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A study in healthy volunteers to compare the test medicine as both a tablet and capsule, to determine the correlation between increases in doses of the test medicine and the amount of test medicine taken up by the body, and to estimate how food affects the test medicine when given as a tablet

Submission date 26/04/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 24/05/2022	**Overall study status** Completed	
Last Edited 30/05/2022	**Condition category** Other	

Plain English summary of protocol

Background and study aims

The sponsor is developing new recipes of the test medicine, RO7486967, to potentially treat diseases such as inflammatory bowel disease, respiratory diseases including chronic obstructive pulmonary disease and severe asthma and Parkinson's disease. These diseases are linked by a type of inflammation caused by a protein called NLRP3. The test medicine (RO7486967) is anticipated to reduce this inflammation by specifically targeting and blocking NLRP3 from being activated. This two-part healthy volunteer study is testing up to three different recipes of the test medicine, and how they are affected when taken with food. The frequency of adverse events and how the recipes of the test medicine are tolerated will also be investigated. Results from Part 1 will determine if Part 2a or Part 2b is selected.

Who can participate?

Healthy male and non-pregnant, non-lactating female volunteers aged 18 to 55 years

What does the study involve?

In Part 1 and Part 2a, the test medicine will be given on three occasions and in Part 2b on four occasions. In all parts, volunteers will all receive the same recipes of the test medicine, but in a different order; the order will be assigned by chance. Volunteers will receive an oral dose of a new recipe of the test medicine in the fed or fasted state. In Part 1 and Part 2b, volunteers will also receive the test medicine that will be compared with the other recipes in the fasted state. Volunteers will be discharged from the clinic 48 hours later and there will be a break of at least 7 days in between each dosing occasion. Volunteers will be discharged 48 hours after their final

dose and will return to the clinic for a follow-up visit 14 to 21 days later. Volunteer’s blood and urine will be collected throughout the study for analysis of the test medicine and for their safety. Volunteers are expected to be involved in this study for about 10 weeks for Part 1 and 11 weeks for Part 2, from screening to the follow-up visit.

What are the possible benefits and risks of participating?
This is a healthy volunteer study. Participants will be administered RO7486967 only for research purposes and it is not intended that the participants will receive any benefit from it. However, the information learned in this study may help future patients. Participants will be compensated for taking part in this research study with an inconvenience allowance. As this is a Phase I study, the most relevant population is healthy volunteers. It is considered that the risk/benefit evaluation in this study supports the use of healthy volunteers. Non-clinical studies have not revealed any reproductive hazards, however as there is no clinical data on pregnant women available, female participants will be required to follow the contraception requirements. Only healthy male and non-pregnant and non-lactating female participants, aged 18 to 55 years are considered suitable for this study. There is always a risk that the stipend in healthy volunteer studies could represent coercion. The time spent in the clinic, travel, inconvenience and other expenses factor in calculating the stipend. Perception of risk is not considered in this calculation. When investigating new medicines there is always a risk of unexpected side effects and occasionally allergic reactions. Volunteers will be closely monitored during the study. Volunteers may experience side effects from the test medicine in this study. Full information on possible side effects is provided to volunteers in the Participant Information Sheet/Informed Consent Forms. There will be an extended period of fasting for the volunteers taking part in this study. To ensure an adequate fluid intake, the volunteers will be allowed to drink water freely and will be monitored for signs of dehydration and fatigue. Blood samples will be collected during the study. Collection of these samples can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks. ECG stickers on volunteers' chests and limbs may cause some local irritation and may be uncomfortable to remove but volunteers will be closely monitored to ensure any local irritation does not persist. As the test medicine is central nervous system (CNS) acting and may have an effect on volunteers' mental health, so they will be required to complete a questionnaire at regular intervals during the study. The questionnaire assesses an individual's mood and mental wellbeing and will be performed by an appropriately trained physician.

Where is the study run from?
Roche (Switzerland)

When is the study starting and how long is it expected to run for?
April 2022 to September 2022

Who is funding the study?
Roche (Switzerland)

Who is the main contact?
global-roche-genentech-trials@gene.com

Contact information

Type(s)
Scientific

Contact name
Dr Trial Information Support Line (TISL)

Contact details
Grenzacherstrasse 124
Basel
Switzerland
4070
+41 (0)616881111
global-roche-genentech-trials@gene.com

Type(s)
Public

Contact name
Dr Trial Information Support Line (TISL)

Contact details
Grenzacherstrasse 124
Basel
Switzerland
4070
+41 (0)616881111
global-roche-genentech-trials@gene.com

Type(s)
Principal Investigator

Contact name
Dr Nand Singh

Contact details
Mere Way
Ruddington Fields
Nottingham
United Kingdom
NG11 6JS
+44 (0)3303031000
recruitment@weneedyou.co.uk

Additional identifiers

EudraCT/CTIS number
2021-005215-31

IRAS number
1004383

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BP43130, IRAS 1004383

Study information

Scientific Title
A two-part, open-label, randomised, cross-over study to compare new tablet formulations of RO7486967 to the capsule formulation, to perform a preliminary dose proportionality assessment and to estimate the effect of food on the pharmacokinetics of the tablet formulations in healthy participants

Acronym
QSC205468

Study objectives
Parts 1 and 2:
1. To determine the pharmacokinetics (what the body does to the test medicine, PK) of RO7486967 in plasma following administration of single oral doses of RO7486967 in the fasted and fed states.
2. To assess the effect of food on the plasma concentration versus time profiles of RO7486967 and RO7428130 (breakdown product) after a single oral dose of RO7486967 as a tablet formulation.

Parts 1 and 2b only:
1. To compare the plasma concentration versus time profiles of RO7486967 and RO7428130 after a single oral dose of 200 mg RO7486967 as a tablet formulation and a capsule formulation.

Part 2 only:
1. To compare the plasma concentration-time profiles of RO7486967 and RO7428130 after a single oral dose of 25 mg RO7486967 as a tablet formulation to a single oral dose of 200 mg RO7486967 as a tablet formulation.

Parts 1 and 2:
1. To assess the safety and tolerability profiles of the RO7486967 capsule and tablet formulations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Fast Track REC (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK), ref: 22/FT/0053

Study design
Open randomized controlled cross over trial

Primary study design
Interventional

Secondary study design

Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Inflammatory bowel disease (IBD), respiratory diseases including chronic obstructive pulmonary disease (COPD) and severe asthma, and Parkinson’s disease

Interventions
Part 1:
Participants will be randomised to receive a single dose of each of reference Hard Capsules RO7486967 200 mg (2 x 100 mg) in the fasted state, RO7486967 Immediate Release Tablet, 200 mg in the fasted state, and RO7486967 Immediate Release Tablet, 200 mg in the fed state, across three periods.
Either option Part 2a or 2b will be chosen based on the results of Part 1.

Part 2a:
Participants will be randomised to receive a single dose of each of RO7486967 Immediate Release Tablet, 200 mg in the fasted state, RO7486967 Immediate Release Tablet, 25 mg in the fasted state and RO7486967 Immediate Release Tablet, 25 mg in the fed state, across three periods.

Part 2b:
Participants will be randomised to receive a single dose of each reference Hard Capsules RO7486967 200 mg (2 x 100 mg) in the fasted state, RO7486967 Modified Release Tablet, 200 mg in the fasted state, and RO7486967 Modified Release Tablet, 200 mg in the fed state and RO7486967 Modified Release Tablet, 25 mg in the fasted state, across four periods.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO7486967

Primary outcome measure
Parts 1 and 2:
1. Pharmacokinetic (PK) parameters, including (but not limited to) Tmax, Cmax, AUC(0-last), AUC (0-inf), lambda-z and T1/2 for RO7486967 in plasma, as applicable, measured using blood samples at pre-dose and at multiple time points, up to 16 hours post-dose on Day 1, and thereafter on Days 2 and 3.

2. Assessment of food effect on plasma PK parameters Cmax, AUC(0-last) and AUC(0-inf) for RO7486967 and RO7428130, as applicable, in the fed state (test regimens) compared to the fasted state (reference regimens), for RO7486967 in plasma measured using blood samples at pre-dose and at multiple time points, up to 16 hours post-dose on Day 1, and thereafter on Days 2 and 3.

Part 1 and Part 2b only:
1. Relative bioavailability of plasma PK parameters Cmax, AUC(0-last) and AUC(0-inf) for RO7486967 and RO7428130, as applicable, for tablet formulations (test regimens) compared to a capsule formulation (reference regimen), in plasma measured using blood samples at pre-dose and at multiple time points, up to 16 hours post-dose on Day 1, and thereafter on Days 2 and 3.

Part 2 only:
1. Dose proportionality of plasma PK parameters Cmax, AUC(0-last) and AUC(0-inf) for RO7486967 and RO7428130, as applicable, in the chosen 25 mg RO7486967 tablet formulation (test regimen) compared to the chosen 200 mg RO7486967 tablet formulation (reference regimen), in plasma measured using blood samples at pre-dose and at multiple time points, up to 16 hours post-dose on Day 1, and thereafter on Days 2 and 3.

Secondary outcome measures
Parts 1 and 2:
1. Additional safety and tolerability information for RO7486967 collected by assessing the incidence of adverse events (AEs), and change from baseline for Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, electrocardiograms (ECGs), and laboratory safety tests, from the time of signing the informed consent form to up to 21 days post-final dose (approximately 11 weeks)

Overall study start date
20/04/2022

Completion date
21/09/2022

Eligibility

Key inclusion criteria
1. Healthy males or non-pregnant, non-lactating healthy females
2. Aged 18 to 55 years inclusive at the time of signing the informed consent
3. Body mass index (BMI) of 18.0 to 30.0 kg/m², inclusive, as measured at screening
4. Participants must be willing and able to communicate and participate in the whole study and comply with study requirements
5. Participants must provide written informed consent
6. Participants must agree to adhere to the contraception requirements defined in the clinical protocol

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
31

Key exclusion criteria
1. Participants who have received any IMP in a clinical research study within the 90 days prior to the planned first dose date of this study (i.e., Day 1 of Period 1), or less than 5 elimination half-lives prior to Day 1 of Period 1, whichever is longer. Participants who are enrolled and dosed in Part 1 are permitted to be enrolled in Part 2, only if there is a minimum of 90 days washout between the final dose of RO7486967 in Part 1 and the first dose of RO7486967 in Part 2.
2. Participants who are, or are immediate family members of, a study site or sponsor employee.
3. Positive test for SARS-CoV-2 within 30 days prior to Day 1 of Period 1 or evidence of recent SARS-CoV-2 symptomatic infection within the last 3 months. Participants who had asymptomatic, incidental, positive findings can be included if tested more than 30 days prior to screening and test negative at screening and prior to admission to the clinical unit.
4. Fever (body temperature >38°C) or symptomatic viral or bacterial infection within 2 weeks prior to screening.
5. History of any drug or alcohol abuse in the past 2 years.
6. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 ml glass of wine, depending on type)
7. A confirmed positive alcohol breath test at screening or admission.
8. Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission.
9. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months.
10. Females who are pregnant or lactating (all female participants must have a negative highly sensitive serum [screening] and urine [admission] pregnancy test). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum follicle-stimulating hormone [FSH] concentration ≥40 IU /l). Female subjects who are currently receiving HRT and have a serum FSH concentration <40 IU /l may be enrolled at the discretion of the investigator.
11. Male participants with pregnant or lactating partners
12. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
13. Clinically significant abnormal clinical chemistry, haematology, coagulation (screening only) or urinalysis as judged by the investigator. Note: Participants with Gilbert's Syndrome are not allowed.
14. ALP, AST, ALT, total bilirubin or GGT >ULN, INR >1.5 or albumin <34 g/l at screening. Repeat testing (one repeat test at screening and one repeat test at admission) is acceptable for out of range values following approval by the investigator or delegate.
15. Confirmed positive drugs of abuse test result.
16. Positive QuantiFERON test at the screening visit or within 2 months prior to screening.
17. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) antibody results.

18. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <70 mL/min using the Cockcroft-Gault equation
19. Abnormal ECG findings at screening and pre-dose that are considered by the investigator to be clinically significant, e.g.
19.1. QTc interval (QTcF >450 msec)
19.2. Notable resting bradycardia (heart rate [HR] <40 bpm)
19.3. Notable resting tachycardia (HR >100 bpm)
19.4. Evidence of atrial fibrillation, atrial flutter, right or left bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
19.5. Any other significant abnormality
20. Personal or family history of congenital long QT syndrome or sudden death
21. Prior or ongoing medical conditions, medical history, physical findings, or laboratory abnormality that, in the investigator's (or delegate's) opinion, could adversely affect the safety of the participant
22. Presence of any underlying physical or psychological medical condition that, in the opinion of the investigator, would make it unlikely that the participant will comply with the protocol or complete the study per protocol
23. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or gastrointestinal (GI) disease, neurological or psychiatric disorder, or cirrhosis, as judged by the investigator
24. History of malignancy except for non-melanoma skin cancer excised more than 2 years ago and Cervical intra-epithelial neoplasia that had been successfully cured more than 5 years prior to screening

Please see the clinical protocol for further exclusion criteria.

Date of first enrolment
26/05/2022

Date of final enrolment
21/09/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Quotient Sciences Limited
Mere Way
Ruddington Fields
Nottingham
United Kingdom
NG11 6JS

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

Sponsor details
Grenzacherstrasse 124
Basel
Switzerland
4070
+41 (0)6168 81111
global-roche-genentech-trials@gene.com

Sponsor type
Industry

Website
http://www.roche.ch/en/index.htm

Funder(s)

Funder type
Industry

Funder Name
Roche

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Publication and dissemination plan

1. Internal report
2. Submission to regulatory authorities

The findings of this Phase I study will be shared with the Sponsor, F. Hoffmann-La Roche Ltd., only. As these findings are confidential due to commercial sensitivity, it is not appropriate to share the results of this study with other researchers at this time.

Intention to publish date

21/09/2023

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No