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A study to evaluate the effect of a single dose of cyclosporine on the processing by the body of a single dose of pralsetinib in healthy subjects

Submission date 26/08/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 14/10/2021	**Overall study status** Completed	
Last Edited 06/06/2023	**Condition category** Other	

Plain English summary of protocol

Background and study aims
The aim of this study is to evaluate the effect of a single dose of the drug cyclosporine on the processing by the body of a single dose of the drug pralsetinib in healthy volunteers.

Who can participate?
Healthy volunteers aged 18 years and over

What does the study involve?
On Day 1, 200 mg of pralsetinib (2 x 100-mg capsules) will be taken orally after an overnight fast of at least 10 hours. On Day 10, 200 mg of pralsetinib (2 x 100-mg capsules) will be taken orally within 5 minutes after a 600-mg dose of cyclosporine (6 x 100-mg capsules) and after an overnight fast of at least 10 hours.

What are the possible benefits and risks of participating?
Participation in this study is purely for research purposes, and will not improve health or treat any medical problems. The information from this study may help patients in the future. Participants may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available upon request. However, if participants are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.
Participants may have side effects from the drugs or procedures used in this study. Side effects can be mild to severe and even life-threatening or fatal, and they can vary from person to person. Pralsetinib has had limited testing in humans. About 200 healthy volunteers and 700 oncology patients have received pralsetinib thus far in human studies. In the largest human study, 578 cancer patients have received pralsetinib daily over several months (mainly double the dose in this study) and their observed side effects are included in the list shown below.

Very common side effects (occur in 10% or more of patients):
1. Decrease in blood cells, such as white blood cells, which may increase the risk of fever and infections, red blood cells (anemia), which may result in fatigue and shortness of breath, and

platelets, which may increase risk of bruising or bleeding. The decrease in blood counts may need to be treated with medicines that stimulate the blood cells to grow or may require a transfusion.
2. Increase in blood pressure
3. Liver problems (increased liver function blood test results). Participants who get any signs or symptoms of liver problems (for example yellowing of your skin or the white part of the eyes (jaundice), dark “tea-colored” urine, sleepiness, bleeding or bruising, loss of appetite, nausea or vomiting) should inform their doctor immediately.
4. Abnormal liver function tests (that is, possible liver damage)
5. Inflammation in the lungs (pneumonitis) that could cause shortness of breath and difficulty breathing, which can sometimes be life-threatening or fatal
6. Diarrhea or loose stools
7. Bleeding (in stomach or intestines but also in other parts of the body)
8. Constipation or difficulty opening the bowels
9. Increases in the amount of phosphate in the blood that may cause minerals to deposit in internal organs, such as the stomach and may lead to kidney damage
10. Increased creatinine in the blood, which can be a sign that the kidneys are not working properly
11. Increase in enzymes (creatine phosphokinase), which can be a sign of muscle or tissue damage
12. Change in taste
13. Fatigue
14. Dry mouth

Common side effects (occur in between 1% and 10% of patients):
1. Infections, mostly not serious, but sometimes life threatening or fatal (for example, pneumonia and lung infections, urinary tract infection, or infection in the blood)
2. Nausea and vomiting
3. Swelling of the hands or feet
4. Headache
5. Rash (local or generalized skin eruption)
6. Abdominal pain
7. Pain in extremities, back pain, pain in muscles, bones, or joints

Uncommon but important side effects (occur in between 0.1% and 1% of patients):
Because of the relatively low number of patients treated to date, it is not possible to determine any side effects in this category.

Cyclosporine is a drug used for the treatment of rheumatoid arthritis and psoriasis. It is also administered to patients receiving organ transplants in order to weaken the immune system to prevent organ rejection. Side effects that may be experienced when taking cyclosporine include:
1. Kidney dysfunction
2. Tremor
3. Hirsutism (excessive hair growth)
4. Hypertension (high blood pressure)
5. Gum hyperplasia (swelling of the gums)

Serious side effects include:
Damage to the kidneys and liver

When more than one drug is taken at a time the side effects can be worse or different than when taking the drug by itself. Please talk to the study doctor or staff about any questions or

concerns that you may have about the procedures required for this study and their risks.
In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of these study drugs, including severe or life-threatening allergic reactions or unexpected interactions with another medication. Symptoms of an allergic reaction may include rash, flushing, itching, sneezing or runny nose, abdominal pain, diarrhoea, swelling of face, tongue or throat, dizziness, lightheadedness or fainting, trouble breathing, irregular or racing heart rate, and seizures.

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

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

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

Who is the main contact?
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Contact information

Type(s)
Public

Contact name
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Additional identifiers

Protocol serial number
GP43162

Study information

Scientific Title
A Phase I, open-label, fixed-sequence study to evaluate the effect of a single dose of cyclosporine on the single-dose pharmacokinetics of pralsetinib in healthy subjects

Study objectives
The aim is to evaluate the effect of a single dose of cyclosporine on the single-dose pharmacokinetics of pralsetinib in healthy subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Primary study design
Interventional

Study design
Phase I single-center open-label fixed-sequence study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Effect of a single dose of cyclosporine on the single-dose pharmacokinetics of pralsetinib in healthy subjects

Interventions
All participants will receive the following treatments:
Day 1: 200 mg pralsetinib (2 x 100-mg capsules) administered orally after an overnight fast of at least 10 hours.
Day 10: 200 mg pralsetinib (2 x 100-mg capsules) administered orally, 5 minutes after a 600-mg dose of cyclosporine (6 x 100-mg capsules) and after an overnight fast of at least 10 hours.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Pralsetinib, cyclosporine

Primary outcome(s)
Current primary outcome measures as of 06/06/2023:
1. Maximum plasma concentration (Cmax), time to maximum observed concentration (t max), area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC 0-t), AUC from Hour 0 to “192,” where “192” is a common nominal timepoint across participants (AUC 0-“192”), AUC from time zero to infinity (AUC 0-∞) and apparent terminal elimination half-life (t 1/2) of pralsetinib when administered alone and in combination with cyclosporine, measured using noncompartmental methods of analysis at pre-dose and 0.5 hour (h), 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144 h, 192 h, 216 h, 240 h (cyclosporine arm only) and 264 h (cyclosporine arm only) post dose

Previous primary outcome measures:
1. t max, time to maximum observed concentration following SC administration measured from plasma samples taken QD with the exception of Days 6, 8, 15, 17, and 19, up to 3 weeks
2. AUC 0-t , area under the concentration-time curve from Hour 0 to the last measurable

concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations, measured from plasma samples taken QD with the exception of Days 6, 8, 15, 17, and 19, up to 3 weeks
3. AUC from Hour 0 to "t," where "t" is a common nominal timepoint across subjects (AUC 0-"t"), measured from plasma samples taken QD with the exception of Days 6, 8, 15, 17, and 19, up to 3 weeks
4. AUC from time zero to infinity (AUC 0-), measured from plasma samples taken QD with the exception of Days 6, 8, 15, 17, and 19, up to 3 weeks
5. AUC from time zero to the last quantifiable concentration (AUC last), measured from plasma samples taken QD with the exception of Days 6, 8, 15, 17, and 19, up to 3 weeks
6. Percentage of AUC that is due to extrapolation from the last measurable concentration, terminal elimination half-life (t 1/2), measured from plasma samples taken QD with the exception of Days 6, 8, 15, 17, and 19, up to 3 weeks

Key secondary outcome(s)
Current secondary outcome measures as of 06/06/2023:
1. Number of participants with treatment-emergent adverse events (TEAEs) and severity measured according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0), from study initiation up to follow-up at Day 38
2. Number of participants with abnormal electrocardiogram (ECG) parameters measured using triplicate 12-lead ECG at screening, check-in (Day -1) Day 1, 2, 5, 9, 10, 11, 14, 18, and at discharge (Day 21)

Previous secondary outcome measures:
1. AEs (incidence, nature, and severity), according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), recorded throughout the study
2. Incidence of electrocardiogram (ECG) abnormalities, as measured by triplicate 12-lead ECG at screening, Day 1, 2, 6, 9, 10, 11, 14, 18, and 21

Completion date
21/04/2022

Eligibility

Key inclusion criteria
1. Within BMI range 18.5 to 30.0 kg/m², inclusive
2. In good health, determined by no clinically significant findings from medical history, physical examination, laboratory profiles, 12-lead ECG, and vital signs
3. Clinical laboratory evaluations (including chemistry panel [fasted at least 10 hours], complete blood count [CBC], and urinalysis [UA] with complete microscopic analysis within the reference range for the test laboratory, unless deemed not clinically significant by the Investigator;
4. Negative test for selected drugs of abuse at Screening (does not include alcohol) and at Check-in (Day -1) (does include alcohol; Appendix A) and agrees to abstain from recreational drug use throughout the study, from screening until follow-up
5. Females will not be pregnant or breastfeeding, and must be either postmenopausal (at least 12 months without a period [i.e., amenorrhea]; in a woman at least 45 years of age and documented by a serum follicle-stimulating hormone [FSH] level consistent with postmenopausal status [i.e., ≥40 IU/l] in the absence of a reversible medical iatrogenic cause), or surgically sterile
6. Males will either be sterile or agree to use contraception
7. Receive an explanation of the mandatory {WGS} [and/or] {WES} component of the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
15

Key exclusion criteria
Current exclusion criteria as of 06/06/2023:
1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator)
2. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study
3. History of significant hypersensitivity, idiosyncratic reaction, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator
4. Use of oral antibiotics to treat an active infection within 4 weeks or intravenous antibiotics to treat an active infection within 8 weeks prior to Screening
5. History of stomach or intestinal surgery or resection prior to first dosing that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy and hernia repair will be allowed
6. History or presence of an abnormal ECG, which, in the Investigator's opinion, is clinically significant
7. History of alcoholism or drug addiction within 2 years prior to Check-in (Day -1)
8. History of active or latent TB, regardless of treatment history, or has a positive screening test for latent mycobacterium infection by QuantiFERON® TB Gold (Appendix A). Indeterminate results may be confirmed by repeat or by a purified protein derivative (PPD) skin test 9. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 5 half-lives or 30 days, whichever is longer, or administered treatment with another investigational drug within 5 times the elimination half-life, if known (if marketed product) or within 30 days (if the elimination half-life is unknown) prior to first dose of pralsetinib (Day 1). The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study
10. Receipt of any vaccines (including coronavirus disease-2019 [COVID-19], seasonal flu, and H1N1 vaccines) within 14 days prior to Screening, unless deemed acceptable by the Investigator and Sponsor
11. Prior exposure to pralsetinib or other RET inhibitors
12. Has a positive pregnancy test or is lactating (females only)
13. Has a positive urine drug or breath or urine alcohol result at Screening or Check-in

14. Has a positive urine cotinine result at Screening or Check-in
15. Use of any prescription medications/products within 14 days prior to Check-in (Day -1), unless deemed acceptable by the Investigator
16. Use of any over-the-counter, nonprescription preparations (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) within 7 days prior to Check-in (Day 1), unless deemed acceptable by the Investigator. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee to treat AEs. Hormone replacement therapy will not be allowed
17. Use of any drugs known to be a strong inhibitor and/or inducer of CYP1A2, CYP2D6, CYP3A4, and/or UGT1A4 enzymes, P-gp, and/or gastric acid reducing agents (e.g., proton-pump inhibitors, H2-receptor antagonists, antacids) for 14 days prior to the first dosing and throughout the study
18. Use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1) and during the entire study
19. Use of grapefruit- or Seville orange-containing foods or beverages within 14 days prior to first dosing and during the entire study duration
20. Use of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and during the entire study duration, unless deemed acceptable by the Investigator
21. Supine blood pressure is less than 90/50 mmHg or greater than 140/90 mmHg at Screening or history of uncontrolled hypertension
22. Supine heart rate is lower than 40 bpm or higher than 99 bpm at screening
23. Positive hepatitis panel (hepatitis B virus core antibody, hepatitis B surface antigen and hepatitis C virus antibody and negative human immunodeficiency virus (HIV) antibody screens (Appendix A)
24. Participants will refrain from strenuous exercise from 7 days prior to Check-in (Day 1) and during the period of confinement at the study site (e.g., will not begin a new exercise program or participate in any unusually strenuous physical exertion)
25. Poor peripheral venous access
26. History of malignancy, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
27. Donation or loss of 50 to 499 ml whole blood within 30 days prior to the first dose or more than 499 ml whole blood within 56 days prior to the first dose
28. Donation of plasma within 7 days prior to the first dose
29. Receipt of blood products within 2 months prior to Check-in (Day 1)
30. Has platelet, hemoglobin, and hematocrit that are below the lower limit of normal at screening or at first Check-in (confirmation of results may be done once)
31. Significant illness, including infections, surgery, or hospitalization within the 2 weeks prior to dosing. Invasive systemic fungal infections are required to have been fully treated prior to study enrollment
32. Any acute or chronic condition that, in the opinion of the Investigator, would limit the subject' s ability to complete and/or participate in this clinical study

Previous exclusion criteria:
1. Mental or legal incapacitation or has significant emotional problems at the time of the Screening visit or expected during the conduct of the study;
2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator)
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study
4. History of significant hypersensitivity, idiosyncratic reaction, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator

5. Use of oral antibiotics to treat an active infection within 4 weeks or intravenous antibiotics to treat an active infection within 8 weeks prior to Screening
6. History of stomach or intestinal surgery or resection prior to first dosing that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy and hernia repair will be allowed
7. History or presence of an abnormal ECG, which, in the Investigator's opinion, is clinically significant
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9. History of active or latent TB, regardless of treatment history, or has a positive screening test for latent mycobacterium infection by QuantiFERON® TB Gold (Appendix A). Indeterminate results may be confirmed by repeat or by a purified protein derivative (PPD) skin test
10. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 5 half-lives or 30 days, whichever is longer, or administered treatment with another investigational drug within 5 times the elimination half-life, if known (if marketed product) or within 30 days (if the elimination half-life is unknown) prior to first dose. of pralsetinib (Day 1). The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study
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13. Has a positive pregnancy test or is lactating (females only)
14. Has a positive urine drug or breath or urine alcohol result at Screening or Check-in
15. Has a positive urine cotinine result at Screening or Check-in
16. Use of any prescription medications/products within 14 days prior to Check-in (Day -1), unless deemed acceptable by the Investigator
17. Use of any over-the-counter, nonprescription preparations (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) within 7 days prior to Check-in (Day 1), unless deemed acceptable by the Investigator. After first dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee to treat AEs. Hormone replacement therapy will not be allowed
18. Use of any drugs known to be a strong inhibitor and/or inducer of CYP1A2, CYP2D6, CYP3A4, and/or UGT1A4 enzymes, P-gp, and/or gastric acid reducing agents (e.g., proton-pump inhibitors, H2-receptor antagonists, antacids) for 14 days prior to the first dosing and throughout the study
19. Use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1) and during the entire study
20. Use of grapefruit- or Seville orange-containing foods or beverages within 14 days prior to first dosing and during the entire study duration
21. Use of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) and during the entire study duration, unless deemed acceptable by the Investigator
22. Supine blood pressure is less than 90/50 mmHg or greater than 140/90 mmHg at Screening or history of uncontrolled hypertension
23. Supine heart rate is lower than 40 bpm or higher than 99 bpm at screening
24. Negative hepatitis panel (hepatitis B virus core antibody, hepatitis B surface antigen and hepatitis C virus antibody and negative human immunodeficiency virus (HIV) antibody screens (Appendix A)
25. Use of ritonavir-boosted saquinavir, atazanavir, darunavir, fosamprenavir, saquinavir, or tipranavir
26. Subjects will refrain from strenuous exercise from 7 days prior to Check-in (Day 1) and during the period of confinement at the study site (e.g., will not begin a new exercise program or

participate in any unusually strenuous physical exertion)
27. Poor peripheral venous access
28. History of malignancy, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
29. Donation or loss of 50 to 499 ml whole blood within 30 days prior to the first dose or more than 499 mL whole blood within 56 days prior to the first dose
30. Donation of plasma within 7 days prior to the first dose
31. Receipt of blood products within 2 months prior to Check-in (Day 1)
32. Any clinically significant deviations from normal ranges in coagulation factors including prothrombin time, international normalized ratio, activated partial thromboplastin time, and fibrinogen results, unless approved by the Investigator (if applicable)
33. Has platelet, hemoglobin, and hematocrit that are below the lower limit of normal at screening or at first Check-in (confirmation of results may be done once)
34. Significant illness, including infections, surgery, or hospitalization within the 2 weeks prior to dosing. Invasive systemic fungal infections are required to have been fully treated prior to study enrollment
35. Any acute or chronic condition that, in the opinion of the Investigator, would limit the subject' s ability to complete and/or participate in this clinical study

Date of first enrolment
09/02/2022

Date of final enrolment
15/03/2022

Locations

Countries of recruitment
United States of America

Study participating centre
Covance Research Unit – Dallas
Dallas
United States of America
75247

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 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 for Phase I studies.

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			06/06/2023	No	No