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A study to evaluate the drug-drug interaction potential of pralsetinib in combination with substrates of various transporters or CYP enzymes or a combined oral contraceptive in participants with advanced or metastatic solid tumors that are not responsive to standard therapies

Submission date 04/01/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 05/01/2023	**Overall study status** Completed	
Last Edited 04/10/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
The study aims to see if a test medicine, named pralsetinib, interacts with different medicines. Interaction of medicines may occur if different medicines are given together. This may result in higher levels of one or both medicines in the body. A high level of medicine equals an overdose and may lead to severe side effects.
Pralsetinib has been approved since September 2020 in the US for the treatment of a type of cancer called metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer under the trade name GAVRETO.
The aims of this study are:
1. To check how repeated doses of pralsetinib, when given along with certain probe drugs like digoxin, furosemide, metformin, and rosuvastatin, affect the way the body absorbs, distributes and eventually eliminates the probe drugs
2. To check how repeated doses of pralsetinib, when given along with probe drugs like midazolam, warfarin and montelukast, and a combined oral contraceptive (COC; birth control pill), affect the way the body absorbs, distributes and eventually eliminates the probe drugs
3. To check how safe and tolerable pralsetinib is when given along with both types of probe drugs

Who can participate?
People who are 18 years or more of age with a confirmed diagnosis of advanced solid tumours for which there is no effective cure

What does the study involve?
Participants may be asked to be in the drug-drug interaction part of the study as long as they receive benefit from the treatment. This includes:
1. A Screening Period where participants will be assessed for their eligibility to participate in the study.
2. An Assessment Period where participants will have to visit the clinic up to five times, which includes two inpatient visits, for a total of 7 days, if enrolled in Arm A and 15 days if enrolled in Arm B.
3. Continued Treatment Period where participants may continue to receive pralsetinib once daily, if the doctor is in agreement, for the treatment of their cancer disease. Participants will have to visit the clinic at least every 4 weeks for an outpatient visit to evaluate tumor assessments and clinical laboratory collections at the discretion of the treating doctor. Pralsetinib treatment may continue until disease progression, loss of benefit, unacceptable toxicity, participant or doctor decision to discontinue, death, or study termination by the Sponsor, whichever occurs first.
4. A Follow-up Period where participants will have to report for a check-up approximately 30 days after receiving the last dose of pralsetinib.

In the drug-drug interaction part of the study, participants will be divided into two groups:
1. Arm A: Participants will have to check into the clinic 1 day before receiving the probe drugs, for an in-house stay with 3 overnight stays until Day 3. Participants will receive the probe drugs: digoxin, furosemide, metformin, and rosuvastatin on the first day of the study after an overnight fast of 10 hours. Participants will receive pralsetinib, once daily, from Day 3 onwards. After getting discharged on Day 3, participants will have to continue taking pralsetinib at home, daily, on an empty stomach, in the morning 1 hour before breakfast. On Day 7 of the study, participants will have to report to the clinic for a check-up. Participants will have to come back on Day 10 for a second in-house stay until Day 12. Participants will receive the probe drugs along with pralsetinib on Day 10 of the study after an overnight fast of 10 hours. Blood samples will be drawn to check the blood levels of the probe drugs and to assess pralsetinib. Participants will continue taking pralsetinib every morning till Day 12.
2. Arm B: Participants will have to check into the clinic one day before receiving the probe drugs, for an in-house stay with 7 overnights until Day 7. Participants will receive midazolam, warfarin, and montelukast as probe drugs on Day 1 and vitamin K on Days 1, 2 and 3 of the study, after an overnight fast of 10 hours. Participants will receive a single dose of combined oral contraceptive (COC) on Day 5. Participants will start receiving pralsetinib from Day 7 onwards. After getting discharged on Day 7, participants will have to continue taking pralsetinib at home, daily, on an empty stomach, in the morning 1 hour before breakfast. On Day 11 of the study, participants will have to report to the clinic for a check-up. Participants will have to come back on Day 14 for a second in-house stay (7 overnight stay) until Day 20. Participants will receive the probe drugs along with vitamin K and pralsetinib on Day 14 after an overnight fast of 10 hours. In the morning of Days 15 and 16, participants will receive vitamin K. On Day 18, participants will receive a single dose of COC along with pralsetinib following an overnight fast of at least 10 hours. Blood samples will be drawn to check the blood levels of the probe drugs and also to assess pralsetinib. Participants will continue taking pralsetinib every morning till Day 20.

Participants may continue receiving pralsetinib alone after Day 12 for Arm A and after Day 20 for Arm B, if the study doctors feel that the participant is receiving clinical benefit from the treatment. Participants will be evaluated with tumor assessments per standard of care at the treating doctor’s discretion. Participants will be permitted to continue pralsetinib therapy until objective radiographic disease progression, loss of benefit, unacceptable toxicity, participant or doctor decision to discontinue, death or study termination by the Sponsor, whichever occurs first.

What are the possible benefits and risks of participating?
There is no guarantee that participants will receive any benefit from taking part in this study. Information obtained from the study may help in the development of a better understanding of the possible drug interactions of pralsetinib when given together with other drugs. However, participants may benefit from the continuous supply of pralsetinib in terms of the treatment of their cancer.
Not all possible side effects of the study medicine(s) are known. Like all medicines, the study medicine(s) can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some people may experience serious side effects and may require treatment.
The side effects or risks of pralsetinib and the drugs that are used as probes in this study are listed below.

Pralsetinib:
The most common (may affect more than 1 in 100 participants) side effects of pralsetinib are listed below:

1. An infection of the air sacs in one or both lungs characterised by cough with phlegm, fever, chills and difficulty in breathing (pneumonia)
2. Swelling of lung tissue due to non-infectious causes, which results in cough without mucus or phlegm, shortness of breath and fatigue (pneumonitis)
3. Decrease in red blood cells (anaemia)
4. An infection of the blood (sepsis)
5. An infection in any part of the urinary system (urinary tract infection)
6. Fever
7. Rapid release of substances from dying cancer cells that could be harmful to the body (tumour lysis syndrome)
8. Decrease of the white blood cells of the body (neutropenia)
9. Decrease of blood platelets, which help the blood to clot (thrombocytopenia)
10. Liver damage (hepatotoxicity)
11. Bleeding (hemorrhagic events)
12. Increase in blood pressure (hypertension)
13. Fatigue
14. Constipation
15. Pain in the muscles, bones, ligaments, tendons, and nerves (musculoskeletal pain)
16. The most common laboratory abnormalities observed were decreased white blood cells (lymphocytes), decreased neutrophils, decreased phosphate, decreased haemoglobin, decreased sodium, decreased calcium, and increased liver enzyme (alanine aminotransferase)

The side effect of rapid release of substances from dying cancer cells that could be harmful to the body (tumor lysis syndrome) has been seen in less than 1% (1 in 100) of participants.

Drug-Interaction Probe Drugs:
The following side effects have been experienced by other people who have taken the medicines that are administered as drug-interaction probes. The frequencies described for the side effects of these drugs below may include the following terms:
1. Very common: may affect more than 1 in 10 people
2. Common: may affect up to 1 in 10 people
3. Uncommon: may affect up to 1 in 100 people

4. Rare: may affect up to 1 in 1,000 people
5. Very rare: may affect up to 1 in 10,000 people
6. Not known: frequency cannot be estimated from the available data

Digoxin - Arm A:
Digoxin is used to treat abnormal heart rhythm (arrhythmia). The side effects are:
1. Common: appetite loss, blurred view, heart rhythm disturbances (cardiac arrhythmia), slow heart rate (sinus bradycardia), nausea
2. Uncommon: mental confusion, headache, dizziness, sleeplessness, loose stools (diarrhoea), vomiting, abdominal pain, tiredness
3. Rare: low platelet count (thrombocytopenia), nightmares, restlessness, depression, hallucinations, death of bowels (intestinal necrosis), allergic reactions (hives, rash), weakness of muscles (myasthenia)
4. Very rare: physical weakness (asthenia), indisposition, fast heart rate (supraventricular tachyarrhythmia), inability to communicate (aphasia), loss of passion or feeling (apathy)

Rosuvastatin - Arm A:
Rosuvastatin is given for the treatment of excess cholesterol in the blood. The adverse events seen with rosuvastatin are generally mild and temporary. The frequencies of adverse events are ranked according to the following:
1. Common: physical weakness, muscle pain (myalgia), constipation, nausea, abdominal pain, headache, dizziness
2. Uncommon: itching, rash and hives
3. Rare: skin reaction that includes swelling (allergic reactions including angioedema), muscular disease (myopathy) and disintegration of muscles following muscle death (rhabdomyolysis), swelling of the pancreas (pancreatitis), elevated liver values
4. Very rare: damage or disease affecting peripheral nerves (polyneuropathy), memory loss, jaundice, joint pain, loss of blood through urine (haematuria), breast pain

Metformin - Arm A:
Metformin is given for the treatment of diabetes mellitus type 2. The frequencies of adverse events are ranked according to the following:
1. Very common: nausea, vomiting, loose stools, abdominal pain, loss of appetite
2. Common: taste disturbance
3. Very rare: rash (skin reactions such as erythema), itching and hives, excess of lactate (lactic acidosis)
4. Not known: isolated reports of liver function tests abnormalities or hepatitis (liver inflammation)

Furosemide - Arm A:
Furosemide is given to increase the urine output of the kidneys in case of a malfunction. The frequencies of side effects are ranked according to the following:
1. Very common: electrolyte disturbances, a condition in which the volume of blood plasma is too low, seen especially in elderly people (dehydration and hypovolemia), low blood pressure (hypotension) and fainting when standing up (orthostatic intolerance), laboratory value indicative for kidney function (creatinine) increased in the blood, blood fat (blood triglyceride) increased
2. Common: hemoconcentration (increase in the proportion of red blood cells in blood due to loss of body water), hyponatremia and hypochloremia (loss of body salt), loss of blood potassium (hypokalemia), blood cholesterol increased, blood uric acid increased and gout, urinary volume increased, loss of brain function as a result of failure in the removal of toxins from the blood due to liver damage (hepatic encephalopathy) in people with liver damage

(hepatic insufficiency)
3. Uncommon: low platelet count, rash, itching and hives, increased blood sugar levels (reduced glucose tolerance and hyperglycemia), hearing disturbance, nausea.
4. Rare: increase in white blood cells (eosinophilia), low count of white blood cells, (life-threatening allergic reaction with itchy rash, throat or tongue swelling, shortness of breath, vomiting, light-headedness, low blood pressure (anaphylactic shock), a condition with a constant ringing sound in the ear in the absence of an external source (tinnitus), inflammation of blood vessels (vasculitis), vomiting, loose stools, inflammation of the kidney (nephritis), fever
5. Very rare: a decrease in red blood cells (hemolytic anaemia), a condition where the body stops the production of white blood cells (agranulocytosis), a decrease in platelets, inflammation of blood vessels, increased excitability (tetany)
6. Not known: Worsening of metabolic alkalosis [severe damage and scarring (decompensated cirrhosis) of the liver], fluid and electrolyte disturbances, increased blood sugar, hives, skin disease (erythema multiforme), skin disease (purpura), skin disease (exfoliative dermatitis), itching, allergic reactions, such as skin rashes and others

Midazolam - Arm B:
Midazolam may cause tiredness, loss of memory, impaired attention and impaired muscular function which may adversely affect the ability to drive or use machines.
Other side effects are: an extremely strong feeling of happiness (euphoria), depression, restlessness, drug dependence, drowsiness, headache, transient loss of memory, a condition where the heart suddenly stops beating (cardiac arrest), reduced breathing rate, gut (gastrointestinal) disorders, skin reactions, weakness of muscles, tiredness, allergy (hypersensitivity).

Ortho-Novum ® (Ethinyl estradiol plus norethindrone) - Arm B:
This medicine is one of the many brands used by fertile women for birth control. Some of the side effects are associated with the female body and thus will not occur in men:
1. Very common: intermediate bleeding
2. Common: mood swings, depression, headache, migraine, breast pain, irregular menstruation cycle, change of body weight (gain or loss)
3. Uncommon: loss of libido, vein pain, nausea, vomiting, abdominal pain, flatulence, acne, rash, gain or loss of body hair, elevated or reduced frequency of monthly bleedings, ovarian cysts (sac-like pocket filled with liquid or a semisolid substance), elevated blood pressure
4. Rare: swelling of the vagina caused by certain bacteria or fungi (vaginitis), allergic reactions, a gain of appetite, state of being nervous (nervosity), sleep disorder, dizziness, visual disturbance, clotting of blood in veins (thrombophlebitis), cramps in legs, swelling caused due to excess fluid accumulation in the body tissues (oedema), hot flush
5. Very rare: elevated heart rate, gain in breast size, vaginal dryness, increased sweating, elevated liver values, elevated uric acid, low blood cell count caused by a lack of iron (iron-deficiency anaemia)

Montelukast - Arm B:
Montelukast is used in the maintenance treatment of asthma (a condition in which the airways narrow and swell and may produce extra mucus). Side effects associated with the administration of montelukast are:
1. Very common: upper respiratory tract infection
2. Common: fever, skin rash, nausea, vomiting, diarrhea, elevated liver values
3. Uncommon: allergic reactions (including anaphylaxis), dizziness, loss of consciousness, seizures, abnormal sensation of the skin (e.g. tingling), numbness or loss of sensation in part of your body, sleep disturbances (such as abnormal dreams, nightmares, sleepwalking, insomnia), depression, anxiety, agitation, aggression, irritability, restlessness, hyperactivity, nosebleed, dry

mouth, trouble digesting food, bruising, allergic reactions (hives, rash), itching, joint stiffness, muscle aches and pain, fatigue, malaise, lack of energy and strength, swelling caused by fluid retention, bedwetting in children
4. Rare: abnormal heartbeat, involuntarily shaking, increased bleeding tendency, attention disorder, memory impairment
5. Very rare: stuttering, seeing, hearing or feeling things that are not there (hallucinations), disorientation, obsessive-compulsive symptoms, suicidal ideation, platelets deficiency, blood vessel inflammation, inflammation of the lungs, inflammation deep in the skin, skin reaction, liver inflammation and injury (hepatitis)

Warfarin - Arm B:
Warfarin is a type of medicine known as a blood thinner. It makes the blood flow through the veins more easily. This means the blood will be less likely to make a dangerous blood clot. The main side effect of warfarin is bleeding. While the risk of major bleeding is low, participants need to be aware of potential problems. The risk of bleeding is higher in elderly participants with a preexisting condition.
Other side effects that have been reported when participants have taken warfarin are:
1. Nausea
2. Vomiting
3. Gas
4. Pale skin
5. Feeling cold
6. Fatigue
7. Changes in the way food tastes

The following side effects are sometimes observed (in 1 in 100 people or more):
1. Bleeding
2. Nausea

Vitamin K – Arm B
Vitamin K is used to counteract any blood-thinning effects of warfarin. Participants may notice a skin rash, redness and itching. In rare cases, shortness of breath, excessive sweating or fainting occurs. These are the symptoms of allergic reactions.

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

When is the study starting and how long is it expected to run for?
July 2021 to May 2025

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

Who is the main contact?
global.trial_information@roche.com

Study website
https://forpatients.roche.com/en/trials/metabolic-disorder/hepatic-insufficiency/a-study-to-evaluate-the-processing-by-the-body-and-safety-of-pra.html

Contact information

Type(s)
Public

Contact name
Dr Clinical Trials

Contact details
Building 1, Grenzacherstrasse 124
Basel
Switzerland
CH-4070
+41 616878333
global.trial_information@roche.com

Additional identifiers

EudraCT/CTIS number
2022-001557-23

IRAS number
1007197

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
GP43164, IRAS 1007197, CPMS 55308

Study information

Scientific Title
A Phase I, two-arm, open-label study to evaluate the clinical drug-drug interaction potential of pralsetinib in combination with sensitive transporter substrates, sensitive CYP substrates, or a combined oral contraceptive in patients with advanced or metastatic solid tumors that are not responsive to standard therapies or for which there is no effective therapy

Study objectives
The purpose of this study is to assess the impact of co-administration of repeat doses of pralsetinib on single-dose pharmacokinetics (PK) of sensitive transporter substrates digoxin (P-gp substrate), furosemide (OAT1 substrate), metformin (MATE substrate), and rosuvastatin (BCRP and OATP1B substrate).

The study also aims to assess the impact of co-administration of repeat doses of pralsetinib on single-dose PK of sensitive cytochrome P450 (CYP) substrates midazolam (CYP3A substrate), warfarin (CYP2C9 substrate), and montelukast (CYP2C8 substrate), and a combined oral contraceptive (COC) norethindrone/ethinyl estradiol.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/02/2022, Ministry of Health of The Republic of Moldova: National Committee for Ethical Expertise of Clinical Trial (Chisinau City, 3, A. Cosmescu Street, MD 2009, Moldova; +373 (0)22 20 54 14; comitetetica@msmps.gov.md), ref: 1242

Study design
Phase I two-arm open-label study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not applicable

Health condition(s) or problem(s) studied
Solid tumors

Interventions
Current interventions as of 30/09/2024:
Participants will be allocated to either treatment arm depending on local circumstances and requirements, based on investigator and sponsor decisions.

Arm A: Pralsetinib and Transporter Drug-Drug Interaction (DDI)
Participants will receive a single oral dose of transporter-substrate cocktail (digoxin 0.25 mg, furosemide 1 mg, metformin 10 mg, and rosuvastatin 10 mg) on Day 1, followed by pralsetinib 400 mg, orally, once daily (QD), from Days 3 to 12. On Day 10 participants will receive a single oral dose of the transporter-substrate cocktail along with pralsetinib. This is the DDI Assessment portion of the study (Cycle 1).

Following the end of the DDI portion of the study (Cycle 1), participants may continue receiving pralsetinib 400 mg, QD monotherapy in Cycle 2 (1 cycle=4 weeks) and beyond with until the first post dose tumor assessments per standard of care at the investigator’s discretion. If participants are deemed to be receiving clinical benefit, pralsetinib monotherapy can be continued at the discretion of the investigator. Participants will be permitted to continue pralsetinib therapy until objective radiographic disease progression, loss of benefit, unacceptable toxicity, participant or doctor decision to discontinue, death, or study termination by the Sponsor, whichever occurs first.

Arm B: Pralsetinib and CYP DDI
Participants will receive a single oral dose CYP-substrate cocktail (midazolam [2 mg], warfarin [10 mg], and montelukast [10 mg]) and vitamin K 10 mg, orally on Day 1, followed by vitamin K, 10 mg, orally on Days 2 and 3. On Day 5 participants will receive a single oral dose of combined

oral contraceptive (COC) (norethindrone [1 mg]/ethinyl estradiol [35 µg]) followed by pralsetinib, 400 mg, orally, QD from Day 7 up to Day 20. On Day 14 participants will receive a single oral dose of the CYP-substrate cocktail along with vitamin K and pralsetinib. On Days 15 and 16 participants will receive vitamin K followed by a single oral dose of COC along with pralsetinib on Day 18. This is the DDI Assessment portion of the study (Cycle 1).

Following the end of the DDI portion of the study (Cycle 1), participants may continue receiving pralsetinib 400 mg, QD monotherapy in Cycle 2 (1 cycle=4 weeks) and beyond with until the first post dose tumor assessments per standard of care at the investigator's discretion. If participants are deemed to be receiving clinical benefit, pralsetinib monotherapy can be continued at the discretion of the investigator. Participants will be permitted to continue pralsetinib therapy until objective radiographic disease progression, loss of benefit, unacceptable toxicity, participant or doctor decision to discontinue, death, or study termination by the Sponsor, whichever occurs first.

Previous interventions:
Participants will be allocated to either treatment arm depending on local circumstances and requirements, based on investigator and sponsor decisions.

Arm A: Pralsetinib and Transporter Drug-Drug Interaction (DDI)
Participants will receive a single oral dose of transporter-substrate cocktail (digoxin 0.25 mg, furosemide 1 mg, metformin 10 mg, and rosuvastatin 10 mg) on Day 1, followed by pralsetinib 400 mg, orally, once daily (QD), from Days 3 to 12. On Day 10 participants will receive a single oral dose of the transporter-substrate cocktail along with pralsetinib.

Arm B: Pralsetinib and CYP DDI
Participants will receive a single oral dose CYP-substrate cocktail (midazolam [2 mg], warfarin [10 mg], and montelukast [10 mg]) and vitamin K 10 mg, orally on Day 1, followed by vitamin K, 10 mg, orally on Days 2 and 3. On Day 5 participants will receive a single oral dose of combined oral contraceptive (COC) (norethindrone [1 mg]/ethinyl estradiol [35 µg]) followed by pralsetinib, 400 mg, orally, QD from Day 7 up to Day 20. On Day 14 participants will receive a single oral dose of the CYP-substrate cocktail along with vitamin K and pralsetinib. On Days 15 and 16 participants will receive vitamin K followed by a single oral dose of COC along with pralsetinib on Day 18.

Intervention Type
Drug

Pharmaceutical study type(s)
DDI study

Phase
Phase I

Drug/device/biological/vaccine name(s)
Pralsetinib, transporter substrates (digoxin, furosemide, metformin, rosuvastatin), CYP substrates (midazolam, warfarin and montelukast), COC (norethindrone, ethinyl estradiol), vitamin K

Primary outcome measure

1. Maximum observed concentration (Cmax) of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Days 1-3 and Days 10-12. Cmax of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20.
2. Area under the concentration-time curve from time 0 to time t (AUC0-t) where 0 is the time point of the last administration, where t is the last point with concentrations above the lower limit of quantification (LLOQ) of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Days 1-3 and Days 10-12. AUC0-t of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20.
3. Area under the concentration-time curve from time 0 to infinity (AUC0-inf) of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Days 1-3 and Days 10-12, AUC0-inf of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20.

All PK parameters will be assessed using standard noncompartmental methods of analysis.

Secondary outcome measures

Current secondary outcome measures as of 30/09/2024:
1. Cmax at steady state of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
2. Minimum observed concentration (Cmin) at steady state of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
3. Time to attain maximum observed concentration (Tmax) of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B). Tmax of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12, Tmax of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively, from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
4. Area under the concentration-time curve up to time t (AUC0-t) where 0 is the time point of the last administration, where t is the last point with concentrations above the LLOQ of pralsetinib measured from blood samples at multiple time-points from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
5. Area under the concentration-time curve from time 0 to infinity (AUC0-inf) of pralsetinib measured from blood samples at multiple time-points Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
6. Percentage of estimated part for the calculation of AUC0-inf ((AUC0-inf-AUC0-t)/AUC0-inf) *100% (%AUCextra) of pralsetinib measured from blood samples at multiple time-points from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B). %AUCextra of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-

administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. %AUCextra of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
7. Terminal elimination rate constant (kel) of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B) . kel of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Days 1-3 and Days 10-12. kel of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
8. Terminal elimination half-life (t1/2) (calculated as 0.693/kel) of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B). t1/2 of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. t1/2 of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
9. Apparent oral clearance (CL/F) (calculated as dose/auc0-inf) of pralsetinib measured from blood samples at multiple timepoints from Days 10 to 12 (Arm A) and Days 14 to 20 (Arm B). CL /F of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. CL/F of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
10. Apparent volume of distribution at terminal phase (Vz/F) of pralsetinib measured from blood samples at multiple timepoints from Days 10 to 12 (Arm A) and Days 14 to 20 (Arm B). Vz/F of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. Vz/F of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
11. Cumulative amount of drug excreted (Ae) of transporter substrates (furosemide, metformin, rosuvastatin) measured from urine samples at multiple timepoints from Days 1-3 and Days 10-12
12. Fraction of the dose administered excreted (unchanged) of transporter substrates (furosemide, metformin, rosuvastatin) measured from urine samples at multiple timepoints from Days 1-3 and Days 10-12
13. Renal clearance (CLr) of transporter substrates (furosemide, metformin, rosuvastatin) measured from urine samples at multiple timepoints from Days 1-3 and Days 10-12
14. Occurrence of adverse events (AEs) and severity of AEs rated according to the common terminology criteria for adverse events (CTCAE) 5-point scale assessed using spontaneous reports from participants and investigator’s questions from screening to end of study (up to 11 weeks)
15. Changes from baseline at each visit in clinical laboratory results measured using blood and urine samples (data collected from eCRF) from screening to end of study (up to 11 weeks)
16. Changes from baseline at each visit in vital signs measured using blood pressure, pulse, body

temperature and respiratory rate values from screening to end of study (up to 11 weeks)
17. Changes from baseline at each visit in ECG parameters measured using 12-lead ECG from screening to end of study (up to 11 weeks)
18. Changes from baseline at each visit in physical examination assessed using measurements of height, weight, BMI, and other symptom-oriented examinations from screening to end of study (up to 11 weeks)

All PK parameters will be assessed using standard noncompartmental methods of analysis.

Previous secondary outcome measures:
1. Cmax at steady state of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
2. Minimum observed concentration (Cmin) at steady state of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
3. Time to attain maximum observed concentration (Tmax) of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B). Tmax of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12, Tmax of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively, from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
4. Area under the concentration-time curve up to time t (AUC0-t) where 0 is the time point of the last administration, where t is the last point with concentrations above the LLOQ of pralsetinib measured from blood samples at multiple time-points from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
5. Area under the concentration-time curve from time 0 to infinity (AUC0-inf) of pralsetinib measured from blood samples at multiple time-points Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B)
6. Percentage of estimated part for the calculation of AUC0-inf ((AUC0-inf-AUC0-t)/AUC0-inf) *100% (%AUCextra) of pralsetinib measured from blood samples at multiple time-points from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B). %AUCextra of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. %AUCextra of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
7. Terminal elimination rate constant (kel) of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B) . kel of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Days 1-3 and Days 10-12. kel of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
8. Terminal elimination half-life (t1/2) (calculated as 0.693/kel) of pralsetinib measured from blood samples at multiple timepoints from Day 10 to Day 12 (Arm A) and Day 14 to Day 20 (Arm B). t1/2 of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. t1/2 of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given

alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
9. Apparent oral clearance (CL/F) (calculated as dose/auc0-inf) of pralsetinib measured from blood samples at multiple timepoints from Days 10 to 12 (Arm A) and Days 14 to 20 (Arm B). CL /F of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. CL/F of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
10. Apparent volume of distribution at terminal phase (Vz/F) of pralsetinib measured from blood samples at multiple timepoints from Days 10 to 12 (Arm A) and Days 14 to 20 (Arm B). Vz/F of transporter substrates (digoxin, furosemide, metformin, rosuvastatin) when given alone on Day 1 and when co-administered with pralsetinib on Day 10 from blood samples collected at multiple timepoints from Day 1-3 and Days 10-12. Vz/F of CYP substrates (midazolam, warfarin and montelukast) and COC (norethindrone, ethinyl estradiol) when given alone on Day 1 and Day 5, respectively, and when co-administered with pralsetinib on Day 14 and Day 18, respectively from blood samples collected at multiple timepoints from Days 1-7 and Days 14-20
11. Cumulative amount of drug excreted (Ae) of transporter substrates (furosemide, metformin, rosuvastatin) measured from urine samples at multiple timepoints from Days 1-3 and Days 10-12
12. Fraction of the dose administered excreted (unchanged) of transporter substrates (furosemide, metformin, rosuvastatin) measured from urine samples at multiple timepoints from Days 1-3 and Days 10-12
13. Renal clearance (CLr) of transporter substrates (furosemide, metformin, rosuvastatin) measured from urine samples at multiple timepoints from Days 1-3 and Days 10-12
14. Percentage of participants with adverse events (AEs) and severity of AEs rated according to the common terminology criteria for adverse events (CTCAE) 5-point scale assessed using spontaneous reports from participants and investigator’s questions from screening to end of study (up to 10 weeks)
15. Percentage of participants with significant changes in clinical laboratory results measured using blood and urine samples (data collected from eCRF) from screening to end of study (up to 10 weeks)
16. Percentage of participants with clinically significant changes in vital signs measured using blood pressure, pulse, body temperature and respiratory rate values from screening to end of study (up to 10 weeks)
17. Percentage of participants with clinically significant changes in ECG parameters measured using 12-lead ECG from screening to end of study (up to 10 weeks)
18. Percentage of participants with clinically significant changes in physical examination assessed using measurements of height, weight, BMI, and other symptom-oriented examinations from screening to end of study (up to 10 weeks)

Concentrations of all analytes will be measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS). All PK parameters will be assessed using standard noncompartmental methods of analysis.

Overall study start date
30/07/2021

Completion date
31/05/2025

Eligibility

Key inclusion criteria
1. Participants who are 18 years or more at the time of informed consent
2. Eastern Cooperative Oncology Group (ECOG) performance ≤2
3. Participants with histologically or cytologically confirmed diagnosis of advanced or metastatic solid tumours that are not responsive to standard therapies or for which there is no effective therapy

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
36

Total final enrolment
22

Key exclusion criteria
1. Clinically relevant abnormal medical history, abnormal findings on physical examination, vital signs, ECG, or laboratory tests at screening that the investigator judges as likely to interfere with the objectives of the trial or the safety of the participant
2. Surgery (e.g., stomach bypass) or medical condition that might significantly affect the absorption of medicines (as judged by the investigator)
3. History of pneumonitis within the last 12 months
4. History of active or latent tuberculosis, regardless of treatment history, or has a positive screening test for latent mycobacterium tuberculosis infection
5. Serious infection requiring intravenous or systemic antibiotics within 7 days prior to initiation of study treatment
6. Cardiovascular issues
7. Central nervous system (CNS) metastases or a primary CNS tumor that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease
8. Radiotherapy or radiosurgery to any site within 14 days before check-in or more than 30 Gy of radiotherapy to the lung in the 6 months before check-in
9. Medical conditions or underlying diseases that constitute contraindications on the use of the substrates or probes used in this study including hypersensitivity to the drugs administered during the study
10. Participation in another investigational drug trial within 30 days prior to study drug administration or exposure to more than 3 new investigational agents within 12 months prior to study drug administration

11. Positive serology for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody at screening. A negative polymerase chain reaction (PCR) test overrides a positive serological test.
12. Human immunodeficiency virus (HIV) antibodies 1/2 at screening (added 30/09/2024: Individuals with a positive HIV test at screening are eligible, provided they are stable on antiretroviral therapy, have a CD4 count ≥200/µL, and have an undetectable viral load).

Date of first enrolment
11/04/2023

Date of final enrolment
01/03/2024

Locations

Countries of recruitment
Bulgaria

Georgia

Moldova

Romania

Ukraine

United Kingdom

Study participating centre
Arensia Exploratory Medicine
30 N. Testemitanu Str
Chisinau
Moldova
2025

Study participating centre
Arensia Exploratory Medicine
I.O.C.N, 34-36 Republicii Street
Cluj-Napoca
Romania
400015

Sponsor information

Organisation

F. Hoffmann-La Roche

Sponsor details
Building 1, Grenzacherstrasse 124
Basel
Switzerland
CH-4070
+41 616878333
global.trial_information@roche.com

Sponsor type
Industry

Website
https://www.roche.com/about/

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

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/05/2026

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