**Official Title:** **AN OPEN-LABEL, FIXED SEQUENCE, TWO-PERIOD STUDY TO INVESTIGATE THE EFFECT OF RO7049389 ON THE PHARMACOKINETICS OF PITAVASTATIN IN HEALTHY VOLUNTEERS**

**NCT Number:** NCT03717064

**Document Date:** Protocol Version 1: 27-Aug-2018

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **AN OPEN-LABEL, FIXED SEQUENCE, TWO-PERIOD STUDY TO INVESTIGATE THE EFFECT OF RO7049389 ON THE PHARMACOKINETICS OF PITAVASTATIN IN HEALTHY VOLUNTEERS** |
| **PROTOCOL NUMBER:** | YP40218 |
| **VERSION:** | 1 |
| **IND NUMBER:** | 137090 |
| **TEST PRODUCT:** | RO7049389 |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | See electronic date stamp below |

## FINAL PROTOCOL APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | Company Signatory | 27-Aug-2018 06:37:06 |

## PROTOCOL ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| **AAV-HBV** | Adeno-associated virus hepatitis B virus |
| **AE** | Adverse event |
| **ALT** | Alanine aminotransferase |
| **aPTT** | Activated partial thromboplastin time |
| **AST** | Aspartate aminotransferase |
| **AUC** | Area under the curve |
| **BP** | Blood pressure |
| **CHB** | Chronic hepatitis B |
| **CL** | Clearance |
| **CL/F** | Apparent clearance |
| **CRO** | Contract research organization |
| **CSR** | Clinical study report |
| **DDI** | Drug-drug interaction |
| **DNA** | Deoxyribonucleic acid |
| **EC** | Ethics Committee |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic case report form |
| **EDC** | Electronic data capture |
| **ESF** | Eligibility screening form |
| **EU** | European Commission |
| **FDA** | Food and Drug Administration |
| **FSH** | Follicle-stimulating hormone |
| **HAP** | Heteroaryldihydropyrimidine |
| **HAV** | Hepatitis A virus |
| **HBcAb** | Total hepatitis B core antibody |
| **HBsAg** | Hepatitis B surface antigen |
| **β-HCG** | Beta-human chorionic gonadotropin |
| **HCV** | Hepatitis C |
| **HDL** | High-density lipoproteins |
| **HIV** | Human immunodeficiency virus |
| **IB** | Investigator's Brochure |
| **$IC_{50}$** | Inhibitory concentration |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IFN** | Interferon |
| **IMP** | Investigational medicinal product |

| | |
|---|---|
| **IND** | Investigational New Drug (application) |
| **INR** | International normalized ratio |
| **IRB** | Institutional Review Board |
| **IUD** | Intrauterine device |
| **LDH** | Lactate dehydrogenase |
| **LDL** | Low-density lipoproteins |
| **LH** | Luteinizing hormone |
| **LPLV** | Last participant, last visit |
| **LPLO** | Last participant, last observation |
| **MAD** | Multiple-ascending doses |
| **NOAEL** | No-observed-adverse-effect level |
| **NSAESI** | Non-serious adverse event of special interest |
| **NUCs** | Nucleos(t)ide analogues |
| **OATP** | Organic anion-transporting polypeptide |
| **OTC** | Over-the-counter |
| **PD** | Pharmacodynamic |
| **PK** | Pharmacokinetic |
| **PT** | Prothrombin time |
| **QRS** | QRS complex |
| **QT** | QT interval |
| **QTc** | QT corrected for heart rate |
| **QTcF** | QT corrected for heart rate using the Fridericia's correction factor |
| **RBC** | Red blood cell |
| **RBR** | Research biosample repository |
| **RNA** | Ribonucleic acid |
| **RR** | RR interval |
| **SAD** | Single-ascending dose |
| **SAE** | Serious adverse event |
| **SoA** | Schedule of activities |
| **SOP** | Standard operating procedure |
| **ULN** | Upper limit of normal |
| **V** | Volume |
| **WBC** | White blood cell |

# 1. PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **PROTOCOL TITLE:** | **AN OPEN-LABEL, FIXED SEQUENCE, TWO-PERIOD STUDY TO INVESTIGATE THE EFFECT OF RO7049389 ON THE PHARMACOKINETICS OF PITAVASTATIN IN HEALTHY VOLUNTEERS** |
| **SHORT TITLE** | **THE EFFECT OF RO7049389 ON THE PK OF PITAVASTATIN** |
| **PROTOCOL NUMBER:** | YP40218 |
| **VERSION:** | 1 |
| **TEST PRODUCT:** | RO7049389 |
| **PHASE:** | I |

**RATIONALE**

The primary objective of this study is to determine the effect of multiple-doses of RO7049389 on the single-dose PK of pitavastatin in healthy participants. Based on the data from in vitro studies of RO7049389 there is a possibility of an organic anion-transporting polypeptide (OATP)-mediated interaction between RO7049389 and OATP1B1 substrates. In vitro, RO7049389 inhibits OATP1B1 mediated transport with a half maximal inhibitory concentration ($IC_{50}$) of 3 μM (1796 ng/mL). This $IC_{50}$ is predicted to be lower than RO7049389 exposures at the expected efficacious dose. The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or 'statins', a class of cholesterol-lowering drugs, are known substrates for OATP1B1. In future clinical trials, a statin may be a concomitant medication with RO7049389. Therefore, it will be important to understand the effect, if any, of RO7049389 on the pharmacokinetics (PK) of such an OATP1B1 substrate. As PK measurements are objectively analysed an open-label study design has been chosen. To minimize the number of participants needed and reduce inter-subject variability, this study will follow a two-period instead of parallel design. The duration of both washout and drug administration periods was established on the basis of the known pharmacokinetic profiles of both RO7049389 and pitavastatin. Accordingly, a fixed sequence design has been chosen for logistical reasons.

**OBJECTIVES AND ENDPOINTS**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To determine the effect of multiple-doses of RO7049389 on the single-dose pharmacokinetics (PK) of pitavastatin in healthy participants. | • Primary PK parameters of pitavastatin: $C_{max,}$ and $AUC_{0\text{-}inf}$<br>• Secondary PK parameters of pitavastatin: $t_{max}$, CL/F, V/F and $t_{½}$.<br>• Other parameters may be calculated if considered appropriate. |

**OBJECTIVES AND ENDPOINTS cont.**

| | |
|---|---|
| **Secondary** | |
| • To evaluate the safety and tolerability of the single-dose pitavastatin alone and in combination with multiple-doses of RO7049389 in healthy participants. | • Incidence and severity of adverse events.<br>• Incidence of laboratory abnormalities based on hematology, clinical chemistry, coagulation, lipids, and urinalysis test results.<br>• ECGs.<br>• Vital signs including blood pressure (BP), pulse rate and body temperature. |
| • To explore the effect of the single-dose of pitavastatin on steady-state PK of RO7049389 in healthy participants. | • Primary PK parameters of RO7049389 and its metabolites (RO7121986, RO7255420 and RO7255422): $C_{max,}$ and $AUC_{tau}$ |
| • To determine the effect of multiple-doses of RO7049389 on the single-dose PK of pitavastatin lactone in healthy participants (if applicable). | • PK parameters of pitavastatin lactone: $C_{max,}$ and $AUC_{0\text{-}inf.}$<br>• The AUC ratio of pitavastatin lactone/pitavastatin. |
| **Exploratory** | |
| • To evaluate the effect of multiple-doses of RO7049389 on OATP activity as assessed by plasma and urine coproporphyrins (CP-I and CP-III). | • Coproporphyrins (CP-I and CP-III) AUC in plasma and amount excreted in urine. |

## OVERALL STUDY DESIGN

This is an open-label, fixed sequence, two-period (Periods 1 and 2) study designed to evaluate the drug- drug interaction between RO7049389 and pitavastatin and the safety and tolerability of single-dose pitavastatin alone and in combination with multiple-doses of RO7049389 in healthy participants.

### Treatment Groups and Duration

#### Treatment Groups

The investigational medicinal products (IMPs) required for completion of this study will be RO7049389 and pitavastatin. RO7049389 will be given orally at a dose of 800 mg twice daily (BID) at the time of a standard meal (30 minutes before study treatment administration) for a total of 6 days. Pitavastatin is administered as a single dose (2 mg), once on Day 1 of Period 1 and with RO7049389 in the morning of Day 4 of Period 2.

#### Length of Study

The total duration of the study for each participant will be about 12 weeks divided as follows:

- Screening: Up to 28 days.
- Period 1:
  - In clinic period: Days -1 to 4.
  - Treatment period: Day 1
- Wash-out Period: Defined as from Period 1 Day 1 to Period 2 Day 1 and lasts at least 7 days but not more than 21 days.

- Period 2:
  - In clinic period: Days -1 to 7
  - Treatment period: Days 1 to 6
- Safety follow-up:
  - Period 2 Day 13
  - Period 2 Day 34 (Telephone call)

The participant has the option to stay in-clinic (with overnight stay) during the whole Period 1 and wash-out period if agreed by Sponsor and the Investigator.

**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 days after the last dose of RO7049389 is administered.

**Data Monitoring Committee: No**

## PARTICIPANT POPULATION

### 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. 18 to 60 years of age, inclusive, at the time of signing the informed consent.

**Type of Participants and Characteristics**

3. Healthy, as judged by the Investigator.

   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 at screening and Day -1.
4. Body mass index (BMI) between 18 to 30 kg/$m^2$ (inclusive) at screening.
5. Male and female participants

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

   a) Female Participants

      Female participants must be either surgically sterile (by means of hysterectomy and/or bilateral oophorectomy and/or tubal ligation) or post-menopausal for at least one year (defined as amenorrhea $\geq$ 12 consecutive months without another cause, and confirmed by follicle-stimulating hormone (FSH) level. Participants must not be pregnant or lactating.

   b) Male Participants

      With female partners who are not pregnant or lactating.

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

With female partners of childbearing potential, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

**Exclusion Criteria**

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

**Medical Conditions**

1. 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.
2. Confirmed (based on the average of 3 separate resting BP measurements in a supine position, after at least 5 minutes rest) systolic BP greater than 140 or less than 90 mmHg, and diastolic BP greater than 90 or less than 50 mmHg at screening and Day -1.
3. Personal history or family history of congenital long QT syndrome and/or cardiac sudden death.
4. History of Gilbert's syndrome.
5. Participants who have had significant acute infection, e.g., influenza, local infection, acute gastrointestinal symptoms or any other clinically significant illness within two weeks of dose administration.
6. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
7. Any clinically significant concomitant diseases or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.

**Prior/Concomitant Therapy**

8. Taking any herbal medications or substances (e.g., tea) or supplements (including vitamins), or traditional Chinese medicines (TCM) 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 include medications listed under Permitted Therapy and those made on a case-by-case basis following discussion and agreement between the Investigator and the Sponsor.
9. History of having received any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids) $\leq$ 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 Trial Experience**

10. 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 30 days or 5 half lives (whichever is longer).
11. Donation or loss of blood or blood products in excess of 500 mL within 3 months of screening.

**Diagnostic Assessments**

12. Positive test for drugs of abuse (including recreational drugs) and/or positive alcohol test and/or positive cotinine test at screening and on Day -1.
13. Clinically relevant ECG abnormalities on screening or Day -1 ECG based upon the average of three ECGs, e.g,:
    a. QTcF $>$ 450 msec or $<$ 300 msec.
    b. Notable resting bradycardia (HR $<$ 45 bpm), or HR $>$ 90 bpm.
    c. Evidence of atrial fibrillation, atrial flutter, complete bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
14. ECG with 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 or on Day -1 (may be repeated for confirmation).
16. Positive test at screening of any of the following: Hepatitis A virus (HAV IgM Ab), hepatitis B virus (HBsAg or HBcAb), hepatitis C virus (HCV RNA or HCV Ab) or human immunodeficiency virus (HIV-1 and HIV-2 Ab).
17. 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 may be repeated once prior to enrollment to confirm eligibility unless deemed not clinically significant by the Investigator.

**Other Exclusions**

18. History of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol) and/or drug abuse within 12 months of screening.
19. Use of $>$ 5 cigarettes or equivalent nicotine-containing product per day prior to screening.
20. Participants under judicial supervision, guardianship or curatorship.
21. Medical or social conditions that would potentially interfere with the participant's ability to comply with the study visit schedule or the study assessments.
22. 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.

## NUMBER OF PARTICIPANTS

A sample size of 18 participants to target 16 evaluable healthy participants has been chosen. Evaluable participants who withdraw, or who are withdrawn, for non-safety reasons from the study will be replaced to meet the enrollment goal.

## CONCOMITANT MEDICATIONS

**Permitted Therapy**

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

The 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 adverse events should be recorded on the Adverse Event 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 2g/day up to 48 hours prior to dosing, not to exceed 4g total during the week prior to dosing) will be permitted.

**Prohibited Therapy**

As a general rule, 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), until the follow-up visit, with the exception of the cases listed in Permitted Therapy. Exceptions may be made on a case-by-case basis following discussion and agreement between the Investigator and the Sponsor after, the rationale for exception is discussed and clearly documented.

## 1.2 SCHEMATIC OF STUDY DESIGN

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

### Figure 1 Overview of Study Design

<table>
<tr><th>Period 1</th><td rowspan="3">Wash out Period<br>(Period 1 Day 1 to Period 2 Day 1)<br>≥ 7 days and ≤ 21 days</td><th colspan="3">Period 2</th></tr>
<tr><td>Day 1</td><td>Days 1 to 3</td><td>Day 4</td><td>Days 5 to 6</td></tr>
<tr><td>Pitavastatin<br>2 mg Single dose</td><td></td><td>Pitavastatin<br>2 mg Single dose</td><td></td></tr>
<tr><td></td><td></td><td colspan="3">RO7049389 800 mg Twice Daily (BID)</td></tr>
</table>

## 1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 and Table 2.

## Table 1 Schedule of Activities – Main Table

| Protocol Activity | Screening | Period 1 | | | | | Washout period[k] | Period 2 | | | | | | | | Follow Up visit | Follow-up call | Early termination[l] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Day -28 to Day -2 | Day -1 | Day 1 | Day 2 | Day 3 | Day 4 | | Day -1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Period 2 Day 14(± 1) | Period 2 Day 35 (± 1) | |
| Time Relative (h) | | | 0 | 24 | 48 | 72 | | | 0 | 24 | 48 | 72 | 96 | 120 | 144 | | | |
| Assessments | | | | | | | | | | | | | | | | | | |
| Informed Consent | x | | | | | | | | | | | | | | | | | |
| Eligibility | x | x | | | | | | | | | | | | | | | | |
| Demography | x | | | | | | | | | | | | | | | | | |
| Medical History | x | | | | | | | | | | | | | | | | | |
| Physical Examination[a] | x | x | | | | | | x | | | | | | | | x | | x |
| Vital Signs[b] | x | x | 3 | x | x | x | | x | 7 | x | x | 7 | x | 7 | x | x | | x |
| ECG-12 lead[c] | x | x | x | | | x | | x | 3 | | | 3 | | 3 | x | x | | x |
| Hematology[d] | x | x | | | | x | | x | | | | x | | | x | x | | x |
| Blood Chemistry[d] | x | x | | | | x | | x | | | | x | | | x | x | | x |
| Coagulation[d] | x | x | | | | x | | x | | | | x | | | x | x | | x |
| Urinalysis[d] | x | x | | | | x | | x | | | | x | | | x | x | | x |
| Viral Serology[e] | x | | | | | | | | | | | | | | | | | |
| Drug/Alcohol Test | x | x | | | | | | x | | | | | | | | | | |
| Cotinine Test | x | x | | | | | | | | | | | | | | | | |
| Pregnancy Test[f] | x | x | | | | | | x | | | | | | | | x | | x |
| Follicle Stimulating Hormone[g] | x | | | | | | | | | | | | | | | | | |
| Administration of Pitavasatin | | | x | | | | | | | | | x | | | | | | |
| Administration of RO7049389 | | | | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | | | | |
| Plasma PK for Pitavasatin and its Metabolite | | | 12 | 2 | x | x | | | | | | 12 | 2 | x | x | | | x |
| Plasma PK for RO7049389 and its Metabolites | | | | | | | | | | | 11 | 11 | | | | | | x |
| Plasma PK for Coproporphyrins | | | 10 | x | | | | | | | | 10 | x | | | | | |
| Urine PK for Coproporphyrins | | x | 2 | | | | | | | | | 2 | | | | | | |
| Clinical Genotyping[h] | | | x | | | | | | | | | | | | | | | |
| RBR Blood[i] | | | x | | | | | | | | | | | | | | | |
| In-Clinic Stay | | x | x | x | x | | | x | x | x | x | x | x | x | | | | |
| Discharge[j] | | | | | | x | | | | | | | | | x | | | |
| Adverse Events | x | | | | | | | | | | | | | | | | | |
| Previous and Concomitant Treatments | x | | | | | | | | | | | | | | | | | |

## Table 1 Schedule of Activities – Main Table (cont.)

a. A full physical exam is required at screening, follow-up and early treatment termination visits. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed at the discretion of the Investigator. Height will only be recorded at screening. BMI will be calculated at screening.

b. Vital signs include triplicate measurements of blood pressure and pulse rate and single assessment of body temperature (tympanic or oral). Blood pressure and pulse measurements will be assessed after at least 5 minutes in a supine position.

c. Twelve-lead ECGs will be obtained in triplicate (three consecutive interpretable 12-lead ECGs in less than 5 minutes) after the participant has been in a supine position for at least 10 minutes. 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) should be collected in the morning of Period 1 Day 4 and Period 2 Day 7 approximately the same time as the 72 hour (Period 1 Day 4) or 12 hour (Period 2 Day 7) post-dose PK samples are collected. At all other time points these samples should be taken at the most appropriate time.

e. Hepatitis A (HAV IgM Ab), total Hepatitis B Core Antibody (HBcAb), Hepatitis B (HBsAg), Hepatitis C (HCV RNA or HCV Ab), human immunodeficiency virus (HIV-1 and HIV-2 Ab).

f. Serum or plasma beta-human chorionic gonadotropin (β-HCG) at screening, urine on all other occasions (females only). If urine is positive, then need confirmatory serum or plasma test.

g. Follicle stimulating hormone (females only; to confirm post-menopausal status).

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

i. RBR blood sample will be collected at pre-dose Period 1.

j. The participant will discharge in the morning after all the samples for the PK and safety assessments have been taken and the participant has the option to stay in clinic during the whole Period 1 and wash-out period if agreed by Sponsor and the Investigator (i.e., discharge Period 2, Day 7).

k. A washout period of at least 7 days, but not more than 21 days, between the two periods. Washout period is defined as from Period 1 Day 1 to Period 2 Day 1.

l. In case of early termination, a participant should be called for an early termination visit and assessments should be performed as listed in the table.

## Table 2 Schedule of Activities – Detailed Table (Period 1)

| Period | Day | Scheduled Time (h) | Vital Signs[a] | ECG-12 Lead[b] | Administration of Pitavasatin | Administration of RO7049389 | Plasma PK for Pitavasatin and its Metabolite | Plasma PK for RO7049389 and its Metabolites | Plasma PK for Coproporphyrins | Urine PK for Coproporphyrins[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Period 1 | Day -28 to Day -2 | | x | x | | | | | | |
| | Day -1 | | x | x | | | | | | x |
| | Day 1 | Pre-dose | x | x | | | x | | x | |
| | | 0 | | | x | | | | | |
| | | 0.5 | | | | | x | | x | |
| | | 1 | x | | | | x | | x | |
| | | 1.5 | | | | | x | | x | |
| | | 2 | | | | | x | | x | |
| | | 3 | | | | | x | | x | |
| | | 4 | | | | | x | | x | |
| | | 6 | x | | | | x | | x | |
| | | 0-7 | | | | | | | | x |
| | | 8 | | | | | x | | x | |
| | | 10 | | | | | x | | | |
| | | 12 | | | | | x | | x | |
| | | 16 | | | | | x | | | |
| | | 7-24 | | | | | | | | x |
| | Day 2 | 24 | x | | | | x | | x | |
| | | 36 | | | | | x | | | |
| | Day 3 | 48 | x | | | | x | | | |
| | Day 4 | 72 | x | x | | | x | | | |

## Table 2 Schedule of Activities – Detailed Table (cont.) (Period 2)

| Period | Day | Scheduled Time (h) | Vital Signs[a] | ECG 12 Lead[b] | Administration of Pitavasatin | Administration of RO7049389 | Plasma PK for Pitavasatin and its Metabolite | Plasma PK for RO7049389 and its Metabolites | Plasma PK for Coproporphyrins | Urine PK for Coproporphyrins[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Period 2 | Day -1 | | x | x | | | | | | |
| | Day 1 | Pre-dose | x | x | | | | | | |
| | | 0 | | | | x | | | | |
| | | 0.5 | x | | | | | | | |
| | | 1 | x | | | | | | | |
| | | 2 | x | x | | | | | | |
| | | 4 | x | | | | | | | |
| | | 6 | x | x | | | | | | |
| | | 12 | x | | | x | | | | |
| | Day 2 | Pre-dose | x | | | | | | | |
| | | 0 | | | | x | | | | |
| | | 12 | | | | x | | | | |
| | Day 3 | Pre-dose | x | | | | | x | | |
| | | 0 | | | | x | | | | |
| | | 0.5 | | | | | | x | | |
| | | 1 | | | | | | x | | |
| | | 1.5 | | | | | | x | | |
| | | 2 | | | | | | x | | |
| | | 3 | | | | | | x | | |
| | | 4 | | | | | | x | | |
| | | 6 | | | | | | x | | |
| | | 8 | | | | | | x | | |
| | | 10 | | | | | | x | | |
| | | Pre-dose | | | | | | x | | |
| | | 12 | | | | x | | | | |
| | Day 4 | Pre-dose | x | x | | | x | x | x | |
| | | 0 | | | x | x | | | | |
| | | 0.5 | x | | | | x | x | x | |
| | | 1 | x | | | | x | x | x | |
| | | 1.5 | | | | | x | x | x | |
| | | 2 | x | x | | | x | x | x | |
| | | 3 | | | | | x | x | x | |
| | | 4 | x | | | | x | x | x | |
| | | 6 | x | x | | | x | x | x | |
| | | 0-7 | | | | | | | | x |
| | | 8 | | | | | x | x | x | |
| | | 10 | | | | | x | x | | |
| | | Pre-dose | x | | | | x | x | x | |
| | | 12 | | | | x | | | | |
| | | 16 | | | | | x | | | |
| | | 7-24 | | | | | | | | x |
| | Day 5 | Pre-dose | x | | | | x | | x | |
| | | 0 | | | | x | | | | |
| | | Pre-dose | | | | | x | | | |
| | | 12 | | | | x | | | | |
| | Day 6 | Pre-dose | x | x | | | x | | | |
| | | 0 | | | | x | | | | |
| | | 0.5 | x | | | | | | | |
| | | 1 | x | | | | | | | |
| | | 2 | x | x | | | | | | |
| | | 4 | x | | | | | | | |
| | | 6 | x | x | | | | | | |
| | | 12 | x | | | x | | | | |
| | Day 7 | 0 | x | x | | | x | | | |
| | Day 14 (± 1) | 0 | x | x | | | | | | |
| Early Termination | | | x | x | | | x | x | | |

## Table 2 Schedule of Activities – Detailed Table (cont.)

a. Vital signs include triplicate measurements of blood pressure and pulse rate and single assessment of body temperature after the participant has been in a supine position for at least 5 minutes.

b. 12-lead ECGs will be obtained in triplicate 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.

c. Urine samples will be collected at -7-0 hours pre-dose (Day -1 of Period 1), 0-7 and 7-24 hours post-dose (Day 1 of Period 1), 0-7 and 7-24 hours post-dose (Day 4 of Period 2).

# 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

Based on the data from in vitro studies of RO7049389 there is a possibility of an organic anion-transporting polypeptide (OATP)-mediated interaction between RO7049389 and OATP1B1 substrates. In vitro, RO7049389 inhibits OATP1B1 mediated transport with a half maximal inhibitory concentration ($IC_{50}$) of 3 μM (1796 ng/mL). This $IC_{50}$ is predicted to be lower than RO7049389 exposures at the expected efficacious dose. The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or 'statins', a class of cholesterol-lowering drugs, are known substrates for OATP1B1. In future clinical trials, a statin may be a concomitant medication with RO7049389. Therefore, it will be important to understand the effect, if any, of RO7049389 on the pharmacokinetics (PK) of such an OATP1B1 substrate.

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

## 2.2 BACKGROUND

### 2.2.1 Background on Hepatitis B Virus

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

Currently, there are two classes of drugs available for the treatment of chronic hepatitis B (CHB): subcutaneously administered interferon (IFN) preparations and orally administered nucleos(t)ide analogues (NUCs). Although both types of treatment can induce the loss of HBV envelope antigen with development of anti-HBeAg antibody (serological response), the suppression of HBV 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 clinical cure. Hepatitis B surface antigen (HBsAg) loss, with various therapies (NUCs or INF) only occurs in approximately 3% after one year of treatment. HBsAg loss rates increase to 9% at 3 years and 12% at 5 years following PEG-IFN-2a therapy (EASL 2017). In clinical studies, the combination of NUCs with PEG-IFN has not been proven superior to PEG-IFN alone for the most prevalent genotypes in the world, i.e., B, C and D (Marcellin 2016). In addition, IFN-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.

### 2.2.2 Background on RO7049389

RO7049389 is an inhibitor of HBV capsid assembly and belongs to the well-studied class of heteroaryldihydropyrimidine (HAP) 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 HBV replication.

[redacted]

The entry-in-human (EIH) study, YP39364, with RO7049389 is ongoing. This is a randomized, Sponsor-open, Investigator-blinded, subject-blinded, placebo-controlled study to investigate the safety, tolerability, PK and pharmacodynamics (PD) of RO7049389 in: (1) single- (with or without food) and multiple- (with midazolam) ascending doses in healthy volunteers (HVs); (2) patients chronically infected with hepatitis B virus.

[redacted]

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

### 2.2.3 Background on Pitavastatin

Pitavastatin is an approved HMG-CoA reductase inhibitor (i.e., statin), used in the treatment of hypercholesterolemia. Statins have been shown to reduce cardiovascular morbidity and mortality, and their efficacy and safety for the primary and secondary prevention of cardiovascular events have been demonstrated in a large number of clinical trials.

Dose-proportional increases in pitavastatin $C_{max}$ and $AUC_{inf}$ were observed following daily administration ranging from 1 to 24 mg. Given with a high-fat and high-calorie meal, $C_{max}$ decreased by 43% but the AUC did not decrease significantly. The mean plasma elimination half-life ($t_{1/2}$) is approximately 12 hours (LIVALO® U.S. Package Insert). Per the transporter expressing HEK293 cells and human cryopreserved hepatocytes, the OATP1B1 and OATP1B3 transporter account for almost all the observed pitavastatin uptake clearance into human hepatocytes and OATP1B1 accounts for about 90% of the clearance (Hirano et al 2004). Pitavastatin has been reported to be sensitive to OATP1B inhibition (Prueksaritanont et al 2014).

Pitavastatin was generally well-tolerated in clinical trials of up to 60-week duration, with a tolerability profile broadly similar to that of atorvastatin and simvastatin (Duggan 2012). The adverse-events (AE) profile of pitavastatin compares favorably with those of other available statins. Reported AEs of pitavastatin included gastrointestinal symptoms (0.7%–2.2%), myopathies (0.3%–1.1%), and elevated hepatic enzyme concentrations (0.0%–8.8%; Yee et al 2011).

A detailed description of the chemistry, pharmacology, efficacy and safety of pitavastatin is provided in the pitavastatin package insert hours (LIVALO® U.S. Package Insert).

## 2.3 BENEFIT/RISK ASSESSMENT

This study has the principal aim of characterizing the drug-drug interaction between RO7049389 and an OATP substrate, the cholesterol-lowering drug pitavastatin, a representative of the statin class, in a population of healthy volunteers. There will be no therapeutic benefit for the healthy volunteers participating in the study. However, assessment of the influence of RO7049389 on the safety and PK of pitavastatin brings valuable information for the development of RO7049389. The target population could be exposed to statins or other OATP1B1 substrates, therefore, the results from the study will provide essential information to guide dosing of statins when co-administered with RO7049389.

The risks for the individual participant due to exposure to RO7049389 and/or pitavastatin or study-related procedures are considered acceptable or low in this study. [redacted] The risks

associated with two administrations of 2 mg single dose of pitavastatin in this study are also considered acceptable or low due to extensive clinical experience with pitavastatin at doses up to 24 mg and over much longer treatment durations, up to 60 weeks (Duggan 2012). In addition, careful safety monitoring of all critical safety parameters will be performed throughout this study and there will be close monitoring of all participants during dosing and in-clinic stay.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected adverse events of RO7049389 is provided in the RO7049389 Investigator's Brochure.

## 3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

### Table 3 Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To determine the effect of multiple-doses of RO7049389 on the single-dose pharmacokinetics (PK) of pitavastatin in healthy participants. | • Primary PK parameters of pitavastatin: $C_{max,}$ and $AUC_{0\text{-}inf}$<br>• Secondary PK parameters of pitavastatin: $t_{max}$, CL/F, V/F and $t_{½}$.<br>• Other parameters may be calculated if considered appropriate. |
| **Secondary** | |
| • To evaluate the safety and tolerability of the single-dose pitavastatin alone and in combination with multiple-doses of RO7049389 in healthy participants. | • Incidence and severity of adverse events.<br>• Incidence of laboratory abnormalities based on hematology, clinical chemistry, coagulation, lipids, and urinalysis test results.<br>• ECGs.<br>• Vital signs including blood pressure (BP), pulse rate and body temperature. |
| • To explore the effect of the single-dose of pitavastatin on steady-state PK of RO7049389 in healthy participants.<br>• To determine the effect of multiple-doses of RO7049389 on the single-dose PK of pitavastatin lactone in healthy participants (if applicable). | • Primary PK parameters of RO7049389 and its metabolites (RO7121986, RO7255420 and RO7255422): $C_{max,}$ and $AUC_{tau.}$<br>• PK parameters of pitavastatin lactone: $C_{max,}$ and $AUC_{0\text{-}inf.}$<br>• The AUC ratio of pitavastatin lactone/pitavastatin. |
| **Exploratory** | |
| • To evaluate the effect of multiple-doses of RO7049389 on OATP activity as assessed by plasma and urine coproporphyrins (CP-I and CP-III). | • Coproporphyrins (CP-I and CP-III) AUC in plasma and amount excreted in urine. |

# 4. STUDY DESIGN

## 4.1 OVERALL DESIGN

This is an open-label, fixed sequence, two-period study designed to evaluate the drug-drug interaction between RO7049389 and pitavastatin and the safety and tolerability of single-dose pitavastatin alone and in combination with multiple-doses of RO7049389 in healthy participants.

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

### 4.1.1 Length of the Study

The total duration of the study for each participant will be about 12 weeks divided as follows:

- Screening: Up to 28 days.
- Period 1:
  - In clinic period: Days -1 to 4.
  - Treatment period: Day 1
- Wash-out Period: Defined as from Period 1 Day 1 to Period 2 Day 1 and lasts at least 7 days but not more than 21 days
- Period 2:
  - In clinic period: Days -1 to 7
  - Treatment period: Days 1 to 6
- Safety follow-up:
  - Period 2 Day 13
  - Period 2 Day 34 (Telephone call)

The participant has the option to stay in clinic during the whole Period 1 and wash-out period if agreed by Sponsor and the Investigator.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

This is an open-label, fixed sequence, two-period study.

The primary objective of this study is to determine the effect of multiple-doses of RO7049389 on the single-dose PK of pitavastatin in healthy participants. As PK measurements are objectively analysed an open-label study design has been chosen. To minimize the number of participants needed and reduce inter-subject variability, this study will follow a two-period instead of parallel design. The duration of both washout and drug administration periods was established on the basis of the known

pharmacokinetic profiles of both RO7049389 and pitavastatin. The half-life [redacted] of RO7049389 was used to calculate the likely time needed for steady state and that of pitavastatin was used to calculate the duration needed to capture its entire elimination phase. To ensure the full potential for an interaction is realized (maximal inhibition of OATP), pitavastatin will be co-administered with RO7049389 while the latter is in steady state. Administration of RO7049389 will be continued throughout the whole elimination phase of pitavastatin. Accordingly, a fixed sequence design has been chosen for logistical reasons.

### 4.2.1 Rationale for Study Population

Male and female healthy volunteers have been selected as the study population for this study as the absence of confounding disease processes is expected to lead to a clear and consistent assessment of drug disposition and biological activity. This population is unlikely to require concomitant treatments that could interfere with the study drug and safety evaluations.

### 4.2.2 Rationale for Biomarker Assessments

Coproporphyrins (CP-I and CP-III) AUC ratios in plasma and amount excreted in urine ratios will be measured as endogenous markers for hepatic OATP1B1 inhibition. CP-I and III are porphyrin metabolites arising from heme synthesis and eliminated through bile and urine. CP-I and CP-III in plasma and the amount excreted in urine are reported to be substrates of OATP1B1 and OATP1B3 (Yurong Lai et al., 2016).

Correlation between pitavastatin clearance and endogenous substances will be explored in this study. If OATP1B1 activity needs be monitored for future RO7049389 clinical studies, the Coproporphyrins (CP-I and CP-III) AUC in plasma and/or amount excreted in urine, instead of pitavastatin, can be conveniently employed in such studies.

[redacted]

[redacted]

[redacted]

[redacted]

RO7049389 will be administered for 6 days with concurrent administration on Day 4 with pitavastatin and any possible OATP inhibition is at its maximum at steady state.

Pitavastatin was approved at dose range of 1 mg to 4 mg once daily. As potential OATP1B1 mediated exposure increase cannot be excluded when given in combination with RO7049389, a single dose of 2 mg of pitavastatin was chosen in this study considering the demonstrated safety and linear pharmacokinetics PK across a dose range of 1 mg to 24 mg following single dose.

The dosing periods selected for this study have been chosen to ensure that steady state will have been reached for RO7049389, and any possible significant drug-drug interaction will be detected, whilst minimizing exposure to any drug to the shortest period necessary.

Further details are provided in the RO7049380 Investigator's Brochure

## 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 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 days after the last dose of RO7049389 is administered.

# 5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants of this study will be healthy male and female volunteers of 18 to 60 years of age (inclusive). The study will enroll up to a total of 18 participants to obtain 16 evaluable participants.

Participants who drop out of the study, or who are withdrawn, for non-safety reasons may be replaced. Participants who withdraw from the study due to poor tolerability or due to study drugs (RO7049389 or pitavastatin) related adverse events 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 will be 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. 18 to 60 years of age, inclusive, at the time of signing the informed consent.

**Type of Participants and Characteristics**

3. Healthy, as judged by the Investigator.

   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 at screening and Day -1.

4. Body mass index (BMI) between 18 to 30 $kg/m^2$ (inclusive) at screening.
5. Male and female participants

   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic

abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

a) Female Participants

Female participants must be either surgically sterile (by means of hysterectomy and/or bilateral oophorectomy and/or tubal ligation) or post-menopausal for at least one year (defined as amenorrhea ≥ 12 consecutive months without another cause, and confirmed by follicle-stimulating hormone (FSH) level. Participants must not be pregnant or lactating.

b) Male Participants

With female partners who are not pregnant or lactating.

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

With female partners of childbearing potential, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

## 5.2 EXCLUSION CRITERIA

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

**Medical Conditions**

1. 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.
2. Confirmed (based on the average of 3 separate resting BP measurements in a supine position, after at least 5 minutes rest) systolic BP greater than 140 or less than 90 mmHg, and diastolic BP greater than 90 or less than 50 mmHg at screening and Day -1.
3. Personal history or family history of congenital long QT syndrome and/or cardiac sudden death.
4. History of Gilbert's syndrome.
5. Participants who have had significant acute infection, e.g., influenza, local infection, acute gastrointestinal symptoms or any other clinically significant illness within two weeks of dose administration.

6. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
7. Any clinically significant concomitant diseases or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.

**Prior/Concomitant Therapy**

8. Taking any herbal medications or substances(e.g., tea) or supplements(including vitamins), or traditional Chinese medicines (TCM) 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 include medications listed under Permitted Therapy and those made on a case-by-case basis following discussion and agreement between the Investigator and the Sponsor.
9. History of having received any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids) $\leq$ 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 Trial Experience**

10. 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 30 days or 5 half lives (whichever is longer).
11. Donation or loss of blood or blood products in excess of 500 mL within 3 months of screening.

**Diagnostic Assessments**

12. Positive test for drugs of abuse (including recreational drugs) and/or positive alcohol test and/or positive cotinine test at screening and on Day -1.
13. Clinically relevant ECG abnormalities on screening or Day -1 ECG based upon the average of three ECGs, e.g.:
    a. QTcF $>$ 450 msec or $<$ 300 msec.
    b. Notable resting bradycardia (HR $<$ 45 bpm), or HR $>$ 90 bpm.
    c. Evidence of atrial fibrillation, atrial flutter, complete bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
14. ECG with 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 at screening or on Day -1 (may be repeated for confirmation).
16. Positive test at screening of any of the following: Hepatitis A virus (HAV IgM Ab), hepatitis B virus (HBsAg or HBcAb), , hepatitis C virus (HCV RNA or HCV Ab) or human immunodeficiency virus (HIV-1 and HIV-2 Ab).
17. 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 may be repeated once prior to enrollment to confirm eligibility unless deemed not clinically significant by the Investigator.

**Other Exclusions**

18. History of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol) and/or drug abuse within 12 months of screening.
19. Use of $>$ 5 cigarettes or equivalent nicotine-containing product per day prior to screening.
20. Participants under judicial supervision, guardianship or curatorship.
21. Medical or social conditions that would potentially interfere with the participant's ability to comply with the study visit schedule or the study assessments.
22. 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.

## 5.3 LIFESTYLE CONSIDERATIONS

### 5.3.1 Meals and Dietary Restrictions

Food and water will be restricted as follows:

- Any nutrients known to modulate activity of CYP enzymes or OATP transporters (e.g., grapefruit-, apple-, or Seville orange-containing products) will be prohibited within 3 days before Period 2 Day -1 through the last dose of RO7049389, which is on Period 2 Day 6.
- Approximately 240 mL of still water at room temperature will be provided for each dose. No water is allowed until 2 hours after each dose, after which time, water is allowed ad libitum.

### 5.3.2 Caffeine, Alcohol, and Tobacco

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

- During each period, 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 PK sample.

- Alcohol must not be consumed from 48 hours before screening, 48 hours before admission until completion of follow-up visit on Day 13 of Period 2.
- 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 the final follow-up visit.

### 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).

## 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 IEC/IRB approved newspaper/radio/television/Social Network Service/campus poster advertisements, mailing lists and other distributable documents, prior to consenting to take place on this study.

# 6. TREATMENTS

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

The investigational medicinal products (IMPs) required for completion of this study will be RO7049389 and pitavastatin. RO7049389 will be supplied centrally by the Sponsor

and pitavastatin (LIVALO® manufactured by Kowa) will be sourced locally and reimbursed by the Sponsor.

All study drug administration will be at the study center under supervision of site staff.

## 6.1 TREATMENTS ADMINISTERED

Table 4 summarizes the treatments administered.

### Table 4 Summary of Treatments Administered

| **Study Treatment Name:** | RO7049389 | Pitavastatin |
|---|---|---|
| **Dosage Formulation:** | Tablet | Tablet |
| **Unit Dose Strength(s):** | 200 mg | 2 mg |
| **Dose:** | 800 mg BID | 2 mg |
| **Route of Administration:** | Oral | Oral |
| **Dosing Instructions:** | 4 tablets to be taken, with food | 1 tablet to be taken, with food |
| **Packaging and Labeling:** | Study treatment will be provided in labeled bottles. | |
| **Manufacturer** | F. Hoffmann-La Roche Ltd | Kowa |

Study treatments will be administered orally to the participants by investigational staff for all dosing with still water at room temperature.

Pitavastatin will be administered orally to participants by investigational staff in the morning on Day 1 of Period 1 and Day 4 of Period 2. Thirty minutes before the administration, a standard meal will be served to participants, which should be consumed within thirty minutes. RO7049389 will be administered orally to participants by investigational staff from Day 1 to Day 6 of Period 2 twice daily. The first daily dosing will be administered in the morning and the second daily dose will be in the evening, with approximately 12 hours interval. In the morning of Day 4 of Period 2, pitavastatin will be administered together with RO7049389.

For RO7049389, please see the RO7049389 Investigator's Brochure for more details.

For pitavastatin, see the local prescribing information for more details.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

For RO7049389, study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the RO7049389 will be in accordance with Roche standard and local regulations.

The investigational site will acknowledge receipt of RO7049389 and confirm the shipment condition and content. Any damaged shipments will be replaced.

Upon arrival of the RO7049389 at the site, site personnel will complete the following:

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

The qualified individual responsible for dispensing the study treatment will prepare the correct dose.

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.

Pitavastatin (LIVALO® manufactured by Kowa) will be sourced locally and reimbursed by the Sponsor.

Only participants enrolled in the study may receive study treatments and only authorized site staff may supply or administer study treatments. 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. Film-coated tablets of RO7049389 should be stored under the recommended storage conditions “Store at 2-8°C, protect from light and moisture’.

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

## 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 instructions given in Section 6.1. This individual will record the date dispensed and participant number on the Drug Accountability Record.

## 6.5 CONCOMITANT THERAPY

### 6.5.1 Permitted Therapy

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

The Medical Monitor should be contacted 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 therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

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 adverse events should be recorded on the Adverse Event 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 2g/day up to 48 hours prior to dosing, not to exceed 4g 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.

As a general rule, 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), until the follow-up visit, with the exception of the cases listed in Permitted Therapy (See Section 6.5.1). Exceptions may be made on a case-by-case basis following discussion and agreement between the Investigator and the Sponsor after, the rationale for exception is discussed and clearly documented.

## 6.6 DOSAGE MODIFICATION

No dose modification of RO7049389 or pitavastatin 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, pitavastatin or other study interventions to participants after conclusion of the study or following early participant withdrawal.

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

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate 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

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

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

- Pregnancy
- Clinically significant study treatment-related changes in safety parameters that are considered not acceptable by the Investigator and/or the Sponsor.
- Poor gastrointestinal (GI) tolerability that is considered to affect the study participant's well-being and/or the PK evaluation

Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.10.3) and may undergo follow-up assessments (see Section 8.10.4). 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 determines, may jeopardize the participant's safety if he/she continues in the study.

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

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

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

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

## 7.3 LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

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

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

# 8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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
- ECG recordings
- Vital signs
- PK and safety blood sampling
- Administer meal
- 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 SoA (Section 1.3).

### 8.2.1 Physical Examinations

A complete physical examination should be performed at time-points indicated in the SoA (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, gastrointestinal, and neurological systems. Any abnormality

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

At all other visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Height (screening only) and weight will also be measured and recorded. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

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

### 8.2.2 Vital Signs

Body temperature (tympanic or oral), pulse rate, and blood pressure will be assessed.

Blood pressure and pulse 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 blood pressure measurements.

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

### 8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, RR, and QTc intervals.

At each time-point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession. The full set of triplicates should be completed in less than 5 minutes. Any clinically significant ECG abnormalities should be captured on the eCRF.

To minimize variability, it is important that participants be in a supine position for at least 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. 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 meals and 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 as 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 Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcF (Fridericia's correction) and 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.

### 8.2.4 Clinical Safety Laboratory Assessments

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

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

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

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

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

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

### 8.2.5 Medical History and Demographic Data

Medical history will include clinically significant diseases, 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.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 2. The non-serious adverse events of special interest are discussed in Sections 8.3.6.

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

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

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

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

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

**Post-study adverse events and serious adverse events:** The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period (28 days after the last dose of study treatment).

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

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

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

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

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

#### 8.3.3.1 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source

data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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

#### 8.3.3.2 Sponsor Follow-Up

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

### 8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

#### 8.3.4.1 Emergency Medical Contacts

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

### 8.3.5 Pregnancy

Female healthy participants of childbearing potential will not be allowed to participate in this study. However, female participants will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the last dose of study drug.

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 28 days after the last dose of study drug.

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

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

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

Non-serious adverse events of special interest 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).

Non-serious adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in 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 patient 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 or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects (see Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications 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 last 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 pitavastatin greater than 2 mg, and/or any dose of RO7049389 greater than 1600 mg within a 24-hour time period (+ 1.0 hours) will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

## 8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate concentrations of study treatment (RO7049389 and its metabolites, RO7121986, RO7255420 and RO7255422, pitavastatin and its metabolite, pitavastatin lactone (as applicable)) will be collected. The date and time of each sample collection will be recorded in the eCRF. Plasma concentrations of RO7049389, RO7121986, RO7255420 and RO7255422, pitavastatin and pitavastatin lactone (as applicable) levels will be analyzed by using validated liquid chromatography tandem mass chromatography (LC-MS/MS) methods. The PK samples will be taken as outlined in the Schedules of Activities (see Section 1.3). A PK sample will also be collected following occurrence of a dose-limiting event or serious adverse event.

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

The plasma samples will be destroyed within 2 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.

## 8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

## 8.7 GENETICS

### 8.7.1 Clinical Genotyping

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

- Genetic variants of transporters (e.g., OATP), which might affect pharmacokinetics of RO7049389 and pitavastatin.

Data arising from all biosamples including samples for analyses of inherited DNA will be subject to confidentiality standards described in Appendix 1. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.8.1).

The samples will be destroyed within 2 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 BIOMARKERS

Endogenous substances levels will be investigated to assess the effect of multiple oral dosing of RO7049389 on OATP1B1 activity. Individual AUC ratios (before and after 3 days of RO7049389 treatment) of plasma and amount excreted in urine of coproporphyrins (CP-I and CP-III) will be listed and summarized using descriptive statistics. Geometric mean ratio of after RO7049389 treatment relative to before RO7049389 treatment and the 90% confidence intervals will be computed.

Any remaining material from plasma or urine may also be used for additional assay validation experiments.

The plasma and urine samples will be destroyed within 2 years after the date of final CSR.

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

### 8.8.1 Samples for Research Biosample Repository

#### 8.8.1.1 Overview of the Research Biosample Repository

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

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

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

#### 8.8.1.2 Sample Collection

RBR samples will be collected at the time-point indicated in the SoA (Section 1.3). The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7049389 or diseases:

- RBR blood sample

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

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

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

## 8.9 HEALTH ECONOMICS

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

## 8.10 TIMING OF STUDY ASSESSMENTS

### 8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (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 must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

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

### 8.10.2 Assessments during Treatment

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

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

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

Participants who complete the last dose administration or discontinue from the study early will be asked to return to the clinic 7 days after the last dose of study treatment for a follow‑up visit and 28 days after the last dose of study treatment for a follow-up call. The follow-up visit and 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 and pitavastatin should be collected at the time of discontinuation. Please also see Section 1.3 for activities that are required to be performed in case of an early termination.

### 8.10.4 Follow-Up Assessments

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

### 8.10.5 Assessments at Unscheduled Visits

Please see Section 1.3 for activities that are required to be performed in case of an unscheduled visit.

If an unscheduled visit is required to ensure safety of study participants, necessary assessments will be undertaken at the discretion of the Investigator. All unscheduled assessments should be reported in eCRF.

Unscheduled local laboratory tests may be ordered per Investigator's discretion and may be used for the individual management of study participants.

## 9. STATISTICAL CONSIDERATIONS

The primary objective of this study is to characterize the pharmacokinetics profile of pitavastatin in healthy participants following multiple dose of RO7049389 on the single-

dose of pitavastatin. Statistical summaries will be descriptive in nature. All participants who receive any amount of study medication will be included in the safety analysis.

## 9.1 STATISTICAL HYPOTHESES

Not Applicable

## 9.2 SAMPLE SIZE DETERMINATION

A sample size of 18 participants to target 16 evaluable healthy participants has been chosen. Evaluable participants who withdraw for non-safety reasons from the study will be replaced to meet the enrollment goal.

Assuming a coefficient of within participant variation of 30% for $C_{max}$ and AUC, with a sample size of 16 evaluable participants per period, the entire 90% confidence interval for a geometric mean ratio (using pitavastatin alone as the reference) in the $C_{max}$ and AUC will be entirely within a range from 80% to 125% of the true (but unknown) geometric mean ratio with a probability of at least 80% (i.e., estimation power).

## 9.3 POPULATIONS FOR ANALYSES

### 9.3.1 Pharmacokinetic Analysis Population

All participants who have received at least one dose of study treatment (RO7049389 or pitavastatin) 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.

### 9.3.2 Safety Analysis Population

All participants, who received at least one dose of the study treatment (RO7049389 or pitavastatin), whether prematurely withdrawn from the study or not, will be included in the safety analysis.

For purposes of analysis, the following populations are defined in Table 5.

**Table 5 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 (RO7049389 or pitavastatin) 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. |

## 9.4 STATISTICAL ANALYSES

### 9.4.1 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, Chinese among Asian), ethnicity, age, weight, height and body mass index. 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.

### 9.4.2 Safety Analyses

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

**Table 6 Safety Statistical Analysis Methods**

| Endpoint | Statistical Analysis Methods |
|---|---|
| Adverse events | The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by appropriate thesaurus level and grouped according to treatment period. |
| Clinical laboratory tests | All clinical laboratory data will be stored on the database in the units in which they were reported. Participant listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.<br>Laboratory test values will be presented by individual listings with flagging of values outside the reference ranges. See Appendix 4 for details on standard reference ranges and data transformation and the definition of laboratory abnormalities. |
| Vital signs | Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate. |
| ECG data analysis | ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. Summary descriptive statistics for the actual values and changes from baseline will be tabulated by nominal time for HR, QRS duration, PR and QTcF. |
| Concomitant medications | The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.<br>Concomitant medications will be presented in summary tables and listings. |

### 9.4.3 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), pitavastatin and pitavastatin lactone 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.

To assess the effect of RO7049389 on the PK of pitavastatin, the logarithmically transformed variables $C_{max}$ and $AUC_{0\text{-}inf}$ of pitavastatin and its metabolite pitavastatin lactone will be subjected to an ANOVA (with factors RO7049389 and participant) for which measurements are available for healthy participants in both with/without

RO7049389. 90% confidence intervals for the ratio of geometric means will be calculated using the pitavastatin alone as the reference.

The same analysis of variance will be applied to the secondary parameters $AUC_{0\text{-}12hr}$ and $C_{max}$ of RO7049389 and its metabolites (RO7121986, RO7255420 and RO7255422) to assess the effect of pitavastatin on the PK of RO7049389.

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

### 9.4.4 Pharmacodynamic Analyses

Not Applicable.

### 9.4.5 Other Analyses

Individual ratios (before and after 3 days of RO7049389 treatment) of coproporphyrins (CP-I and CP-III) will be listed and summarized using descriptive statistics. Geometric mean ratio of after RO7049389 treatment relative to before RO7049389 treatment and the 90% confidence intervals will be computed.

## 9.5 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) and Appendix 3 (procedures of recording), Appendix 5 (contraceptive guidance and collection of pregnancy information). 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 EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

### 1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

### 1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. 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, 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 or the participant’s legally authorized representative.

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

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

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

### Consent to Participate in the Research Biosample Repository

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

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

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

If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

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

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

### Withdrawal from the Research Biosample Repository

Participants who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a participant wish to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study YP40218 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study YP40218. Data already generated before time of withdrawal of consent to RBR will still be used.

## 1.4. CONFIDENTIALITY

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

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

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

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

## 1.5. FINANCIAL DISCLOSURE

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

# 2. DATA HANDLING AND RECORD

## 2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

### 2.1.1. Data Quality Assurance

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

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

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

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

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

### 2.1.3. Source Data Records

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

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

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

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

### 2.1.4. 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 unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## 2.3. STUDY RECORDS

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

### 2.3.1. Protocol Amendments

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

### 2.3.2. Publication Policy

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

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

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

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

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

### 2.3.3. Dissemination of Clinical Study Data

A clinical study report containing the results of this trial will be made available to anyone who requests a copy. A description of this clinical trial and a summary of its results will be available at http://www.ClinicalTrials.gov.

### 2.3.4. Site Inspections

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

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

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

The 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.

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

## 1. DEFINITION OF ADVERSE EVENTS

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

An adverse event can therefore be:

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

**Events Meeting the AE Definition:**

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

**Events NOT Meeting the AE Definition:**

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

## 2. DEFINITION OF SERIOUS ADVERSE EVENTS

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

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

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

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

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

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

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

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

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

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

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

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

The Investigator will then record all relevant AE/SAE information in the 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 adverse event severity).

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

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

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

**Table 1 Adverse Event Severity Grading Scale**

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

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

## 3.2. ASSESSMENT OF CAUSALITY

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

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

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

## 4. FOLLOW-UP OF AES AND SAES

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

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

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

# 5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)
- Accidental overdoses or medication errors (see Appendix 2, Section 5.2 for details on reporting requirements)

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

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

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

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

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

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

**Events that Occur after Study Treatment Initiation**

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

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

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

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

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

## 5.2 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error are defined as follows:

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

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

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with RO7049389 and pitavastatin, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

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

For RO7049389 and pitavastatin, each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). For RO7049389 and pitavastatin, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

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

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

- RO7049389 Investigator's Brochure
- Local prescribing information for pitavastatin

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

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

# Appendix 3
# Procedures for Recording Adverse Events

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

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

## 1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

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

## 2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

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

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

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

## 3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the

Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

## 4. ABNORMAL LABORATORY VALUES

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

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

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

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

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

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

## 5. ABNORMAL VITAL SIGN VALUES

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

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

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

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

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

## 6. ABNORMAL LIVER FUNCTION TESTS

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 3, Section 4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Appendix 2, Section 5.1).

## 7. DEATHS

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

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

## 8. PREEXISTING MEDICAL CONDITIONS

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

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

## 9. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

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

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

- Hospitalization for respite care
- Planned hospitalization 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 adverse event.

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

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

# Appendix 4
# Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory.

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

All study-required laboratory assessments will be performed by a local laboratory:

| 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) and reticulocyte counts. |
| • Clinical Chemistry | • Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total, direct and indirect bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (at screening only), creatinine phosphokinase (at screening only), total protein, albumin, urea, creatinine, creatinine clearance (CrCl) (at screening and Day −1 only using the Cockcroft-Gault formula), uric acid, fasting glucose, sodium, chloride, potassium, calcium, phosphorus. |
| • Coagulation | • INR, aPTT, PT. |
| • Viral Serology | • Hepatitis A virus (HAV IgM Ab), hepatitis B virus (HBsAg and HBcAb), hepatitis C virus (HCV RNA or HCV Ab), human immunodeficiency virus (HIV-1 and HIV-2 Ab). |
| • Lipids | • Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides. |

**Table 1 Protocol-Required Safety Laboratory Assessments (cont.)**

| | |
|---|---|
| • Hormone | • FSH (females only to confirm post-menopausal status). |
| • Pregnancy Test | • Serum or plasma beta-human chorionic gonadotropin (β-HCG) at screening, urine on all other occasions (females only). If urine is positive, then need confirmatory serum or plasma test. |
| • Urinalysis | • Dipstick: pH, glucose, protein, blood, and leucocytes<br>• If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.<br>• Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal. |
| • Urine drug screen | • Cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates. |
| • Cotinine | • Cotinine test as per local practice. |
| • Alcohol | • Alcohol breath test. |

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

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

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

- Definition of Laboratory Abnormalities

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

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

# Appendix 5
# Contraceptive Guidance and Collection of Pregnancy Information

## 1. DEFINITIONS

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

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

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

a) Pre-menarchal

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

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

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

c) Post-menopausal female

- A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high 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 will not be allowed to participate in this study.

- **Male Participants**

Male Participants are eligible to participate if they and their female sexual partner agree to use a highly effective method of contraception consistently and correctly as described in Table 1 below.

**Table 1** Highly Effective Contraceptive Methods

| **Highly Effective Methods That Are User-Independent[a]** |
|---|
| **Highly effective non-hormonal contraception**<br>• Intrauterine device (IUD)<br>• Bilateral tubal occlusion<br>**Vasectomy**<br>Vasectomy is a highly effective contraception method. |
| **Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. |

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

## 3. PREGNANCY TESTING

Female participants of childbearing potential will not be allowed to participate in this 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.

## 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**

Female participants of childbearing potential will not be allowed to participate in this study. However, the Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study

treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

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

## 5 ABORTIONS

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

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

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

## 6 CONGENITAL ANOMALIES/BIRTH DEFECTS

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