ISRCTN63295298 https://doi.org/10.1186/ISRCTN63295298

Study to evaluate the safety, tolerability, and effect of the body and food on RO7308480 following oral administration in healthy participants

Submission date 24/01/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 11/02/2022	**Overall study status** Completed	
Last Edited 10/02/2022	**Condition category** Other	

Plain English summary of protocol

Background and study aims
This is the first study where the drug RO7308480 will be given to humans. The aims of this study are to test the safety of RO7308480 at different dose levels, determine how well it is tolerated by the participants; measure how the body absorbs, distributes, and gets rid of it (this is called pharmacokinetics); and to determine the effect that food can have on its pharmacokinetics. The study results will be used to support further clinical development of RO7308480.

Who can participate?
Healthy volunteers between 18 to 55 years of age

What does the study involve?
This study consists of two parts, Part 1, and Part 2. Participants will be assigned to either Part 1 or Part 2.

Part 1
Participants may be asked to be in the study for about 8 weeks in Part 1. This includes:
1. A screening visit within 28 days before treatment administration where tests will be done to check if the participants are eligible to take part in the study
2. An inpatient stay at the clinic for 8 days and 7 nights (from 2 days before until 6 days after treatment)
3. Six walk-in visits on Days 7, 8, 10, 12, 14, and 28 after treatment.

Part 1 or the “single-ascending dose” stage will evaluate the safety, tolerability, and pharmacokinetics of RO7308480. Participants will be divided into seven different groups, with each group receiving a higher dose level than the preceding group. A higher dose level will only be administered in participants after the lower dose levels have been shown to be safe and well-tolerated in previous participants. Each group will have a maximum of 12 participants of which 9 will receive RO7308480 and 3 will receive a placebo (a drug without the active substance).

Each of the seven dose levels will be split into two groups. Two participants will be dosed on Day 1 (one participant will receive RO7308480 and one participant will receive a placebo). The rest of the group (a minimum of five participants on active treatment and a minimum of one participant on placebo) will be dosed no earlier than 24 hours later.
Participants will be given RO7308480 or matching placebo capsules to be swallowed whole with about 240 ml water at room temperature on the morning of Day 1 after an overnight fast of at least 10 hours.

Part 2
Participants may be asked to be in the study for about 14 weeks in Part 2. This includes:
1. A screening visit within 28 days before treatment administration where tests will be done to check if the participants are eligible to take part in the study
2. An inpatient stay at the clinic twice – each time for 7 days and 6 nights (from 1 day before each of the treatments until 6 days after each treatment)
3. A period in between the two treatment administrations of 14 to 28 days where the drug is expected to be eliminated after the first administration (wash-out)
4. Six ambulatory visits on Days 7, 8, 10, 12, 14, and 28 after the second treatment.

Part 2 or the "food effect" (FE) assessment will evaluate the effect of food on the levels of RO7308480 in the body, whether and how food affects the speed and extent with which the body absorbs, distributes, and gets rid of RO7308480. A maximum of 12 participants will be enrolled in Part 2.
There will be two study periods in Part 2. In the first period, six participants will receive RO7308480 under fasted conditions (overnight fasting) and the remaining six will receive the same dose of the drug under fed conditions (after breakfast). In the second period, participants will receive the same dose of RO7308480 under the other condition. In other words, if the first study drug administration was done under fasted conditions, the second one will be done in the fed condition, and vice-versa. There will be an interval of about 14 to 28 days between both periods (wash-out period).

What are the possible benefits and risks of participating?
Participants will not receive any benefit from participating in this study, but the information that is learned may help further the clinical development of RO7308480.
Participants may experience side effects from the treatments or procedures in this study. Side effects can vary from mild to very serious and may be different from person to person.
RO7308480 has not yet been tested in humans, and the side effects of this drug are not known at this time. Based on laboratory studies and knowledge of other drugs, the potential risks listed below may occur.
1. Allergic reactions such as itching, difficulty breathing, a rash, and/or a drop in blood pressure
2. Central nervous system related effects
3. Slurred speech (e.g., mumbling)
4. Mental disturbances such as mood disorders, prolonged periods of extreme sadness, agitation, and irritability
5. Symptoms of overdose may include sedation, unconscious state, and slow or ineffective breathing
There may be a risk in exposing an unborn child to the study treatment, and not all potential consequences are known at this time. Women and men must take precautions to avoid exposing an unborn child or a breastfed baby to the study treatment. Participants who are pregnant, become pregnant, or are currently breastfeeding cannot take part in this study.

Where is the study run from?
F. Hoffmann-La Roche Ltd (USA)

When is the study starting and how long is it expected to run for?
November 2021 to July 2022

Who is funding the study?
F. Hoffmann-La Roche Ltd (USA)

Who is the main contact?
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Contact information

Type(s)
Public

Contact name
Dr Clinical Trials

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-004128-13

Protocol serial number
BP43318

Study information

Scientific Title
A Phase I randomized, investigator/participant-blind, adaptive, single ascending dose, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics, and food effects of RO7308480 following oral administration in healthy participants

Study objectives
The purpose of this study is to assess the safety, tolerability, pharmacokinetics (PK), and food effects (FE) of single-ascending oral doses of RO7308480 in healthy participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 11/01/2022, Committee for the Protection of Persons South-East IV (Centre Léon Bérard 28 rue Laennec - 69373 Lyon Cedex 08; +33 (0)4 78 78 27 61; cppse4@lyon.unicancer.fr), ref: 21.04076.000032

Primary study design
Interventional

Study design
Phase I randomized two-part study:
Part 1: adaptive investigator/participant-blind single-ascending dose (SAD) placebo-controlled parallel design
Part 2: open-label single-dose two-period two-sequence two-treatment ("fed-fasted", "fasted-fed") crossover design

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Safety, tolerability, pharmacokinetics, and food effects of single-ascending oral doses of RO7308480 in healthy participants

Interventions
Part 1: RO7308480-SAD Cohorts: Participants will receive a single dose of RO7308480 capsule, orally, under fasted conditions on Day 1 in cohort 1. The dose will be escalated in subsequent cohorts in six steps as per the Sponsor's clinical pharmacologist and Principal Investigator's judgment

Part 1: Placebo-SAD Cohorts: Participants will receive a single dose of RO7308480 matching placebo capsule, orally, under fasted conditions on Day 1 of the SAD stage

Part 2: Food Effect Assessment (FE)-Fasted Period: Participants will receive a single dose of RO7308480 capsule, orally, under fasted conditions on Day 1 of the FEC-fasted period

Part 2: FE-Fed Period: Participants will receive a single dose of RO7308480 capsule, orally, 30 minutes after a standardized high fat, high-calorie breakfast on Day 1 of the FE-fed period

This study consists of two parts, Part 1, and Part 2. Participants will be assigned to either Part 1 or Part 2.

Part 1
Participants may be asked to be in the study for about 8 weeks in Part 1. This includes:
1. A screening visit within 28 days before treatment administration where tests will be done to check if the participants are eligible to take part in the study
2. An inpatient stay at the clinic for 8 days and 7 nights (from 2 days before until 6 days after treatment)
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Part 1 or the "single-ascending dose" stage will evaluate the safety, tolerability, and pharmacokinetics of RO7308480. Participants will be divided into seven different groups, with each group receiving a higher dose level than the preceding group. A higher dose level will only

be administered in participants after the lower dose levels have been shown to be safe and well-tolerated in previous participants. Each group will have a maximum of 12 participants of which 9 will receive RO7308480 and 3 will receive a placebo (a drug without the active substance).
Each of the seven dose levels will be split into two groups. Two participants will be dosed on Day 1 (one participant will receive RO7308480 and one participant will receive a placebo). The rest of the group (a minimum of five participants on active treatment and a minimum of one participant on placebo) will be dosed no earlier than 24 hours later.
Participants will be given RO7308480 or matching placebo capsules to be swallowed whole with about 240 ml water at room temperature on the morning of Day 1 after an overnight fast of at least 10 hours.

Part 2
Participants may be asked to be in the study for about 14 weeks in Part 2. This includes:
1. A screening visit within 28 days before treatment administration where tests will be done to check if the participants are eligible to take part in the study
2. An inpatient stay at the clinic twice – each time for 7 days and 6 nights (from 1 day before each of the treatments until 6 days after each treatment)
3. A period in between the two treatment administrations of 14 to 28 days where the drug is expected to be eliminated after the first administration (wash-out)
4. Six ambulatory visits on Days 7, 8, 10, 12, 14, and 28 after the second treatment.

Part 2 or the “food effect” (FE) assessment will evaluate the effect of food on the levels of RO7308480 in the body, whether and how food affects the speed and extent with which the body absorbs, distributes, and gets rid of RO7308480. A maximum of 12 participants will be enrolled in Part 2. There will be two study periods in Part 2. In the first period, six participants will receive RO7308480 under fasted conditions (overnight fasting) and the remaining six will receive the same dose of the drug under fed conditions (after breakfast). In the second period, participants will receive the same dose of RO7308480 under the other condition. In other words, if the first study drug administration was done under fasted conditions, the second one will be done in the fed condition, and vice-versa. There will be an interval of about 14 to 28 days between both periods (wash-out period).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO7308480

Primary outcome(s)
1. Part 1 and 2: Percentage of participants with adverse event (AEs), recorded by non-leading verbal questioning of the participant, from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in single-ascending dose (SAD) and food effect assessment (FE) stages, respectively
2. Part 1 and 2: Percentage of participants with the severity of AEs as assessed by the investigator (mild, moderate, or severe) from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in SAD and FE stages, respectively
3. Part 1 and 2: Percentage of participants with clinically significant changes in vital signs values measured using body temperature (tympanic), pulse rate, respiratory rate, and blood pressure

from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in SAD and FE stages, respectively
4. Part 1 and 2: Percentage of participants with clinically significant changes in physical findings measured by assessment of cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal systems in addition to head, eyes, ears, nose, throat, neck, and lymph nodes from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in SAD and FE stages, respectively
5. Part 1 and 2: Percentage of participants with clinically significant changes in neurological findings assessed using measurement of motor and sensory skills, functioning of cranial nerves (including pupillary responses), coordination, gait, reflexes, and mental status from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in SAD and FE stages, respectively
6. Part 1 and 2: Percentage of participants with clinically significant changes in electrocardiogram (ECG) parameters measured using 12-lead ECG and Holter ECG (only in Part 1) from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in SAD and FE stages, respectively
7. Part 1 and 2: Percentage of participants with significant changes in clinical laboratory results measured using blood or urine samples collected from screening up to Day 14 and 28 days after study drug administration (up to approximately 6 months) in SAD and FE stages, respectively

Key secondary outcome(s)

Measured from blood samples using a specific and validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method:
1. Part 1: Maximum observed plasma concentration (Cmax) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 hours (h) thereafter up to Day 14 in SAD stage
2. Part 1: Time to maximum observed concentration (Tmax) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
3. Part 1: Area under the plasma concentration-time curve from time zero up to the last measurable concentration (AUClast) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
4. Part 1: Area under the plasma concentration-time curve from time zero up to 24 h (AUC0-24h) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
5. Part 1: Area under the plasma concentration-time curve from time zero extrapolated to infinity (AUCinf) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
6. Part 1: Area under the plasma concentration-time curve from zero up to a given time (AUC0-t) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
7. Part 1: Terminal rate constant (λz) calculated by linear regression of the log-transformed terminal part of the concentration-time curve of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
8. Part 1: Apparent terminal half-life (t1/2), computed as log (2) per λz (ln(2)/λz) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
9. Part 1: Apparent clearance (CL/F) calculated from Dose/AUCinf of RO7308480 measured using

blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in SAD stage
10. Part 1: Cumulative amount excreted (Ae) unchanged into urine of RO7308480 and its metabolites, as appropriate, measured using urine samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 6 in Part 1 (SAD) only
11. Part 1: Fraction of dose excreted (Fe) unchanged in urine of RO7308480 and its metabolites, as appropriate, measured using urine samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 6 in Part 1 (SAD) only
12. Part 1: Calculated renal clearance (CLR), computed as Ae/AUC of RO7308480 measured using urine samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 6 in Part 1 (SAD) only
13. Part 2: Maximum observed plasma concentration (Cmax) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
14. Part 2: Time to maximum observed concentration (Tmax) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
15. Part 2: Area under the plasma concentration-time curve from time zero up to the last measurable concentration (AUClast) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
16. Part 2: Area under the plasma concentration-time curve from time zero up to 24 h (AUC0-24h) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
17. Part 2: Area under the plasma concentration-time curve from time zero extrapolated to infinity (AUCinf) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
18. Part 2: Area under the plasma concentration-time curve from zero up to a given time (AUC0-t) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
19. Part 2: Terminal rate constant (λz) calculated by linear regression of the log-transformed terminal part of the concentration-time curve of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
20. Part 2: Apparent terminal half-life (t1/2), computed as log (2) per λz (ln(2)/λz) of RO7308480 and its metabolites, as appropriate, measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 in FE (fed and fasted state) stage
21. Part 2: Apparent clearance (CL/F) calculated from Dose/AUCinf of RO7308480 measured using blood samples at pre-dose and multiple time-points post-dose on Day 1 and every 12 h thereafter up to Day 14 FE (fed and fasted state) stage

Completion date
19/07/2022

Eligibility

Key inclusion criteria

1. 18 to 55 years of age inclusive, at the time of signing the informed consent
2. Male and female participants who are overtly healthy (defined by the absence of evidence of any active or chronic disease) as determined by medical evaluation
3. Participants able to communicate with the study staff
4. Body mass index (BMI) of 18 to 30 kg/m² inclusive

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Any condition or disease detected during the medical interview/physical examination that could relapse during or immediately after the study
2. Use of any psychoactive medication, or medications known to have effects on central nervous system (CNS) or blood flow taken within 4 weeks prior to first dosing
3. History of convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or CNS infections (e.g., meningitis)
4. Any major illness within one month before the screening examination (e.g., COVID-19 infection) or any febrile illness within 1 week prior to screening and up to first study drug administration
5. Clinically significant abnormalities in laboratory test results
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities
7. Participants who, in the Investigator's judgment, pose a suicidal or homicidal risk, or any participant with a history of suicidal or homicidal attempts
8. Participants likely to need concomitant medication during the study period
9. Use of isotretinoin within 2 years prior to screening
10. Incomplete SARS-CoV-2/COVID-19 vaccinations scheme 2 weeks prior to administration of the first dose
11. Participation in an investigational drug or device study within 90 days prior to screening, as calculated from the day of follow-up from the previous study, or more than four times a year
12. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies
13. Positive result on hepatitis B virus (HBV) or hepatitis C virus (HCV) at screening or within 3 months prior to starting study treatment
14. Any suspicion or history of alcohol abuse
15. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that contraindicates the participation in the study
16. Participants who regularly smoke more than 5 cigarettes daily or equivalent amount of tobacco and nicotine substitutes as determined by history, and unable or unwilling not to smoke during the in-house period

Date of first enrolment
15/02/2022

Date of final enrolment
20/06/2022

Locations

Countries of recruitment
France

Study participating centre
Biotrial
7-9 Rue Jean-Louis Bertrand
Rennes
France
35000

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location

Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement

IPD sharing plan summary
Not expected to be made available