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A study to investigate the effect of enzyme inhibition on the bodily processing of RO6953958 in healthy participants

Submission date
20/10/2021

Recruitment status
No longer recruiting

Registration date
03/11/2021

Overall study status
Completed

Last Edited
23/05/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
This is a Phase 1 study, looking at how the study drug (RO6953958) works in the human body and the safety of this drug in healthy volunteers. This trial does not test if the drug helps to improve health.
The main purpose of this study is to determine if a drug interaction exists when the study drug (RO6953958) and itraconazole are taken together. A drug interaction means one drug alters how another drug works or how it is processed in the body. A drug interaction may cause one of the drugs to not work very well or have worse side effects. This study will look at:
- effect of itraconazole and its metabolites (drug breakdown byproducts) on the pharmacokinetics (PK, the amount of study drug in the blood stream and how long the body takes to get rid of it) of a single dose of RO6953958 and its metabolites (study drug breakdown byproducts) in healthy participants.
- how safe and tolerable a single dose of RO6953958 is, when taken alone and when co-administered with itraconazole in healthy participants.
- pharmacokinetics (PK) of multiple doses of itraconazole and its metabolites in healthy participants when given alone and when co-administered with RO6953958.
- taste of RO6953958.
- genetic variations play a role in how a RO6953958 is metabolized when given in combination with itraconazole.

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

What does the study involve?
Participants may be asked to be in the study for up to 9 weeks. This includes: 1) Screening Period (questions and tests to see if participants are eligible for the study) that will occur up to 28 days before the beginning of the study period. Participants will not be confined to the study center during the Screening period; 2) Two in-house Study Treatment Periods. Participants will be confined to the study center for up to 5 days and 4 nights for the first Study Treatment Period and up to 14 days and 13 nights for the second Study Treatment Period; 3) 5 ambulatory (out-

patient) visits. Three of these visits will occur between the first in-house period and the second in-house period, and two of these visits will occur after the second in-house period; 4) Follow-up Visit (Day 18) approximately 14 days after the last dose of RO6953958.

There will be pharmacogenomic testing involving human genes. Pharmacogenomics is the study of differences in how our bodies respond to or handle medicines. The participant's sample will be tested to see if there are genetic variations in the participant's body's proteins that may affect how the study drug is absorbed, distributed, broken down, and removed from the participant's body. The genetic testing done in this study focuses on finding out if a gene (or combinations of genes) can be used to predict the response to RO6953958.

What are the possible benefits and risks of participating?
There is no particular benefit in participating in this research. Participants' health may or may not improve in this study, but the information that is learned may help other people who have a related medical condition in the future.
There are some most common side effects related to RO6953958, reported are headache and sleepiness. To date, there have been no safety concerns and participants have tolerated RO6953958 well.

Potentially related side effects could be a decrease in blood pressure and may inhibit platelet aggregation, resulting in bleeding. But no relevant blood pressure changes or bleeding events have been reported in the previous clinical trial with RO6953958 (see above).
There may be other risks that are unknown. These include Itraconazole-related risks such as upset stomach nausea, vomiting, rash; allergic reaction Risks; drug interaction risks (drugs working with or against each other); other potential risks including blood draw and intravenous injection, ECG Risks, fasting Risks, and other unknown ones.

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

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

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
BP43293

Study information

Scientific Title
A non-randomized, open-label, single-sequence, two-period phase I study to investigate the effect of CYP3A inhibition on the pharmacokinetics of RO6953958 in healthy participants

Study objectives
To investigate the effect of multiple oral doses of itraconazole on the bodily processing of a single oral dose of RO6953958.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/10/2021, Advarra IRB (6100 Merriweather Dr., Suite 600, Columbia, MD, 21044, USA; +1 410-884-2900; cirbi@advarra.com), ref: MOD01132386

Primary study design
Interventional

Study design
Phase 1 single-centre single-sequence non-randomized open-label study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Non-respiratory sleep disturbances in people with neurodevelopmental disorders (NDDs)

Interventions
Period 1: Participants will be administered a single oral dose of RO6953958 under fed conditions (30 minutes after starting a standard breakfast). Follow up for 7 days.
Period 2: Participants will be administered a single oral dose of RO6953958 on Day 4 after repeated administration of itraconazole (twice a day on day 1 and once a day on days 2-10) under fed conditions. Follow up for 15 days.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO6953958

Primary outcome(s)
Current primary outcome measure as of 23/05/2024:

1. Maximum observed plasma concentration (Cmax) of RO6953958, and its metabolites (M1, and M3) measured using non-compartmental methods
2. Area under the concentration-time curve from time 0 to infinity (AUC0-inf) of RO6953958, and its metabolites (M1, and M3) measured using non-compartmental methods
3. Area under the concentration-time curve up to last measurable concentration (AUClast) of RO6953958, and its metabolites (M1, and M3) measured using non-compartmental methods

Cmax, AUC0-inf, and AUClast were assessed based on samples collected at the following timepoints:
Period 1: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 1, and on Days 2, 3, 4, 5, 6, 7; Period 2: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 4, and on Days 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 18

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Previous primary outcome measure:

1. Plasma concentrations and pharmacokinetic parameters of RO6953958, M1, and M3 measured using blood samples on days 1, 2, 3, 4, 5, 6, 7 of period 1 and days 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 of period 2 and at follow up. The following PK parameters will be calculated if data allows: Maximum concentration (Cmax), area under the concentration-time curve from time 0 to infinity (AUC0-inf), or area under the concentration-time curve up to last measurable concentration (AUClast) if AUCinf can’t be estimated.

Key secondary outcome(s)
Current secondary outcome measures as of 23/05/2024:

1. Percentage of participants with adverse events and severity of AEs assessed by the investigator as mild, moderate, or severe from screening up to follow up (approximately 9 weeks)
2. Concentrations of itraconazole and its metabolite hydroxy-itraconazole measured using non-compartmental methods from blood samples collected on days 2, 3, 4, 6, 8, and 10 of period 2.

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Previous secondary outcome measures:

1. Percentage of participants with adverse events measured by the investigator throughout the study.
2. Concentrations of itraconazole and its metabolite hydroxy-itraconazole measured using blood samples on days 2, 3, 4, 6, 8, and 10 of period 2.

Completion date
05/01/2022

Eligibility

Key inclusion criteria
1. Participants who are healthy as determined by medical evaluation including medical history, surgical history, physical examination, laboratory tests, and cardiac monitoring
2. Body mass index within the range 18 to 32 kg/m² (inclusive).

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
16

Key exclusion criteria
1. Any condition or disease detected during the medical interview/physical examination that would render the participant unsuitable for the study, place the participant at undue risk, or interfere with the ability of the participant to complete the study, as determined by the investigator.
2. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs. This includes a surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract.
3. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological, or allergic disease; unexplained syncope (within 12 months prior to screening); metabolic disorder; cancer; or cirrhosis.
4. Use of any psychoactive medication, or medications known to have effects on the CNS or blood flow, taken within 30 days prior to the first dosing (or within 5 times the elimination half-life of the medication) prior to the first dosing (whichever is longer).
5. 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).
6. History of clinically significant hypersensitivity (e.g., drugs, excipients) or allergic reactions.
7. Any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to the first study drug administration.
8. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
9. Known active infection or any major episode of infection within 4 weeks prior to the start of drug administration.
10. Participants who test positive for SARS-CoV-2 should not be enrolled.

11. Known hypersensitivity to itraconazole or to any of the other excipients, or to any other triazole antifungals.
12. Any other known contraindications to itraconazole as stated in the U.S. Prescribing Information.
13. Have used or intend to use over-the-counter (OTC or prescription medication including herbal medications as described in the list of prohibited medications.
14. Participants likely to need concomitant medication during the study period (including for dental conditions).
15. Positive result on hepatitis B or hepatitis C virus (HCV), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. NOTE: Participants with positive hepatitis C antibody test due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid test is obtained.
16. A positive pregnancy test (women of childbearing potential only).
17. Positive test for drugs of abuse or alcohol.
18. Show evidence of human immunodeficiency virus (HIV) infection and/or positive test for HIV antibody at screening.
19. Dietary restrictions that would prohibit the consumption of standardized meals.
20. Participants who regularly smoke more than 5 cigarettes daily on average or vape equivalent amounts of nicotine and are unable or unwilling to stop smoking/vaping during the in-house period.
21. Only for the participants who will undergo taste assessment in Period 1: history or evidence of any medical condition that has altered taste sensory perception including ageusia and dysgeusia.
22. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse in the last 5 years.

Date of first enrolment
16/11/2021

Date of final enrolment
01/12/2021

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			23/05/2024	No	No