l]
Urine sampling for PK, radioactivity counting and metabolic profiling[g]			X	X	X		
Feces sampling for radioactivity counting and metabolic profiling[g]		X[k]	X	X	X		
Clinical Genotyping[h]			X				
In-Clinic Stay		X	X	X	X		
Discharge[i]					X		
Adverse Events	X						
Previous and Concomitant Treatments	X						

Table 1 Mass Balance Cohort – Main Table (cont.)

a) A full physical examination is required at screening and day of discharge. At other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator. Body weight will be recorded each time. Height and BMI will only be done at screening.

b) Vital signs include triplicate measurements of blood pressure and heart rate (taken approximately 1 minute apart) and a single assessment of body temperature (oral). Blood pressure and heart rate measurements will be assessed in a supine position after ≥ 5 minutes of rest.

c) 12-lead ECGs will be obtained after the participant has been in a supine position for at least 10 minutes. Automated ECG intervals (PR [PQ], QRS, QT, QTcF, RR) and HR will be captured or calculated, and the changes in T-wave and U-wave morphology will be documented.

d) Samples for clinical laboratory tests (hematology, chemistry, coagulation, urinalysis, and lipids) should be collected in the morning/at the most appropriate time. Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula at screening *and on Day -1*.

e) Hepatitis A virus (HAV) IgM antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) RNA, total hepatitis D virus (HDV) antibody, hepatitis E virus (HEV) IgM antibody, human immunodeficiency virus (HIV-1 antibody and HIV-2 antibody, or HIV-1/2 antibody).

f) Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, SARS-CoV-2 antibody will be done at screening. SARS-CoV-2 antigen will be done at screening, pre-admission, day before discharge *or* day of discharge.

g) Radioactivity counting will be continued until discharge criteria are met.

h) If the blood sample is not collected on Day 1, it may be collected at any time during the conduct of the clinical study.

i) The participant will not be discharged until criteria are met. This is up to a maximum of 264 hours post-dose (Day 12) in-clinic stay, and could include a further 5 days collection of urine and feces samples at home, if required.

j) Assessments done on the day of discharge. Tests should be performed after an overnight fast (for at least 10 hours).

k) Only one sample is collected. It will be kept and processed only if the pre-dose sample on Day 1 cannot be obtained.

l) Only collecting the PK sample.

Table 2 Mass Balance Cohort – Detailed Table

Period	Day	Scheduled Time (h)	Oral Administration of [^{14}C] RO7049389 suspension	IV Administration of [^{13}C] RO7049389 solution	Blood sampling for PK of [^{12}C] RO7049389 and its [^{12}C] metabolites	Blood sampling for PK of [^{13}C] RO7049389 and [^{13}C] M5	Blood sampling for [^{14}C] drug related material radioactivity counting	Blood sampling for [^{14}C] drug related material metabolic profiling	Urine sampling for [^{14}C] drug related material radioactivity counting and metabolic profiling	Feces sampling for [^{14}C] drug related materialradioactivity counting and metabolic profiling
Screening	Day -28 to Day -2									
Period 1	Day -1									X[f]
	Day 1	Pre-dose			X		X	X	X[e]	X
		0	X[a]						0-4 hr	0-24 hr
		0.5			X		X			
		1			X		X	X		
		1.5			X		X			
		2		X[b]	X[c]	X[c]	X[c]	X[c]		
		2.1333				X[d]				
		3			X	X	X			
		4			X	X	X	X		
		6			X	X	X		4-8 hr	
		8			X	X	X	X		
		10			X	X	X		8-12 hr	
		12			X	X	X	X		
	Day 2	24			X	X	X	X	12-24 hr	
		36			X	X	X	X	24-48 hr	24-48 hr
	Day 3	48			X	X	X	X		
	Day 4	72			X	X	X	X	48-72 hr	48-72 hr
	Day 5	96					X	X	72-96 hr	72-96 hr
	Day 6	120					X	X[g]	96-120 hr	96-120 hr
	Day 7	144					X	X[g]	120-144 hr	120-144 hr
	Day 8	168					X		144-168 hr	144-168 hr
	Day 9	192					X[h]		168-192 hr[h]	168-192 hr[h]
	Day 10	216					X[h]		192-216 hr[h]	192-216 hr[h]
	Day 11	240					X[h]		216-240 hr[h]	216-240 hr[h]
	Day 12	264					X[h]		240-264 hr[h,i]	240-264 hr[h,i]

Table 2 Mass Balance Cohort – Detailed Table (cont.)

a) Participants will fast overnight for at least 10 hours prior to oral administration and fasted 4 hours post administration.

b) Intravenous infusion administration over 10 minutes.

c) Collected prior to start of infusion.

d) Collected at the end of infusion.

e) Spot urine sample.

f) Only one sample is collected. It will be kept and processed only if the pre-dose sample on Day 1 cannot be obtained.

g) Metabolic profiling analyses may not be done depending on the radioactivity level.

h) Continued until discharge criteria are met.

i) If on Day 12 the discharge criteria are not met, the participant will be discharged and, urine and feces samples will be collected by the subject at home in 24 hours intervals for up to 5 days or until the discharge criteria are met.

Table 3 Absolute BA Cohort – Main Table

Assessments	Screening	Treatment Period					Follow Up Call	Early termination or Unscheduled visit
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Period 2, Day 29±3	
Time Relative (h)			0	24	48	72		
Assessments								
Informed Consent	X							
Eligibility	X	X						
Demography	X							
Medical History	X	X						
Vein assessment for venipunctures/cannulation	X							
Physical Examination[a]	X	X				X		X
Vital Signs[b]	X	X	X			X		X
ECG-12 lead[c]	X	X	X			X		X
Hematology[d]	X	X				X		X
Blood Chemistry[d]	X	X				X		X
Coagulation[d]	X	X				X		X
Urinalysis[d]	X	X				X		X
Viral Serology[e]	X							
SARS-CoV-2[f]	X	X				X		X
Lipids[d]	X	X				X		X
Drug/Alcohol Test	X	X						
Pregnancy Test[g]	X	X						X
Follicle Stimulating Hormone[h]	X							
Oral Administration of [^{12}C] RO7049389 tablet			X					
IV Administration of [^{13}C] RO7049389 solution			X					
Blood sampling for PK			X	X	X	X		X
Urine sampling for PK			X	X	X	X		
Clinical Genotyping[i]			X					
In-Clinic Stay		X	X	X	X			
Discharge[j]						X		
Adverse Events	X							
Previous and Concomitant Treatments	X							

Table 3 Absolute BA Cohort – Main Table (cont.)

a) A full physical examination is required at screening and day of discharge. At other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator. Body weight will be recorded each time. Height and BMI will only be done at screening.

b) Vital signs include triplicate measurements of blood pressure and heart rate (taken approximately 1 minute apart) and a single assessment of body temperature (oral). Blood pressure and heart rate measurements will be assessed in a supine position after ≥ 5 minutes of rest.

c) 12-lead ECGs will be obtained after the participant has been in a supine position for at least 10 minutes. Automated ECG intervals (PR [PQ], QRS, QT, QTcF, RR) and HR will be captured or calculated, and the changes in T-wave and U-wave morphology will be documented.

d) Samples for clinical laboratory tests (hematology, chemistry, coagulation, urinalysis, and lipids) should be collected in the morning/at the most appropriate time. Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula at screening *and on Day -1*.

e) Hepatitis A virus (HAV) IgM antibody, Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) RNA, total hepatitis D virus (HDV) antibody, hepatitis E virus (HEV) IgM antibody, human immunodeficiency virus (HIV-1 antibody and HIV-2 antibody, or HIV-1/2 antibody).

f) Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, SARS-CoV-2 antibody will be done at screening. SARS-CoV-2 antigen will be done at screening, pre-admission, day before discharge *or* day of discharge.

g) Serum beta-human chorionic gonadotropin (b-HCG) at screening, urine on all other occasions (females only). If urine test is positive, then a confirmatory serum test is needed.

h) *Follicle stimulating hormone (females only to confirm post-menopausal status, performed at screening only).*

i) If the blood sample is not collected on Day 1, it may be collected at any time during the conduct of the clinical study.

j) Assessments will be performed after an overnight fast (for at least 10 hours).

Table 4 Absolute BA Cohort – Detailed Table

Period	Day	Scheduled Time (h)	Oral Administration of [^{12}C] RO7049389 tablet	IV Administration of [^{13}C] RO7049389 solution	Blood sampling for PK of [^{12}C] RO7049389 and its [^{12}C] metabolites	Blood sampling for PK of [^{13}C] RO7049389 and [^{13}C] M5	Urine sampling for PK of [^{12}C] RO7049389 and its [^{12}C] metabolites
Screening	Day -28 to Day -2						
Period 1 and Period 2	Day -1						
	Day 1	Pre-dose			X		X[e]
		0	X[a]				0-4 hr
		0.5			X		
		1			X		
		1.5			X		
		2		X[b]	X[c]	X[c]	
		2.1333				X[d]	
		3			X	X	
		4			X	X	
		6			X	X	4-8 hr
		8			X	X	
		10			X	X	8-12 hr
		12			X	X	
	Day 2	24			X	X	12-24 hr
		36			X	X	24-48 hr
	Day 3	48			X	X	
	Day 4	72			X	X	48-72 hr

a) Participants will fast overnight for at least 10 hours prior to oral administration and fasted 4 hours post administration.

b) Intravenous infusion administration over 10 minutes.

c) Collected prior to start of infusion.

d) Collected at the end of infusion.

e) Spot urine sample.

2. INTRODUCTION

RO7049389 is an orally administered small molecule that is being developed for the treatment of chronic hepatitis B virus (HBV) infection.

2.1 STUDY RATIONALE

[redacted] In order to better understand the disposition of RO7049389, it is important to characterize its metabolic profile and the rate and routes of elimination. To do this, it is necessary to administer a small amount of the drug, which has been radiolabeled in a stable position with carbon 14 [^{14}C]. The intravenously (carbon 13 [^{13}C]) will help differentiate non-absorbed drug and biliary secreted [^{13}C] parent/metabolites in feces. [redacted] Therefore, in the absolute oral BA cohort of this study, RO7049389 will be administered orally (unlabeled) and intravenously [^{13}C] to allow the quantification of absolute BA [redacted] The results from the study will provide a more comprehensive understanding of the PK of RO7049389 and metabolites and allow for a more complete comparison of the routes of elimination and metabolic pattern of RO7049389 between animals and humans. The risks to the individual participant due to exposure to RO7049389, radiation, or study-related procedures are considered acceptable in this study. [redacted] the doses have been demonstrated to be safe and well tolerated in the Phase 1 study YP39364.

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

2.2 BACKGROUND

HBV infection is a major cause of both acute hepatitis and chronic liver diseases, including cirrhosis and hepatocellular carcinoma. Approximately 257 million people worldwide are living with chronic HBV infection (defined as hepatitis B surface antigen [HBsAg] positive). In 2015, HBV resulted in an estimated 887,000 deaths, mostly from complications including cirrhosis and hepatocellular carcinoma (WHO 2020; EASL 2017).

Currently, there are two classes of drugs available for the treatment of chronic HBV: subcutaneously administered interferon preparations and orally administered nucleos(t)ide analogues (NUCs). Although both types of treatment can induce the loss of

hepatitis B e antigen (HBeAg) with the development of anti-HBeAg antibody (serological response), the suppression of HBV deoxyribonucleic acid (DNA) to an undetectable level by sensitive polymerase chain reaction (PCR) methods (virological response), and are able to normalize liver transaminases levels (biochemical response), neither treatment achieves a high rate of functional cure. HBsAg loss only occurs in approximately 3% of patients after one year of treatment and in <15% after 1 to 5 years follow-up (EASL 2017). In addition, interferon-based therapies are associated with many side effects, while NUCs frequently require prolonged or possibly life-long therapy, and some are associated with a high risk of viral resistance. Thus, there is an unmet medical need for a therapy that can achieve a higher rate of functional cure, has a finite treatment duration, and is well tolerated.

RO7049389 is an inhibitor of HBV capsid assembly and belongs to the well-studied class of heteroaryldihydropyrimidine compounds. This class of compounds induces formation of abnormal HBV core protein aggregates, which are subsequently recognized and depleted. Depleting functional core protein results in interruption of viral assembly and inhibition of HBV replication.

Three Phase I clinical studies of RO7049389 have been completed: YP39364 (Parts 1 and 2), YP39406, and YP40218.

In Study YP39364, Parts 1 and 2 were randomized, Sponsor open, Investigator blinded, and participant-blinded. Part 1 was a single-ascending dose (SAD) and multiple-ascending doses (MAD) investigation of the safety, tolerability, and PK of RO7049389 following oral administration in HVs, including the effect of food on the PK of single-dose RO7049389 and the effect of multiple-dose RO7049389 on the PK of midazolam. Part 2 evaluated the safety, tolerability, PK, and pharmacodynamics (PD) of orally administered RO7049389 in patients chronically infected with HBV.

Study YP39406 was a single center, randomized, Sponsor-open, Investigator-blinded, participant-blinded, placebo-controlled, SAD, and MAD study to investigate single and multiple doses of RO7049389 in HVs of Chinese descent for comparison with HVs in Part 1 of Study YP39364.

Study YP40218 was a DDI study to assess the effects of RO7049389 as an OATP inhibitor on the PK of OATP substrate (pitavastatin as a probe drug).

[redacted]

[redacted]

[redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of RO7049389 is provided in the RO7049389 Investigator's Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

This study has the principal aim of characterizing the MB, metabolite identification, metabolism routes, rates of elimination, and absolute oral BA of RO7049389, in a population of HVs. There will be no therapeutic benefit for the HVs participating in the study. However, assessment of the MB and absolute BA of RO7049389 brings valuable information for the development of RO7049389.

[redacted]

The total burden of radioactivity associated with the dose planned in this MB cohort (not more than 59.3 µCi; 2.2 MBq) is 0.57 mSv which is well below the maximum effective dose of 1 mSv to fall into, International Commission on Radiological Protection (ICRP) Category IIa.

Furthermore, an assessment was conducted to determine whether there is any impact of the COVID-19 pandemic on the benefit/risk assessment of this study protocol, including but not limited to the participants in this study and the study treatment evaluated. Based on that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk mitigation measures provided in the study protocol are considered adequate.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7049389 is provided in the RO7049389 IB.

2.3.1 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to parts of the study, which will be conducted during the coronavirus disease 2019 (COVID-19) pandemic.

2.3.1.1 IMP-related Risk

Against the background of the COVID-19 pandemic, the potential risk of a participant developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the investigational medicinal product (IMP)–as an inhibitor of HBV capsid assembly – has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a participant would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to HVs enrolled in the study.

2.3.1.2 General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient Sciences clinical unit's monitoring and prevention-control measures.

COVID-19 testing may be performed on the basis of current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen PCR test performed at screening, the day before admission to each treatment period, and discharge or the day before discharge from each treatment period. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the Investigator site file (ISF) via the Clinical Kick-Off Meeting minutes.

The risk mitigation measures, where applicable, will be amended on the basis of emerging government guidance.

2.3.1.3 *Assessment Regarding COVID-19 Vaccination*

Against the background of the COVID-19 pandemic, the risk assessment of the effect of the IMP RO7049389 and concomitant administration of a COVID-19 vaccination has been evaluated for this study. The mode of action of the IMP – as an inhibitor of HBV capsid assembly – has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that COVID-19 vaccinations are simple concomitant medicines with no interaction with the IMP. However, all concomitant medications are prohibited within 14 days prior to the first dosing or within 5 half-lives

of the medication prior to the first dosing until after collection of the final sample (Section 6.5.2). This is due to the nature and short duration of the study, but not for safety reason. As a mass balance and absolute bioavailability study conducting in healthy volunteers, prohibition of all concomitant medications is required to ensure the integrity of the study by minimizing any potential physiological changes.

3. OBJECTIVES AND ENDPOINTS

	Objectives	Endpoints
Primary		
	• To characterize the mass balance (MB), routes, and rates of elimination of [^{14}C] RO7049389. • To determine the absolute oral bioavailability (BA) of RO7049389.	• Percentage of dose excreted in urine. • Percentage of dose excreted in feces. • Absolute oral BA for RO7049389.
Secondary		•
	• To determine the plasma concentration of RO7049389, its identified three metabolites (RO7121986, RO7255420, and RO7255422), total drug-related radioactivity and related pharmacokinetic (PK) parameters.	• C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$, t_{max}, CL/F, CL, CLr, Ae, V/F, and $t_{½}$ of RO7049389 and its identified three metabolites, and total drug-related radioactivity, if appropriate.
	• To identify and quantify circulating and excreted metabolites of RO7049389 in plasma, urine, and fecal samples based on radioactive metabolic profiling.	• A metabolic profile for RO7049389 and metabolites, and their structural elucidation, if appropriate. • C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$, t_{max}, CL/F, CLr, Ae, V/F and $t_{½}$ of other major metabolites related radioactivity, if appropriate.
	• To evaluate the safety and tolerability of one or two single-doses of RO7049389 in healthy participants.	• Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG), and physical examination.

OBJECTIVES AND ENDPOINT (CONT.)

Exploratory		
	• To determine whether genes relating to drug-metabolizing enzymes and/or drug transporters affect the PK and/or the safety profile of RO7049389.	• The pharmacogenetics of metabolizing enzymes (CYP3A4, UGT1A3) and transporters (OATP1B) possibly involved in the absorption, distribution, metabolism, and excretion of RO7049389 and its major metabolites.
	• To determine the relative BA of RO7121986.	• C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$ of RO7121986 after oral and intravenous (IV) administration of RO7049389.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, two-cohort (i.e., a MB cohort and an absolute BA cohort), single-dose study designed to evaluate the MB and absolute BA of RO7049389 in HVs.

An overview of the study design is provided in Section 1.2. The investigational medicinal products (IMPs) required for completion of this study will be [^{12}C] RO7049389 tablet, 200 mg, [^{14}C] RO7049389 oral suspension, 600 mg (NMT 2.2 MBq), and [^{13}C] RO7049389 solution for infusion, 20 µg/mL.

Male participants in the MB cohort will receive a 600 mg dose of [^{14}C] RO7049389 as an oral suspension under fasted conditions. Participants will then receive 100-µg dose of [^{13}C] RO7049389 administered as a 10-minute intravenous (IV) infusion, 2 hours after the oral dose of [^{14}C] RO7049389.

In the absolute BA cohort, each participant will take part in both Period 1 and Period 2. Male or female participants in Period 1 of the absolute BA cohort will receive a 600 mg dose of [^{12}C] RO7049389 administered orally as a clinical formulation under fasted conditions. Participants will then receive a 100-µg dose of [^{13}C] RO7049389 administered as a 10-minute IV infusion, 2 hours after the oral dose of RO7049389.

After a washout period of at least 7 days, in Period 2, male or female participants will receive a 1000 mg dose of [^{12}C] RO7049389 administered orally as a clinical formulation under fasted conditions. Participants will then receive 100 µg of [^{13}C]

RO7049389 administered as a 10-minute IV infusion, 2 hours after the oral dose of RO7049389.

4.1.1 Discharge Criteria for Mass Balance Cohort

In the MB cohort, total urine and feces will be collected at appropriate time intervals in the unit until the following discharge criteria are met:

At least 90% of the total radioactivity has been recovered in urine and feces, or < 1% of the administered dose excreted in two consecutive 24-hour urine and fecal samples, whichever is shorter.

All participants are required to stay in the unit at least until the morning of Day 8. If the results from the samples collected for up to 144 hours show that all participants meet the discharge criteria, then all participants are discharged from the unit on Day 8.

If the samples collected up to 144 hours show that not all participants meet the discharge criteria, then all participants will be kept in the unit to collect additional samples until the results from the samples collected for up to 192 hours show that all participants meet the discharge criteria. All participants are therefore discharged either on Day 9 or on Day 10, depending on when the discharge criteria are met by all participants.

If the samples collected up to 192 hours show that not all participants meet the discharge criteria, then all participants will be kept in the unit for a maximum of 2 additional days (until the morning of Day 12) to collect additional samples. Based on the results from the samples collected up to 240 hours, participants are allowed to be discharged on an individual basis if the discharge criteria are met.

The remaining participants who do not meet the discharge criteria by the morning of Day 12 will be discharged from the unit and will be required to collect further samples (urine/feces) at home for up to a maximum of five additional days, until the discharge criteria are met.

4.1.2 Length of the Study

The identity of the participants will be confirmed at admission and pre-dose. In addition, the ongoing eligibility of participants will be re-assessed at admission/pre dose, as described in Section 5.1 and Section 5.2. Admission/pre-dose safety procedures such as safety bloods tests, ECGs, vital signs, urinalysis, and drugs of abuse tests can be repeated as clinically indicated under the discretion of Investigator or sub-investigator if there is a concern regarding a participant's safety or eligibility to participate in the clinical trial. Reserve participants for the first dose occasion, in any group, will not require admission procedures to be repeated if dosing is within 2 days.

The participants will be admitted to the clinical unit on the morning before dosing (Day -1).

In addition, participants may be required to visit the clinical unit on the day before admission for each treatment period for SARS-CoV-2 antigen tests (if required).

In the MB cohort, the total duration of the study for each participant will be about 8 weeks, divided as follows:

- Screening: Up to 28 days.
- In-clinic period: Day -1 to the day when the discharge criteria (See Section 4.1.1) are met. This is up to a maximum of 12 days.
- Safety follow-up: One call on Day 29 ± 3.

In the absolute BA cohort, the total duration of the study for each participant will be $at\ least\ 9\ weeks$, depending on the duration of the washout period, divided as follows:

- Screening: Up to 28 days.
- In-clinic period: Days -1 to 4 for both Periods 1 and 2.
- Washout period: Defined as from Period 1 Day 1 to Period 2 Day 1 and lasts at least 7 days.
- Safety follow-up: One call on Period 2 Day 29 ± 3.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

The primary objectives of this study are to characterize the routes and rates of elimination of [^{14}C]-labeled RO7049389 and to assess the absolute oral BA of a single-dose of 600 mg and 1000 mg of RO7049389. Drug concentrations or radioactivity in plasma, urine, and feces is assumed to be objective measurements, which cannot be affected by volunteer or staff behavior. Therefore, it is generally accepted to conduct MB study and absolute BA study with an open-label design, without placebo treatments, and since the evaluation of safety and tolerability is not a primary objective of this study, an open-label design was deemed appropriate.

For the absolute BA cohort, to minimize the number of participants needed and reduce inter-subject variability, this study will follow a two-period design instead of a parallel design. The duration of the washout period was established based on the known PK profile of RO7049389.

The concept of simultaneous dosing with a labeled IV dose and an unlabeled oral dose to determine absolute oral BA is well-established using stable non-radioactive isotope such as ^{13}C. This technique allows the fate of the IV dose to be distinguished from the

oral dose by means of the isotopic tracer. Plasma concentrations will be determined by LC-MS/MS and the [^{13}C]-labeled drug administered intravenously will be distinguished from the [^{12}C]-unlabeled drug (i.e., in this study RO7049389) administered orally by virtue of their different molecular masses, using mass spectrometry detection. Dose-normalized AUCs of [^{12}C]-unlabeled drug on the one hand and [^{13}C]-labeled drug on the other hand will be compared to determine absolute oral BA. The principle advantage of the isotopic method is that the plasma drug concentration relating to the IV and oral doses will be measured in the same plasma sample, thereby eliminating inter-occasional variability and, in theory, eliminating any concentration-dependent clearance.

In this study, 100 µg of [^{13}C] RO7049389, the IV tracer, will be administered 2 hours (the estimated t_{max} of the oral dose) after the oral dose of RO7049389 as a 10-minute infusion. Administering IV dose at the t_{max} of the oral dose is expected to reduce errors in BA estimation due to concentration dependent clearance considering the observed non-linear PK of RO7049389 in the Phase 1 studies.

4.2.1 Rationale for Study Population

In this study, HVs have been chosen to avoid any confounding disease processes, thus ensuring a clear and more consistent assessment of drug disposition. Additionally, HVs are unlikely to require concomitant treatments, which could interfere with the absorption, distribution, metabolism, or excretion of RO7049389.

[redacted]

We acknowledge that the Administration of Radioactive Substances Advisory Committee (ARSAC) Notes for Guidance recommend that wherever possible, HVs selected for research projects should be aged over 50 years. However, the current MB cohort of the study is designed to generate data for supporting the investigation of the human absorption, metabolism, distribution, and excretion (ADME) of a drug, as well as generating samples for metabolite profiling and structural identification.

There are two main reasons for generating these data within a clinical development program. The first is to provide human metabolite data that can be used to interpret the metabolism profiles seen in the preclinical species employed in the longer-term toxicity studies, to ensure that there is adequate toxicology coverage for the safe development of the drug in patients. The second is to provide data to understand how the drug is processed in physiologically normal participants, because understanding the routes of metabolism and elimination in a healthy population generates the appropriate data to guide the clinical pharmacology package required to fulfil the regulatory requirements of a New Drug Application.

In order to address these two main aims of a MB study, investigation of the drug under development is required in a population with normal physiological function, as it is recognized that certain physiological processes e.g., renal function, deteriorate with age and therefore it is preferable to use as healthy a population to possibly mitigate against factors which may make interpretation of the data difficult. In addition, healthy subjects as a trial population are ideal, because they have a relatively stable physiological, biochemical and hormonal status, which removes any disease-related variations and variations due to concomitant medications. Therefore, given the aims of this MB cohort, our target age range for the MB cohort of this study will be 35 to 65 years.

There are potential risks to female subjects with respect to pregnancy from exposure to ionizing radiation. Thus, evaluation in a group of healthy male volunteers, the population most widely used in this type of study, is appropriate for the MB cohort.

4.3 JUSTIFICATION FOR DOSE

4.3.1 Justification for Dose selection

[redacted] Therefore, a single oral dose of 600 mg of RO7049389 has been selected for this study. In addition, a dose of 1000 mg RO7049389 in the absolute BA cohort will be studied to investigate the dose-dependent changes in oral BA and/or clearance.

In this study, an IV micro dose of [^{13}C] RO7049389 is administered following administration of an oral dose of RO7049389 to determine the BA of the oral dose compared with that of the IV dose. According to the International Council for Harmonisation (ICH) M3 guidance, a micro dose is a dose that is $<$1/100th of the pharmacologically active dose up to a maximum of 100 µg. In addition, to ensure that the IV micro dose does not contribute significantly to the exposure following oral dosing, the IV dose has been reduced further and in this study will be 1/6000th (600 mg) or 1/10000th (1000 mg) of the oral dose, and hence is an appropriate ‘IV microtracer dose’.

4.3.2 Justification for Radioactive Dose Selection

The oral radioactive dose of not more than 2.2 MBq (59.3 µCi) was chosen based on calculations using the tissue distribution data from studies in rats to identify the critical organs and restrict the exposure of the participants to radioactivity within the limits set by the ICRP. A radioactive dose is necessary to investigate potential minor metabolites, as well as quantitatively measure the major metabolites of RO7049389 in urine and feces. The committed effective dose obtained for oral administration of [^{14}C]-RO7049389 to male participants was calculated as 2.6×10^{-10} Sv Bq^{-1}.

On this basis, the maximum administered activity that would comply with the World Health Organization (WHO) recommendation (WHO 1977) of a 500 µSv maximum for

Category 1 projects would be 1.92 MBq (52.4 µCi). The WHO categories have been modified by ICRP in the light of the 1990 recommendations, which call for the special consideration of dose constraints for scientific and clinical studies involving the exposure of participants. The dose to male participants proposed in the MB cohort of this study will be 0.57 mSv and so classed as ICRP Category IIa.

To ensure that the [^{14}C] drug product to be used in this study does not exceed the limit for radioactive dose approved by the ARSAC, the target radioactive dose of the drug product will be set at 90% of the threshold radioactive dosing limit. This will allow for tolerance in the manufacturing processes for both drug substance and drug product, thereby providing continued assurance for compliance with the ARSAC-approved limit for drug-product radioactivity dose.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all parts of the study, including the last scheduled procedure shown in the SoAs.

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur 28±3 days after the last dose of RO7049389 is administered.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

Participants of this study are healthy male (both MB cohort and absolute BA cohort) and female (absolute BA cohort only) volunteers of 35 to 65 years (MB cohort) or 18 to 60 years (absolute BA cohort) of age, inclusive.

For the absolute BA cohort, each participant will take part in both Period 1 and Period 2. The number of either gender of the enrolled participants should not exceed 12 participants of the same gender, nor should they all be in the same ethnic group (Caucasian or East Asian).

Participants who drop out of the study for non-safety reasons in the absolute BA cohort may be replaced. Participants who withdraw from the study due to poor tolerability or due to study drugs (RO7049389) related AEs will not be replaced.

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

5.1 INCLUSION CRITERIA

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

Informed Consent

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

Age

2. 35 to 65 years (MB cohort) or 18 to 60 years (absolute BA cohort), inclusive, at the time of signing the informed consent.

Type of Participants

3. Caucasian (both MB cohort and absolute BA cohort must have Caucasian parents and grandparents) or East Asian (for the absolute BA cohort only, participants must have Chinese, Korean or Japanese parents and grandparents).
4. Healthy, as judged by the Investigator based on the following definition.

   5. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12 lead ECG, and based on the laboratory safety test results.

Weight

6. Body mass index between 18 to 30 kg/m^2 (inclusive), and a weight range of 50 kg to 100 kg (inclusive) at screening.

Sex

7. Male (both MB cohort and absolute BA cohort) and female (absolute BA cohort only) participants

   The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

   Female Participants

   For women of childbearing potential: agree to use two methods of contraception, with at least one method considered as highly effective during the study and for at least 90 days after the last dose of study drug (Appendix 5).

   a. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
   b. Contraceptive methods considered as highly effective (failure rate < 1% per year when used consistently and correctly):

- Combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion/ligation
- Vasectomized partner
- Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study treatment and at least 90 days after the last dose of study drug. In such case, there is no need to use two contraceptive methods. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

Male Participants

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agree to use contraceptive measures, and agree to refrain from donating sperm, as defined below:

- Men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating semen during this same period.

Inclusions for Mass Balance Cohorts Only

8. Must have regular bowel movements (i.e., average stool production of ≥ 1 and ≤ 3 stools per day).

For both cohorts, inclusion criterion 4 from the list above will be re-assessed at admission/pre-dose of each treatment period.

5.2 EXCLUSION CRITERIA

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

Medical Conditions

1. Pregnant (positive pregnancy test) or lactating women, and male participants with partners who are pregnant or lactating.

2. Have a history or symptoms of any clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal (GI), endocrine, hematological, oncologic, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study treatment; or of interfering with the interpretation of data.
3. Confirmed (based on the average of three separate resting blood pressure [BP] measurements in a supine position, after at least 5 minutes of rest) systolic BP greater than 140 mmHg or less than 90 mmHg, and diastolic BP greater than 90 mmHg or less than 50 mmHg at screening and Day -1.
4. Personal history or family history of congenital long QT interval (QT) syndrome and/or cardiac sudden death.
5. History of Gilbert syndrome.
6. Participants who have had significant acute infection, e.g., influenza, local infection, acute GI symptoms, or any other clinically significant illness within two weeks of dose administration.
7. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
8. Any clinically significant concomitant diseases or condition that could interfere with the conduct of the study, or in the opinion of the Investigator, would pose an unacceptable risk to the participant in this study.

Prior/Concomitant Therapy

9. Taking any herbal medications or substances, supplements (including vitamins), traditional Chinese medicines, prescription medicine, or over-the-counter (OTC) medications within 14 days of first dosing or within 5 times the elimination half-life of the medication prior to first dosing, whichever is longer.

   Exceptions are medications listed under Permitted Therapy (Section 6.5.1).
10. History of having received any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids) 6 months prior to the first dose of study drug or the expectation that such treatment will be needed at any time during the study.

Prior/Concurrent Clinical Study Experience

11. Are currently enrolled in or have participated in any other clinical study involving an investigational product or in any other type of medical research within the last 90 days (or within 5 half-lives of the investigational product, whichever is longer).
12. Donation or loss of blood or blood products in excess of 500 mL within three months of screening.

Diagnostic Assessments

13. Clinically relevant ECG abnormalities on screening, Day −1, or Day 1 (pre-dose), e.g.:

a. QT corrected for heart rate (HR) using the Fridericia's correction factor (QTcF) $>$ 430 msec (males), $>$ 450 msec (females), or $<$ 300 msec (males and females).

b. Notable resting bradycardia (HR $<$ 45 beats per minute [bpm]), or HR $>$ 90 bpm.

c. Evidence of atrial fibrillation, atrial flutter, complete bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.

14. Clinically significant ECG with QRS complex (QRS) and/or T-wave judged by the Investigator to be unfavorable for a consistently accurate QT measurement (e.g., neuromuscular artifact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves).
15. Creatinine clearance (CrCl) $\leq$ 70 mL/min (using the Cockcroft-Gault formula) at screening (may be repeated for confirmation) $or\ on\ Day\ -1.$
16. Evidence of current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., the virus that causes COVID-19) infection.
17. Positive test at screening of any of the following: hepatitis A virus (HAV immunoglobulin M [IgM] antibody), hepatitis B virus (HBV, HBsAg), hepatitis C virus (HCV ribonucleic acid [RNA]), hepatitis D virus (total HDV antibody), hepatitis E virus (HEV IgM antibody), and human immunodeficiency virus (HIV-1 antibody and HIV-2 antibody, or HIV-1/2 antibody).
18. Any other clinically significant abnormalities in laboratory test results at screening or on Day -1. In the case of uncertain or questionable results, tests performed during screening or Day -1 may be repeated once prior to enrollment to confirm eligibility unless deemed not clinically significant by the Investigator.

Other Exclusions

19. History of any drug or alcohol abuse in the past 2 years.
20. Regular alcohol consumption in males > 21 units per week and in females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
21. A confirmed positive alcohol breath test at screening and on Day -1.
22. Use of $>$ five cigarettes or equivalent nicotine-containing product per day prior to screening.
23. Participants under judicial supervision, guardianship, or curatorship.
24. Medical or social conditions that would potentially interfere with the participant's ability to comply with the study visit schedule or the study assessments.
25. Sensitivity to any of the study treatments, or excipients thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the participation in the study.
26. Participants who do not have suitable veins for multiple venipunctures/cannulation as assessed by the Investigator or delegate at screening.

27. Participants who planned to attempt to have children within 90 days of dosing.

Exclusions for Mass Balance Cohorts Only

28. Regular work with ionizing radiation or radioactive material.
29. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic X-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last five years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study.
30. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton [excluding spinal column]), during work, or during participation in a medical trial in the previous year.
31. History of GI surgery (with the exception of appendectomy unless it was performed within the previous 12 months).
32. Acute diarrhea or constipation in the past seven days prior to admission. Diarrhea will be defined as the passage of liquid feces and/or a stool frequency of greater than three times per day. Constipation will be defined as a failure to open the bowels more frequently than every other day.

For both study parts, exclusion criteria 1, 3, 6, *7, 8,* 9, 12, 13, 14, *15, 16,* 18, 21, 22, 27, and 31 from the list above will be re-assessed at admission/pre-dose of each treatment period.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

Food and water will be restricted as follows:

- [redacted]
- Participants should refrain from eating food containing poppy seeds for 48 hours prior to screening and from 48 hours prior to admission until after collection of the final sample.
- Still water at room temperature will be provided for each dose. No water is allowed from 1 hour prior to dosing until 1 hour after each oral dose, after which time, water is allowed ad libitum, up to a maximum of three liters a day.
- Participants in the MB cohort must not eat anything likely to disturb GI transit (e.g., spicy or high-fat meals such as curry or fish and chips or foods of a high-fiber content such as All Bran) from 24 hours prior to admission until after collection of the final sample.

5.3.2 Caffeine, Alcohol, and Tobacco

Caffeine, alcohol, and tobacco will be restricted as follows:

- Participants must abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final sample.
- Alcohol must not be consumed from 48 hours before screening, 48 hours before admission until after collection of the final sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be allowed from screening until after collection of the final sample.

5.3.3 Activity

Participants must abstain from strenuous exercise for at least 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during study (e.g., watching television, reading).

Participants must not donate blood or plasma (outside of this study) from clinical unit admission, throughout the study duration, and for at least 90 days following last dose of study medication.

Participants in the MB cohort will not be permitted to shower for 24 hours post-dose (to ensure the collection of all samples).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled to study treatment. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

If a participant fails an inclusion/exclusion criterion due to a transient and non-clinically significant condition at screening, the Investigator may repeat the relevant screening assessment(s) within the 28-day screening period. If the participant fails a second time, they will be classed as a screen failure and cannot be re-screened.

Re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria but failed to be enrolled within 28 days after the start of screening period because the enrollment was suspended. In order to re-screen such a participant, all inclusion and exclusion criteria should be re-evaluated, and all applicable screening assessments repeated if done more than 28 days prior to the enrollment.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using; clinical database and independent ethics committee (IEC)/Institutional Review Board (IRB) approved

newspaper/radio/television/social network service/campus poster advertisements, mailing lists, and other distributable documents prior to consenting to take place on this study.

6. TREATMENTS

Study intervention is defined as any investigational product intended to be administered to a study participant according to the study protocol.

The IMPs for this study are [^{12}C] RO7049389 tablet, 200 mg, [^{14}C] RO7049389 oral suspension, 600 mg (NMT 2.2 MBq), and [^{13}C] RO7049389 solution for infusion, 20 µg/mL. All study drug administration will be at the study center under supervision of site staff.

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

6.1 TREATMENTS ADMINISTERED

Table 5 summarizes the treatments administered. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

6.1.1 [^{14}C] RO7049389 Oral Suspension, 600 mg (NMT 2.2 MBq)

On the morning of Day 1 for MB cohort, a 20-mL drinking suspension containing 600 mg of RO7049389, providing a maximum of 2.2 MBq of [^{14}C]-labeled RO7049389 (equivalent to 59.3 µCi) will be administered to all eligible participants after an overnight fast of at least 10 hours, followed by another four hours of fasting until lunch. Each participant will receive 190 mL of still water immediately after the dose has been swallowed, followed by a further 50 mL which will be used to rinse out the dosing vessels (50 mL will be used in five separate rinses). Water will be allowed ad libitum until 1 hour prior to dosing and from 1-hour post dosing, at a maximum of three liters a day.

6.1.2 [^{13}C] RO7049389 Solution for Infusion, 20 µg/mL

On Day 1 of MB cohort, on Day 1 of both Period 1 and Period 2 of absolute BA cohort, a single microdose of [^{13}C]-labeled RO7049389 100 µg will be administered by a 10-minute constant IV infusion. *Dilution of the [^{13}C]-labeled RO7049389 solution for infusion using 0.9% saline will be performed at bedside.* The IV infusion will start 2 hours after administration of the oral dose of RO7049389.

Details on study drug preparation by the Quotient Sciences clinical unit will be described in the manufacturing batch record, which will be prepared by the Quotient Sciences pharmacy.

6.1.3 RO7049389 Tablet, 200 mg

An oral dose of RO7049389 600 mg (Period 1) or 1000 mg (Period 2) in the absolute BA cohort will be administered as a clinical formulation in the morning of Day 1 of Period 1 or Period 2, study drug administration will be after an overnight fast of at least 10 hours, followed by another 4 hours of fasting until lunch. Water will be allowed ad libitum until 1 hour prior to dosing and from 1-hour post dosing, at a maximum of three liters a day.

Study drug will be swallowed whole with still water. Please see the dosing instructions and RO7049389 IB for more details.

Table 5 Summary of Treatments Administered

Study Treatment Name:	RO7049389	[^{14}C]-labeled RO7049389	[^{13}C]-labeled RO7049389
IMP and NIMP	IMP	IMP	IMP
Dose Formulation:	Tablet	Suspension	Solution
Unit Dose Strength(s)/Dosage Level(s):	200 mg	20 mL	20 μg/mL *
Dose:	600 mg or 1000 mg	600 mg	100 μg
Route of Administration:	oral	oral	IV infusion
Sourcing:	Provided by the Sponsor.	API will be provided by the Sponsor and the formulation will be provided locally by the trial site.	API will be provided by the Sponsor and the formulation will be provided locally by the trial site.
Packaging and Labeling:	Study treatment will be provided in labeled bottles.	Study treatment will be provided in labeled bottles.	Study treatment will be provided in labeled bottles.

* *Dilution will be performed at bedside.*

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

[^{13}C]-labeled and [^{14}C]-labeled RO7049389 API will be provided by the Sponsor. The investigational site will acknowledge receipt of [^{13}C]-labeled and [^{14}C]-labeled RO7049389, and confirm the shipment condition and contents. Any damaged shipments will be replaced. The investigational site will manufacture a drinking suspension using the API supplied for [^{14}C]-labeled RO7049389 and a solution for infusion using the API supplied for [^{13}C]-labeled RO7049389.

The RO7049389 tablets (clinical formulation) will be provided by the Sponsor.

Study drug packaging will be overseen by the Sponsor's clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations.

The study site should follow all instructions included with each shipment of IMP. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized staff.

The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol. Upon arrival of the IMPs at the site, site personnel will complete the following:

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

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

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

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

The Investigator, Institution, or the Head of the Medical Institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

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

Refer to the dosing instructions, the RO7049389 IB, and/or Investigational Medicinal Product Dossier for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

According to Title 21, Part 320 of the U.S. Code of Federal Regulations, reserve samples of the clinical supplies used in a bioavailability or bioequivalence study must be retained by the organization that conducted the study and stored under conditions that will maintain the integrity, identity, strength, quality and purity of the samples. The samples for retention will be randomly selected by the Investigator or by a representative of the Investigator. All samples must be retained at the study site for a period of at least 5 years following the date on which the application or supplemental application is approved by the U.S. Food and Drug Administration (FDA). If such application is not approved, all samples must be retained for at least 5 years following the date of completion of any bioavailability or bioequivalence study from which the reserve samples were obtained.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

This is a fixed sequence study. Randomization is not applicable.

6.3.2 Blinding

This is an open-label study; blinding procedures are not applicable.

6.4 TREATMENT COMPLIANCE

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

During all clinical phases of the study, participants will be observed by study staff to assure compliance to all study procedures, including dose administration.

Mouth and hand checks will be conducted after oral dosing to ensure the IMP has been swallowed.

The IV dose will be administered by trained staff to ensure dosing compliance.

The date and time that each participant is dosed will be recorded in the participant's source data. Any violation of compliance will require evaluation by the Investigator and Sponsor to determine if the participant can continue in the study.

6.5 CONCOMITANT THERAPY

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

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

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

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

6.5.1 Permitted Therapy

The following medications will be permitted:

- Medications used to treat AEs may only be prescribed after consultation with the Sponsor (with the exception of acetaminophen/paracetamol), unless there is a medical need to ensure the well-being of the participant that should not be delayed. All therapy and/or medication administered to manage AEs should be recorded on the AE eCRF.
- Hormone replacement therapy (HRT): permitted if initiated at least 2 months prior to study start.
- Occasional use of acetaminophen (up to a maximum dose of 2 g/day up to 48 hours prior to dosing, not to exceed 4 g total during the week prior to dosing) will be permitted.

6.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of study screening will be recorded on the appropriate eCRF.

No concomitant medication will be permitted within 14 days prior to the first dosing or within 5 half-lives of the medication prior to the first dosing (whichever is longer), with the exception of medications listed in Section 6.5.1.

6.6 DOSE MODIFICATION

No dose modification of RO7049389 for safety reasons is expected in the study.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO7049389 or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

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

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

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

7.1 DISCONTINUATION OF STUDY TREATMENT

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

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Participant withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Experiencing a serious or severe AE including but not limited to:
    - corrected QT interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)
    - alanine aminotransferase (ALT) concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.
- Pregnancy.
- Poor GI tolerability that is considered to affect the study participant's well-being and/or the PK evaluation.

- Evidence of current SARS-CoV-2 infection.

Every effort should be made to obtain information on participants who withdraw from the study but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.9.3) and may undergo follow-up assessments (see Section 8.9.4), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

When a participant voluntarily withdraws from the study or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data.

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the absolute BA cohort of the study for other reasons may be replaced.

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

7.3 LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the

assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time points are summarized in the SoAs (Section 1.3). Protocol waivers or exemptions are not allowed.

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

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

Emesis is not expected to occur; however, in the event that a participant spontaneously vomits within 6 hours after study drug administration in the MB cohort, the vomit will be collected and analyzed for radioactivity.

At time points when several assessments coincide, the following sequence is suggested; at the discretion of the Investigator, the order can be adjusted to optimize site personnel and participant's time management:

- Urine collection
- Feces collection (MB cohort only)
- ECG recordings
- Vital signs
- PK and safety blood sampling
- Study treatment administration

8.1 EFFICACY ASSESSMENTS

No efficacy assessments will be performed in this study.

8.2 SAFETY ASSESSMENTS

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

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

8.2.1 Physical Examinations

A complete physical examination should be performed at time points indicated in the SoAs (Section 1.3) and includes, at a minimum, assessments of the head, eyes, ears, nose, throat, neck and lymph nodes; and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, and neurological systems.

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 participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

8.2.2 Vital Signs

Oral temperature, heart rate, and BP will be assessed.

BP and heart rate measurements will be assessed in a supine position for at least 5 minutes with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm should be used for all BP measurements.

Vital signs (to be taken before blood collection for laboratory tests) will be measured in a supine position after at least 5 minutes rest and will include temperature, systolic and diastolic BP, and heart rate. Three readings of BP and heart rate will be taken approximately 1 minute apart. The mean of three consecutive replicates will be used as the value for the defined time point to be recorded in the eCRF.

The acceptable deviations from the nominal vital signs measurement time points are:

- The pre-dose vital signs measurements will be taken ≤ 2 hours before dosing.
- Post-dose vital signs measurements will be taken ± 15 minutes from the nominal post-dose time points.
- Discharge vital signs measurements will be taken ± 1 hour from the nominal time point.
- For return visits, vital signs measurements will be taken ± 2 hours from the nominal return visit time point.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoAs (see Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QT corrected for HR (QTc) intervals.

To minimize variability, it is important that participants be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in HR. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement potentially contributing to the ECG abnormality.

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

ECG characteristics, including HR, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcF (Fridericia's correction) and RR interval (RR) will be calculated by the Sponsor. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

The acceptable deviations from the nominal ECG measurement time points are:

- The pre-dose ECG measurements will be taken ≤ 2 hours before dosing
- Post-dose ECG measurements will be taken ± 15 minutes from the nominal post-dose time point.
- Discharge ECG measurements will be taken ± 1 hour from the nominal time point.
- For return visits, ECG measurements will be taken ± 2 hours from the nominal return visit time point.

8.2.4 Clinical Safety Laboratory Assessments

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

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

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the CRF.

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

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

Where the clinical significance of abnormal laboratory results at screening is considered uncertain, screening laboratory tests may be repeated before admission 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.

The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:

- The pre-dose blood sample will be taken ≤ 2 hours before dosing
- Post-dose blood samples will be taken ± 1 hour from the nominal blood sampling time
- The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- The pre-dose urine sample will be the first void of the day or a sample collected ≤ 3 hours before dosing

- Post-dose urine samples will be taken ± 2 hours from the nominal urine sampling time.

8.2.5 Medical History and Demographic Data

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

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

8.2.6 SARS-CoV-2 Tests (If Required)

Testing for the SARS-CoV-2 virus may be performed based on current infection rates and availability of tests. Tests will be performed according to the time schedule presented in Section 1.3. The samples will be collected and processed as detailed in the Screening Sample Processing Manual and Clinical Sample Processing Manual.

Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The NSAESI are discussed in Sections 8.3.6.

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

Procedures used for recording AEs are provided in Appendix 3:

– Diagnosis versus signs and symptoms:
  - Infusion reactions
  - Other AEs
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values

- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
- Preexisting medical conditions
- Hospitalization or prolonged hospitalization

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

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

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

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

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until 28 days after the last dose of study treatment.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (28 days after the last dose of study treatment).

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

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

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

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

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

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

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

8.3.3.2 Sponsor Follow-Up

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

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

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

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

8.3.4.1 Emergency Medical Contacts

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

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 90 days after the final dose of study treatment.

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 90 days after the final dose of study treatment.

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

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

8.3.6 Non-Serious Adverse Events of Special Interest

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

NSAESI for this study include the following:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an

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

8.4 TREATMENT OF OVERDOSE

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

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis within 24 hours from the date of the final dose of study treatment, if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

For this study, any dose of RO7049389 greater than 1600 mg within a 24-hour time period (+ 1.0 hour) will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

8.5 PHARMACOKINETICS

Mandatory blood and urine samples to evaluate concentrations of study treatment (RO7049389) and its metabolites (RO7121986, RO7255420, and/or RO7255422) will be collected. Mandatory blood, urine, and feces samples to measure the radioactivity and metabolic profiling will be also collected. The date and time of each sample collection will be recorded in the eCRF. The PK samples will be taken as outlined in the SoAs (Section 1.3).

A PK sample will also be collected following occurrence of a dose-limiting event or SAE.

- Total radioactivity will be measured in plasma, whole blood, urine, and feces samples from MB cohort by liquid scintillation counting (LSC, Pharmaron, Hoddesdon EN11 9FH UK). Samples with low levels of radioactivity that cannot be quantified by LSC may be analyzed using AMS, if necessary.

- Metabolic profiling will be conducted in plasma, urine, and feces and blood pellet (if appropriate). The metabolic profiling samples may not be assessed if there are insignificant levels of [^{14}C]-radioactivity present. The best approach for the pooling strategy of metabolic profiling samples (e.g., urine, feces, plasma, and blood pellet) must be agreed upon between the clinical study site and the Sponsor prior to being performed. The results of the metabolic profiling analysis may be reported separately from the main clinical study report.
- Concentrations of [^{12}C] RO7049389, [^{12}C] RO7121986, [^{12}C] RO7255420 and [^{12}C]-RO7255422 in plasma samples from both MB cohort and absolute BA cohort will be measured using a validated liquid chromatography–mass spectrometry (LC-MS/MS) method by Q2 solution (Ithaca, NY 14850 USA).
- Concentrations of [^{13}C] RO7049389 and [^{13}C] RO7121986 in plasma samples from both MB cohort and absolute BA cohort will be measured using a validated LC-MS/MS method by Q2 solution (Ithaca, NY 14850 USA).
- Concentrations of [^{12}C] RO7049389, [^{12}C] RO7121986, [^{12}C] RO7255420 and [^{12}C] RO7255422 in urine samples from absolute BA cohort will be measured using a validated LC-MS/MS method by Q2 solution (Ithaca, NY 14850 USA).
- Concentrations of RO7049389 other new identified metabolite(s) from absolute BA cohort as appropriate in plasma and urine samples may be measured using a validated LC-MS/MS method by Q2 solution (Ithaca, NY 14850 USA).

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

The PK blood samples will be destroyed 2 years after the date of final clinical study report (CSR), unless regulatory authorities require specimens to be maintained for a longer period. Details on sampling procedures, sample storage, and shipment are given in the Sample Handling Manual.

The acceptable deviations from the nominal blood sampling times are as follows:

- The pre-dose samples will be taken ≤ 1 hour before dosing
- 0 to 1 hour post-dose samples will be taken within ± 2 minutes of the nominal post-dose sampling time
- 1.5 to 12 hours post-dose samples will be taken within ± 10 minutes of the nominal post-dose sampling time
- 24 hours to 264 hours post-dose samples will be taken within ± 30 minutes of the nominal post-dose sampling time.

8.6 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

PD parameters are not evaluated in this study.

8.6.1 Clinical Genotyping

The DNA will be used for, but analysis is not limited to:

- [redacted]

Data arising from all biosamples including samples for analyses of inherited DNA will be subject to confidentiality standards described in Appendix 1.

8.7 PHARMACODYNAMICS AND BIOMARKER SAMPLES

No PD samples would be collected in this study.

A mandatory whole blood sample will be taken for DNA extraction from every participant. If the sample is missed on Day 1, it can be collected at any other scheduled visit.

The samples will be destroyed within 5 years after the date of final CSR, unless regulatory authorities require specimens to be maintained for a longer time period. Details on sampling procedures, sample storage, and shipment are given in the Sample Handling Manual.

8.8 HEALTH ECONOMICS

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

8.9 TIMING OF STUDY ASSESSMENTS

8.9.1 Screening and Pre-treatment Assessments

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

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

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

Screening and pre-treatment assessments will be performed within 28 days prior to Day 1, unless otherwise specified.

8.9.2 Assessments during Treatment

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

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

8.9.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the last dose administration or discontinue from the study early will receive a follow-up call 29±3 days after the last dose of study treatment. The follow-up call will be reported as the study completion visit in eCRF.

In case of early termination of a participant, a blood sample for PK assessment of RO7049389 should be collected at the time of discontinuation. Please also see the SoAs tables (Section 1.3) for activities that are required to be performed in case of an early termination.

8.9.4 Follow-Up Assessments

After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

8.9.5 Assessments at Unscheduled Visits

For activities that are required to be performed in case of an unscheduled visit, refer to the SoAs (Section 1.3).

9. STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

No formal sample size calculation has been performed. The sample size was determined by practical considerations and not based on statistical power calculations.

A sample size of 6 healthy male participants for MB cohort was selected for practical purposes. Six participants are customary for this type of study, and should suffice to meet the objectives of the study while limiting the exposure of healthy male participants to radiolabeled study drug.

For the absolute BA cohort, the sample size of 16 participants (8 East Asian HVs and 8 Caucasian HVs) was chosen to estimate the absolute BA of the 600 mg and 1000 mg single-dose with sufficient precision for each ethnic group.

Participants prematurely discontinued from the absolute BA cohort of this study may be replaced to ensure adequate numbers of evaluable participants. Participants withdrawn for safety reasons will not be replaced.

9.2 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 6.

Table 6 Analysis Populations

Population	Description
Safety	All participants who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants 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.

9.3 STATISTICAL ANALYSES

9.3.1 Demographics and Baseline Characteristics

Descriptive statistics will be used for demographic and baseline characteristics as applicable and will include sex, race (Asian and non-Asian), ethnicity, age, weight, height and BMI. For continuous variables, mean, standard deviation, median, and minimum and maximum values will be presented. For categorical data, the proportion of participants in each category will be summarized。

9.3.2 Safety Analyses

All safety analyses will be based on the safety analysis population grouped according to cohort (see Table 7).

Table 7 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events grading will be used to present shifts from baseline to the worst grade observed during treatment. For details on standard reference ranges, and data transformation and the definition of laboratory abnormalities, see Appendix 4.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.

9.3.3 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population.

Individual and mean plasma concentrations at each sampling time point for RO7049389 and its metabolites (RO7121986, RO7255420, and RO7255422) as appropriate will be presented by listings and descriptive summary statistics, including means, geometric means, ranges, standard deviations, and coefficients of variation. Individual and mean concentration versus time will be plotted on semi-logarithmic scales.

Non-compartmental analysis will be employed for estimation of PK parameters. All PK parameters will be presented by individual listings and summary statistics for each period including means, geometric means, medians, ranges, standard deviations, and coefficients of variation.

The main parameters of interest for the MB cohort are the recoveries of drug-related total radioactivity from urine and feces and its rate of elimination from plasma (and blood if appropriate). Data will be interpreted through inspection and descriptive analysis.

The following PK parameters were estimated if appropriate:

Plasma PK parameters for non-radiolabeled drug and metabolites (**[**^{12}C] and/or [^{13}C] entities) and [^{14}C] Total Radioactivity, if appropriate:

- C_{max}: the maximum observed plasma concentration
- t_{max}: time to maximum observed plasma concentration time
- $t_{1/2}$: apparent terminal half life
- $AUC_{0\text{-}inf}$: the area under the plasma concentration versus time curve extrapolated to infinity
- AUC_{last}: the area under the plasma concentration-time curve from time zero to the last measurable plasma concentration time point (t)
- CL/F: oral plasma clearance,
- CL: plasma clearance after IV dosing
- V/F: apparent volume of distribution based on terminal phase
- V_{ss}: volume of distribution at steady-state (calculated after IV dosing)
- F: absolute BA

Absolute BA was calculated using dose-normalized geometric mean ratios and 90% confidence intervals (CIs) for AUC for oral versus IV dosing

In case $AUC_{0\text{-}inf}$ cannot be determined reliably, an appropriately truncated AUC may be used.

Urinary PK parameters for non-radiolabeled drug and metabolites [^{12}C] entities and [^{14}C] total radioactivity：

- % of dose recovered as total [^{14}C]-radioactivity
- Ae: cumulative urinary amount of total [^{14}C]-radioactivity
- % of dose recovered for RO7049389 and its three metabolites from absolute BA cohort
- Ae: cumulative urinary amount of RO7049389 and its metabolites from absolute BA cohort
- CL_r: renal clearance of RO7049389 and its metabolites from absolute BA study

Feces PK parameters for [^{14}C] Total Radioactivity：

- % of dose recovered as total [^{14}C]-radioactivity

Additional PK parameters may be derived if deemed necessary.

A population PK model analysis and a physiologically based PK model analysis may be performed. The results of those analyses will be reported in separated documents.

9.4 SUMMARIES OF CONDUCT OF STUDY

The number of participants who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized by treatment period. Protocol deviations will be listed and evaluated for their potential impact on interpretation of study results. Study drug administration will be summarized by treatment period. Descriptive statistics will be used in evaluating the conduct of the study.

10. REFERENCES

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as:

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

Appendix 2 (For AE definitions, reporting),

Appendix 3 (Procedures of recording),

Appendix 4 (Clinical laboratory tests),

Appendix 5 (Contraceptive guidance and collection of pregnancy information),

Appendix 6 (Cockcroft Gault Equation for Calculation CrCl).

Appendices are listed here below. Additional study-related appendices are in order of appearance in the protocol.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the United Kingdom (UK) will comply with the Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031, the Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928, the Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984, the Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941.

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (ICF) (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) will be provided to each site. If

applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant

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

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

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

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

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

1.4. CONFIDENTIALITY

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

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

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

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

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

1.5. FINANCIAL DISCLOSURE

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

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

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

2.1.2. Source Data Records

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

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

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

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

2.1.4. Use of Computerized Systems

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

2.2. RETENTION OF RECORDS

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

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

2.3. STUDY RECORDS

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

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

2.3.1. Protocol Amendments

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

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

2.3.2. Publication Policy

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

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

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

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

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

2.3.3. Dissemination of Clinical Study Data

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

2.3.4. Management of Study Quality

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

2.3.5. Site Inspections

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

3. ADMINISTRATIVE STRUCTURE

- 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.

4. STUDY AND SITE CLOSURE

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

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

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

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

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

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

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

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A serious adverse reaction (ie a SAE considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (ie severe non-serious AE considered as, at least possibly related to the investigational medicinal product [IMP] administration) in two subjects in the same cohort, independent of within or not within the same system organ class.

Relatedness to IMP will be determined by the Investigator.

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

The Administration of Radioactive Substances Advisory Committee (ARSAC) Practitioner will also be informed of the temporary halt.

Once exposure to dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe AEs, as defined in Appendix 2 Section 2 and Section 3.1, if considered to be related to the IMP, as defined in Appendix 2 Section 3.2, on the dosing day.
- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in Section 2.3 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances, termination can only take place with the agreement of the Investigator and Sponsor. The MHRA, EC, ARSAC practitioner and ARSAC will be informed of study termination.

If it becomes necessary to consider termination of the study on the dosing day, dosing may be suspended pending discussion between the Investigator, Sponsor and ARSAC practitioner (where discussion is related to administration of radiation). Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

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

1. DEFINITION OF ADVERSE EVENTS

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

An AE can therefore be:

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

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Events NOT Meeting the AE Definition:

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

2. DEFINITION OF SERIOUS ADVERSE EVENTS

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

A SAE is defined as any untoward medical occurrence that at any dose:

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

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

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - Disability means substantial disruption of the participant's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

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

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

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

3.1. ASSESSMENT OF SEVERITY

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (according to pre-defined Division of AIDS [DAIDS] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

The AE severity grading scale for the DAIDS (v2.1) will be used for assessing severity for AEs (see Table 1).

Table 1 DAIDS Adverse Event Severity Grading Scale

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

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see above). DAIDS v2.1 grading scale is available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

3.2. ASSESSMENT OF CAUSALITY

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

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

4. FOLLOW-UP OF AES AND SAES

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

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

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

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

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

Events that Occur prior to Study Treatment Initiation

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

Events that Occur after Study Treatment Initiation

For reports of SAEs and NSAESI (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be

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

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

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

Reporting of Post-Study Adverse Events and Serious Adverse Events

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

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error are defined as follows:

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

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

Special situations are not in themselves AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the AE eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7049389, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with RO7049389, regardless of whether they result in an AE, should be recorded on the AE eCRF and should be recorded as described below:

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

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

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

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

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

- RO7049389 IB

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

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

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse event (AEs) on the AE eCRF. Avoid colloquialisms and abbreviations.

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

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION REACTIONS

AEs considered to be infusion reactions that occur during or within 24 hours after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., infusion-related reaction, infusion site reaction *or* "anaphylactic reaction") on the AE eCRF. If possible, avoid ambiguous terms such as “systemic reaction”. Associated signs and symptoms should be recorded on the dedicated Infusion Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the AE eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

1.2. OTHER ADVERSE EVENTS

For AEs other than infusion reactions (see Section 8.3), a diagnosis (if known) should be recorded on the AE 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 AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between participant evaluation time points. Such events should only be recorded once on the AE 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 AE eCRF should be updated to reflect this.

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

4. ABNORMAL LABORATORY VALUES

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

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

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be

characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

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

5. ABNORMAL VITAL SIGN VALUES

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

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

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

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

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

6. ABNORMAL LIVER FUNCTION TESTS

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 AE the occurrence of either of the following:

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

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

7. DEATHS

All deaths that occur during the protocol-specified AE reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the AE eCRF and immediately reported to the Sponsor.

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 AE eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

8. PREEXISTING MEDICAL CONDITIONS

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

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

9. LACK OF EFFICACY OR WORSENING OF CONDITION BEING STUDIED

Not applicable in this HV study.

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration and intensive PK sampling).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The participant has not suffered an AE.

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

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

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory (The Doctors Laboratory, London, UK); the results must be captured in source documentation and entered into the eCRF.

The full contact details of the local laboratory:

The Doctors Laboratory

The Halo Building

1 Mabledon Place

London WC1H 9AX

Tel: + 44 (0)207 3077 404)

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

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

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume, and reticulocyte counts.
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine (creatinine clearance will be calculated at screening and Day −1 using the Cockcroft-Gault formula), protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, creatine kinase, gamma glutamyl transferase, bile acid.
Coagulation	• International normalized ratio (INR), activated partial thromboplastin time (aPTT), prothrombin time (PT).
Viral Serology	• HIV (HIV-1 antibody and HIV-2 antibody, or HIV-1/2 antibody), hepatitis A virus (HAV) IgM antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) ribonucleic acid (RNA), total hepatitis D virus (HDV) antibody, hepatitis E virus (HEV) IgM antibody.
Lipids	• Cholesterol, low-density lipoproteins (LDL) cholesterol, HDL cholesterol, triglycerides.
Hormone	• Follicle-stimulating hormone (FSH) in females.
Pregnancy Test	• All female participants will have a blood human chorionic gonadotropin (hCG) pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes • If there is a clinically significant positive result (e.g., 2+ or greater for blood, protein or leukocytes) confirmed by a positive repeated sample, urine will be sent to the laboratory for microscopy and/or microbiology, at the discretion of the Investigator. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy. • Microscopic examination: sediment, red blood cells (RBCs), white blood cells (WBCs), casts, crystals, epithelial cells, bacteria.
Other Screening Tests	• Urine drug screen includes amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, tricyclic antidepressants. • Alcohol breath test. • SARS-CoV-2 Antibody and SARS-CoV-2 Antigen

The results of each test must be entered into the CRF.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data
- Potential analysis considerations for analyzing Laboratory data includes the use of Standard Reference Ranges and potential transformation of data for specific lab tests.
- In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

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

- Definition of Laboratory Abnormalities

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

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

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

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

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

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

f) Pre-menarchal

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

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

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

h) Post-menopausal female

- A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use two methods of contraception, with at least one method considered as highly effective during the study and for at least 90 days after the last dose of study drug.

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly as described in Table 1.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Injectable

Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion/ligation **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide [b] • Cap, diaphragm, or sponge with spermicide [b]

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

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

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

3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

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

4. COLLECTION OF PREGNANCY INFORMATION

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

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

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

- **Female participants who become pregnant**

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

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

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

5 ABORTIONS

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

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

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

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male participant exposed to study treatment should be classified as a SAE, recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 3, Section 5.1).

Appendix 6
Cockcroft Gault Equation for Calculation CrCl

The Cockcroft-Gault equation will be used to calculate creatinine clearance (CrCl) (Conventional units = mL/min or SI units = mL/sec). Baseline body weight (ABW) will be used for calculation of CrCl.

Conventional Units:

$$\textit{Males (mL/min)} = \frac{\textit{(140 – Age) * ABW (kg)}}{\textit{72 * Serum Creatinine (mg/dL)}}$$

Females (mL/min) = Male value x 0.85

Conversion Factor for Creatinine Clearance:

- SI Units (mL/sec) = Conventional units (mL/min) $\times$ 0.0167
- Conventional Units (mL/min) = SI Units (mL/sec) / 0.0167

Conversion Factor for Serum Creatinine:

- Conventional units (mg/dL) = SI units (µmol/L) / 88.4
- SI Units (µmol/L) = Conventional Units $\times$ 88.4