ForPatients
by Roche

Healthy Volunteers

What happens to a medicine (entrectinib) when given to people in different forms

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

Trial Status	Trial Runs In	Trial Identifier
Completed	1 Countries	GP44192

The source of the below information is the publicly available website ClinicalTrials.gov. It has been summarised and edited into simpler language.

Trial Summary:

This clinical trial was done to study a medicine (entrectinib) that has been approved for the treatment of patients with certain cancers. This was an open-label, single-dose, randomized, five-treatment, three-way crossover study. The objective was to compare how much medicine was available in the body – the “bioavailability” of entrectinib – when taken in different formulations. Researchers also wanted to find out if taking another medicine (proton pump inhibitor) interfered with the bioavailability of entrectinib. The study took place at one study center in one country – the USA.

Genentech, Inc. (A part of F. Hoffmann-La Roche Ltd., Switzerland)
Sponsor

Phase 1
Phase

GP44192
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
Both	18 to 55 years	Yes

Background and study aims:

Thirty-two healthy volunteers were enrolled at one study site in USA to evaluate the pharmacokinetics of entrectinib, a tyrosine kinase inhibitor for the treatment of certain

cancers. Four different formulations (one with a proton pump inhibitor) were tested and gave similar (but not the same) levels of entrectinib in the body as the reference hard capsules. There were differences in some of the measurements for the different formulations, but these did not impact their effect – the differences were not “clinically relevant.” Five people (16%) had at least one side effect that was not considered serious but considered related to the study treatments.

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.