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A study to evaluate the safety, tolerability, processing by the body and mechanism of action of multiple doses of ralmitaront with a single dose of risperidone administered to healthy participants

Submission date	Recruitment status	[X] Prospectively registered
21/10/2021	No longer recruiting	[ ] Protocol
Registration date	Overall study status	[ ] Statistical analysis plan
01/11/2021	Completed	[ ] Results
Last Edited	Condition category	[ ] Individual participant data
01/11/2021	Other	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The main aim of this study is to determine if a drug interaction exists when the study drug (ralmitaront) and risperidone are taken together. A drug interaction means one drug alters how another drug works or how it is processed in the body. Ralmitaront is an investigational drug being developed as a treatment for psychotic and affective disorders, including schizophrenia.

Who can participate?
Healthy people aged between 18 to 55 years old

What does the study involve?
The study duration is up to 8 weeks. This includes a screening period for up to 28 days before the beginning of the study period; an in-house period consisting of two study treatment periods staying at the study center for up to 20 days or 19 nights; and a follow-up visit for 14 days after the last dose of ralmitaront on Day 14. Participants will be asked to come to the study center about three times, if not needed for additional visits. When taking the research drug, the sponsor, study doctor and staff will know what participants are receiving at all times openly.

Study Treatment Period 1:
On Day 1 of the study treatment period, participants will receive a single oral (by mouth) dose of risperidone 0.5 mg or 1 mg (2 x 0.5 mg tablets). The study drug will be administered with a cup of water. Beginning on Day 2 and continuing through Day 5, participants will undergo a washout period, a period of time where participants will not take any study drug.

Study Treatment Period 2:
On Days 6 through 15, participants will receive a daily dose of ralmitaront. Participants will take the capsules by mouth with a cup of water. On Day 14, participants will receive risperidone 0.5

mg or 1 mg (2 x 0.5 mg tablets) 30 minutes after taking the daily dose of ralmitaront. Samples collected for study-related tests will be stored until the study results have been reported. If participants withdraw from the study, any sample collected prior to participant's withdrawal may still be tested, unless participants specifically ask for their samples to be destroyed or local laws require the destruction of the samples.

What are the possible benefits and risks of participating?
The participants' health may or may not improve in this study, but the information collected may help other people who have a similar medical condition in the future. There have been ralmitaront and risperidone related risks reported involving headache, dizziness, fatigue, skin irritation, diarrhea/soft feces, nausea, abdominal pain, musculoskeletal chest pain, high blood pressure, respiratory viral infection, palpation, abnormal blood biochemistry, difficult or painful swallowing, dry mouth, weight gain, increased appetite, common cold, fever and Parkinson-like symptoms (tremors, unstable balance, rigidity). There could also be risks of allergic reactions including drug interaction risks (medicines working with or against each other) and risks specific to lumbar puncture.

Where is the study run from?
PRA Health Sciences (USA)

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

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

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

Contact information

Type(s)
Public

Contact name
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Additional identifiers

Protocol serial number
BP43026

Study information

Scientific Title
A single-center, single-sequence, open-label, two-period study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of the combination of multiple doses of ralmitaront with a single dose of risperidone in healthy subjects

Study objectives
To assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of ralmitaront with a single dose of risperidone in healthy participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/10/2021, Advarra IRB (6100 Merriweather Dr., Suite 600, Columbia, MD 21044, USA; +1 (0)410 884 2900; cirbi@advarra.com), ref: MOD01120493

Primary study design
Interventional

Study design
Phase I single-centre single-sequence open-label study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Safety, tolerability, pharmacokinetics and pharmacodynamics of ralmitaront and risperidone in healthy participants

Interventions
The study duration is up to 8 weeks. This includes a screening period for up to 28 days before the beginning of the study period; an in-house period consisting of two study treatment periods staying at the study center for up to 20 days or 19 nights; and a follow-up visit for 14 days after the last dose of ralmitaront on Day 14. Participants will be asked to come to the study center about three times, if not needed for additional visits. When taking the research drug, the sponsor, study doctor and staff will know what participants are receiving at all times openly.

Study Treatment Period 1:
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Study Treatment Period 2:
On Days 6 through 15, participants will receive a daily dose of ralmitaront. Participants will take the capsules by mouth with a cup of water. On Day 14, participants will receive risperidone 0.5 mg or 1 mg (2 x 0.5 mg tablets) 30 minutes after taking the daily dose of ralmitaront. Samples collected for study-related tests will be stored until the study results have been reported. If

participants withdraw from the study, any sample collected prior to participant's withdrawal may still be tested, unless participants specifically ask for their samples to be destroyed or local laws require the destruction of the samples.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Ralmitaront, risperidone

Primary outcome(s)
Plasma concentrations and pharmacokinetic parameters of risperidone and 9-OH-risperidone measured using blood samples on days 1, 2, 3, 4, 5 of period 1 and days 14, 15, 16, 17, 18 of period 2

The following PK parameters will be calculated: maximum concentration (Cmax), area under the concentration-time curve from time 0 to infinity (AUC0-inf) and time to reach maximum plasma concentration (tmax)

In addition, other parameters may be calculated as outlined below:

Risperidone only: Last measurable plasma concentration (Clast), time of Clast (tlast), terminal rate constant (lambda z), t1/2, AUC from time 0 to 24 hours postdose (AUC0-24h), AUC from time 0 to last measurable concentration (AUC0-last), CL/F, and apparent volume of distribution after oral administration (V/F)

9-OH-risperidone only: Clast, tlast, lamda z, t1/2, AUC0-24h, AUC0-last and metabolic ratio of 9-OH-risperidone and risperidone for Cmax and AUC0-inf

Key secondary outcome(s)
1. Plasma concentrations and pharmacokinetic parameters of ralmitaront measured using blood samples on days 6-18 of period 2. The following PK parameters will be calculated:
Cmax, AUC0-inf and tmax.
In addition, other parameters may be calculated as outlined below.
Clast, tlast, lamda z, t1/2, AUC0-24h, CL/F*, V/F*, AUC0-last and metabolic ratio of M5 versus ralmitaront for Cmax and AUC0-inf (*not for M5)
2. Percentage of participants with adverse events recorded throughout the study
3. Involuntary movement disorders (Parkinsonism, akathisia, dystonia, and dyskinesia) assessed using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) on days -1 and 1 of period 1 and days 13 and 14 of period 2
4. Suicidal thoughts and behaviours assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, day -2 of period 1, days 13 and 14 of period 2 and at follow up
5. QTcF (QT corrected for heart rate using the Fridericia's correction factor) measured from 12-lead ECGs extracted from continuous (Holter) recordings on day 5 of period 1, days 6, 7, 13 and 14 of period 2
6. Heart rate (HR), PR and QRS (QRScomplex) interval measured from 12-lead ECGs extracted from continuous (Holter) recordings on day 5 of period 1, days 6, 7, 13 and 14 of period 2

Completion date
12/04/2022

Eligibility

Key inclusion criteria
1. A body mass index (BMI) between 18–30 kg/m², inclusive, at screening
2. Fluent in English

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological or allergic disease, metabolic disorder, or cancer
2. Disorders of the CNS that are clinically significant as determined by the Investigator, including psychiatric disorders, behavioral disturbances, cerebrovascular events, depression, bipolar disorder, migraine, Parkinson's, parkinsonism, and seizures
3. Elevated risk of clinically significant suicidal ideation and/or behavior within 2 years prior to screening as determined by the C-SSRS
4. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs. Uncomplicated appendectomy and cholecystectomy are acceptable
5. A history of clinically significant hypersensitivity (e.g. drugs, excipients) or allergic reactions
6. Hypersensitivity to risperidone or paliperidone, as stated in the prescribing information for risperidone
7. In the opinion of the Investigator, any major illness within 1 month before the screening examination, or any febrile illness within 1 week prior to screening and up to first study treatment administration
8. Use of prohibited medications (vaccines, over-the-counter [OTC] or prescription medication including herbal medications) taken within 14 days (or 5 times the elimination half-life of the medication, whichever is longer) prior to dosing, with the exception of acetaminophen up to 2 g per day, which is allowed up to 48 hours before dosing, and stable hormonal replacement or contraception therapy; COVID vaccine must be at least 21 days before dosing
9. Use of any drug or herbal inducers of CYP3A, CYP2C19, CYP2D6, or Pgp within 28 days prior to dosing
10. Participants likely to need concomitant medication during the study period (including for dental conditions)

11. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse in the last 5 years
12. Positive alcohol breath test or urine drug screen at screening or admission to the study site
13. Smokers who regularly smoke more than 5 cigarettes daily or equivalent and are unable or unwilling not to smoke during the confinement in CRU
14. Positive test result for human immunodeficiency virus (HIV) 1 and HIV 2, hepatitis C virus (HCV) antibody, or hepatitis B surface antigen (HBsAg)
15. Dietary restrictions that would prohibit the consumption of standardized meals
16. Participants under judicial supervision, guardianship, or curatorship
17. Women who are lactating
18. History of clinically significant back pain, back pathology, and/or back injury (e.g., degenerative disease, spinal deformity, spinal surgery, lumbar radiculopathy, chronic/recurrent headaches, intracranial tumors, and/or increase intracranial pressure) that may predispose to complications from, or technical difficulty with, a lumbar puncture
19. Criteria that would preclude a lumbar puncture, such as a local infection at the site of the lumbar puncture; clinically significant coagulation parameter abnormalities, thrombocytopenia, or treatment with an anticoagulant or with antiplatelet agents within 6 weeks prior to the day of lumbar puncture
20. History of clinically significant hypersensitivity to local anesthetics that may be used for lumbar puncture (e.g., lidocaine)

Date of first enrolment
03/11/2021

Date of final enrolment
07/12/2021

Locations

Countries of recruitment
United States of America

Study participating centre
PRA Health Sciences
1255 East 3900 South
Salt Lake City
United States of America
84124

Sponsor information

Organisation
Roche (Switzerland)

ROR
https://ror.org/00by1q217

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 are not expected to be made available due to there being no regulatory requirement to do so.

IPD sharing plan summary
Not expected to be made available