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A study to assess the distribution of entrectinib capsule in the blood of healthy adults compared to nasogastric and oral suspension of entrectinib

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Registration date 03/08/2022	**Overall study status** Completed	
Last Edited 08/08/2022	**Condition category** Other	

Plain English summary of protocol

Background and study aims
Cancer is a disease in which abnormal cells divide without control and can invade nearby tissues. Certain proteins, called tyrosine receptor kinases (TRK), present on the cell surface control a message that tells the cells to grow and multiply. Dysregulation of the TRK proteins often causes cells to lose the ability to grow normally leading to cancer. Entrectinib, the drug that is being studied, is designed to block the wrong messaging caused by the dysregulation of these proteins. Entrectinib has been approved by health authorities in an oral capsule formulation for cancer treatment. A new investigational form of the drug (i.e., a liquid with solid particles in it [suspension form]) is being evaluated in this study. The use of entrectinib in this study is experimental, which means health authorities have not approved the oral suspension of entrectinib for the treatment of cancer.
The aim of Part 1 of this study is to compare how much of the study drug enters the circulation of the body (to have an active effect) when given as the original reference capsule formulation given by mouth (oral) compared to the new suspension formulation given orally or through a special tube that carries medicine to the stomach through the nose (nasogastric tube).
In Part 2, the original capsule formulation will be compared with oral lansoprazole given along with the new suspension formulation given orally to determine how safe and tolerable entrectinib is when given in the different forms, and to evaluate the effect of lansoprazole on the amount of study drug that reaches the bloodstream and how long the body takes to get rid of it.

Who can participate?
Healthy volunteers of age between 18 and 55 years

What does the study involve?
The study includes two parts: Part 1 and Part 2. The participants will be enrolled in one of the two parts of the study. The total duration of the participation in either part of the study will be about 10 weeks, including the screening visit. Each part of the study involves three stages:

1. Screening: The participants will be screened to make sure they are a good fit for the study. They may have to visit the clinic once during the screening period which will be done within 28 days before the first dosing.
2. Dosing/Confinement Phase: The participants will receive three study treatments in three study periods in both parts of the study. The study treatments administered in this study include: entrectinib oral capsule, entrectinib suspension (given with water or milk) and lansoprazole oral capsule. Both the entrectinib formulations will be administered on Day 1 in Part 1 (periods 1, 2 and 3) and Part 2 (periods 1 and 2). Entrectinib oral suspension on Day 5, Part 2 (period 3). Lansoprazole will be administered on Days 1 to 5 in Part 2 (period 3). The order of dosing will be determined by chance (like a flip of a coin). There will be at least 14 days between each dosing. Participants will have to fast for at least 8 hours prior to dosing and 4 hours after the dosing.
3. During this study, the participants will have three clinic confinements lasting either 6 days/5 nights each or 10 days/9 nights depending upon the part of the study or the visits.
4. Follow-up (to check on the participant after treatment is finished): Participants will receive a follow-up phone call after 12 to 14 days of the final dosing.

What are the possible benefits and risks of participating?
The study is for research purposes only and is not intended to treat any medical condition. Participants may not receive any direct medical benefit from participating in this study, but the information collected will help people with cancer in the future. Participants might receive compensation of up to a maximum of $10,525 depending upon the part of the study and the visits. Participants may have side effects from the drugs or procedures used in this study; these may range from mild to severe and even life-threatening, and they can vary from person to person. There is a risk of death from side effects. Certain side effects have been determined to be associated with entrectinib following dosing over an extended period and are not likely to occur with administration of only one dose of entrectinib, based on clinical trial experience in participants with advanced cancer the known side effects are described below:

Very common (occurs in more than 10% of participants):
1. Feeling weak or lack of energy (fatigue)
2. Swelling or fluid retention of the face, arms, legs, or a part of the body (oedema)
3. Pain (including back pain, neck pain, pain in the chest, muscle or bone pain, pain in arms or legs)
4. Fever (pyrexia)
5. Constipation
6. Diarrhoea
7. Nausea
8. Vomiting
9. Abdominal pain
10. Taste alteration (dysgeusia)
11. Dizziness (including a sense of spinning, and dizziness when changing position)
12. Abnormal sensation of touch (including burning or prickling sensation, increase or decrease in sensitivity of skin) (dysesthesia)
13. Difficulty with memory, learning, and judgment, including confusion, disturbance in attention, hallucination, and mental status changes (cognitive disorders)
14. Effects on nerves that control arms and legs resulting in weakness (peripheral neuropathy)
15. Headache
16. Loss of muscle control and balance (ataxia)
17. Changes in sleep (sleep disturbances)
18. Shortness of breath (dyspnoea)
19. Cough

20. Decrease in red blood cells, which may result in symptoms such as tiredness, weakness, or shortness of breath (anaemia)
21. Decrease in neutrophils (a type of white blood cell), which may affect your body's ability to fight infection (neutropenia)
22. Weight increased
23. Decreased appetite
24. Difficulty swallowing (dysphagia)
25. Increased level of creatinine in blood, which may mean your kidneys are not working normally (creatinine elevated)
26. Joint pain (arthralgia)
27. Muscle pain (myalgia)
28. Muscle weakness
29. Changes in liver tests which may mean your liver is not working normally (aspartate aminotransferase increased, alanine aminotransferase increased)
30. Lung infection, including bronchitis, upper or lower respiratory tract infection, and pneumonia
31. Urinary tract infection
32. Blurred vision
33. Rash, including rash that may be red, itchy, with small bumps on skin
34. Decreased blood pressure (hypotension)

Common (occurs in 1%-10% of participants):
1. Broken bone (fracture)
2. Fainting due to drop in blood pressure (syncope)
3. Weakness of the heart muscle causing decreased pumping of blood, which may cause breathing difficulty, reduced kidney function, and fluid accumulation (congestive heart failure)
4. Dehydration
5. Electrocardiogram (ECG) QT prolonged, which may mean your heart is not working normally (QT prolongation)
6. Mood changes (Mood disorders)
7. Increased blood level of uric acid, a waste material from food digestion (hyperuricemia)

Uncommon (occurs in less than 1% of participants):
1. Signs and symptoms from rapid breakdown of cancer cells that can occur after cancer treatment has started and can cause increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure (Tumour lysis syndrome)

Side effects that may be experienced when taking lansoprazole:
1. Increased risk of diarrhoea associated with bacterial infection, especially in hospitalized participants.
2. Bone fracture: increased risk of the hip, wrist, or spine fractures-related to osteoporosis. The risk was increased in patients who received high and long-term lansoprazole therapy.
3. Low magnesium in blood has been rarely reported in participants who received lansoprazole for at least 3 months, but in most cases after 1-year treatment.

Risks associated with study procedures:
1. Nasogastric (NG) tube: Placing the NG tube may cause the participants to gag, and the tube may irritate the nose and throat. The tube might cause a nosebleed. Rarely, a serious internal injury may occur.
2. Radiography (x-ray): This test will expose the participant to radiation. Although all radiation is cumulative over the lifetime, small doses from x-rays should not be significant.

There may be a risk in exposing an unborn or breastfed child to a study drug, and all risks are not known at this time. Women and men must take precautions to avoid exposing an unborn child to the study drug. Participants who are pregnant, become pregnant, or are currently breastfeeding, cannot take part in this study.

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

When is the study starting and how long is it expected to run for?
May 2022 to October 2022

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

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
GP44192

Study information

Scientific Title
A two-part, open-label, comparative, single-dose, randomized, five-treatment, three-way crossover sequential study to assess the relative bioavailability of entrectinib capsule compared to nasogastric and oral administration of suspension in healthy subjects

Study objectives
The purpose of the study is to assess the relative bioavailability of the entrectinib treatments compared to the reference capsule formulation in healthy participants. The study also aims to

assess the effect of lansoprazole on entrectinib exposure following oral co-administration of lansoprazole tablet with entrectinib suspension in water (test) compared to administration of entrectinib suspension in water alone (reference).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/07/2022, Study Institutional Review Board Salus IRB (2111 West Braker Lane, Suite 100, Austin, Texas, 78758, USA; +1 (0)512 380 1244; salus@salusirb.com), ref: GP44192

Primary study design
Interventional

Study design
Two-part open-label comparative single-dose randomized five-treatment three-way crossover relative bioavailability study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bioavailability of entrectinib in healthy participants

Interventions
The study will consist of two parts where participants will be randomly assigned to receive the study treatments in a cross-over manner.
Part 1: The treatments administered to participants in Part 1 of the study will be as follows:
Treatment A: Nasogastric administration of 600 mg entrectinib, delivered as a suspension in water on Day 1 following an 8-hour fast
Treatment B: Oral administration of 600 mg entrectinib delivered as a suspension in milk on Day 1 following an 8-hour fast
Treatment C: Oral administration of 600 mg entrectinib capsules on Day 1 following an 8-hour fast.

Part 1 – Sequence ABC: Participants will receive three treatments in sequence ABC on Day 1 of Periods 1, 2, and 3 respectively. There will be a 14-day washout period between each treatment period. Participants will be monitored up to Day 14 after the last dose of the study drug.
Part 1 – Sequence BCA: Participants will receive three treatments in sequence BCA on Day 1 of Periods 1, 2, and 3 respectively. There will be a 14-day washout period between each treatment period. Participants will be monitored up to Day 14 after the last dose of the study drug.
Part 1 - Sequence CAB: Participants will receive treatments in sequence CAB on Day 1 of Periods 1, 2, and 3 respectively. There will be a 14-day washout period between each treatment period. Participants will be monitored up to Day 14 after the last dose of the study drug.

Part 2: The treatments administered to participants in Part 2 of the study will be as follows:
Treatment C: Oral administration of 600 mg entrectinib capsules on Day 1 following an 8-hour fast
Treatment D: Oral administration of 600 mg entrectinib delivered as a suspension in water on Day 1 following an 8-hour fast
Treatment E: Oral administration of 30 mg lansoprazole orally disintegrating delayed-release

tablet at 24-hour intervals on days 1 to 4. On Day 5, 30 mg lansoprazole orally disintegrating delayed-release tablet will be administered along with oral dosing of 600 mg entrectinib suspension in water following an 8-hour fast.

Part 2 – Sequence CD: Participants will receive two treatments in sequence CD on Day 1 of Periods 1 and 2 respectively. There will be a 14-day washout period between each treatment period. Participants will be monitored up to Day 14 after the last dose of the study drug.
Part 2 – Sequence DC: Participants will receive two treatments in sequence DC on Day 1 of Periods 1 and 2 respectively. There will be a 14-day washout period between each treatment period. Participants will be monitored up to Day 14 after the last dose of the study drug.
Part 2 - Treatment E: In period 3, all participants will receive treatment E alone and will be monitored for up to Day 14 after the last dose of the study drug.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Entrectinib, lansoprazole

Primary outcome(s)
1. Maximum observed plasma concentration (Cmax) of entrectinib and M5 (its metabolite) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2
2. Area under the plasma concentration versus time curve from time zero extrapolated to infinity (AUC0-inf) of entrectinib and M5 (its metabolite) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2

Key secondary outcome(s)
1. Time to maximum observed plasma concentration (Tmax) of entrectinib and its metabolite, M5 (as appropriate) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2
2. Area under the plasma concentration versus time curve from hour zero to the last measurable concentration (AUC0-t) of entrectinib and its metabolite, M5 (as appropriate) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2
3. Apparent terminal elimination half-life (t1/2) of entrectinib and its metabolite, M5 (as appropriate) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2
4. Relative bioavailability for AUCinf (Frel) of entrectinib and its metabolite, M5 (as appropriate) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2
5. Metabolite (M5) to parent (entrectinib) ratio for AUCinf (MPR) measured from blood samples collected at pre-dose and multiple timepoints up to 96 hours post entrectinib administration in each of the three periods (1, 2 and 3) in both Part 1 and Part 2
6. Percentage of participants with adverse events (AEs) and severity of AEs determined

according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) collected from screening up to 14 days after the final dose of entrectinib (up to approximately 70 days)

Completion date
17/10/2022

Eligibility

Key inclusion criteria
1. Female of non-childbearing potential or male, between 18 and 55 years of age, inclusive, at Screening
2. Within body mass index (BMI) range of 18.0 to 32.0 kg/m², inclusive, and weighing at least 50 kg at Screening
3. Healthy in the opinion of the investigator. Healthy is defined by the absence of evidence of any active disease or clinically significant medical condition based on a detailed medical history, physical examination, vital signs and 12-lead ECG assessment, and clinical laboratory evaluation results
4. Negative hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and negative human immunodeficiency virus (HIV) antibody screens
5. Females must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at each Check-in (Day -1)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Women of childbearing potential, women who are pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of entrectinib
2. Males who have a pregnant partner
3. A clinically significant medical history of gastrointestinal (GI) surgery (e.g., gastric bypass) or other GI disorder (e.g., malabsorption syndrome) that might affect absorption of medicines from the GI tract.
4. Clinically significant lactose intolerance
5. Presence of a clinically significant disease, illness, medical condition or disorder, or any other medical history determined by the investigator to be clinically significant and relevant. Ongoing chronic disorders which are not considered clinically significant are permissible provided they are stable

6. A clinically significant abnormal physical examination finding
7. Use of moderate or potent inhibitors or inducers of CYP3A4 enzyme or P-glycoprotein (P-gp) transporter within 28 days or 5 half-lives, whichever is longer, before Period 1 dosing (Day 1). Additionally, for subjects enrolled in Part 2, use of moderate or potent inhibitors or inducers of CYP2C19 within 28 days or 5 half-lives, whichever is longer, before Period 1 dosing (Day 1)
8. Use of gastric pH-modifying agents such as protein pump inhibitor (PPIs), H2 receptor antagonists, and antacids, within 28 days or 5 half-lives, whichever is longer, before Period 1 dosing (Day 1)
9. Administration of a Coronavirus Disease 2019 vaccine in the past 7 days prior to Period 1 dosing (Day 1)
10. Participation in any other clinical study involving an investigational medicinal product (IMP) or device within 60 days or 5 half-lives (if known), whichever is longer, prior to Period 1 dosing (Day 1)
11. Known history of clinically significant hypersensitivity, or severe allergic reaction, to entrectinib or related compounds (Part 1 and Part 2) or lansoprazole or related compounds (Part 2 only)
12. Previous enrollment in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2

Date of first enrolment
10/08/2022

Date of final enrolment
03/10/2022

Locations

Countries of recruitment
United States of America

Study participating centre
Clinical Pharmacology of Miami, Inc.,
United States of America
33014

Sponsor information

Organisation
F. Hoffmann-La Roche

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.

IPD sharing plan summary
Not expected to be made available