ISRCTN47564876 https://doi.org/10.1186/ISRCTN47564876

# A study to assess the distribution and effect of food and pH on belvarafenib in the blood of healthy adults

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| **Submission date**<br>16/09/2022 | **Recruitment status**<br>No longer recruiting | [X] Prospectively registered<br>[_] Protocol<br>[_] Statistical analysis plan<br>[_] Results<br>[_] Individual participant data<br>[_] Record updated in last year |
| **Registration date**<br>20/09/2022 | **Overall study status**<br>Completed | |
| **Last Edited**<br>26/02/2024 | **Condition category**<br>Other | |

## Plain English summary of protocol

Background and study aims
Belvarafenib (the study drug) is an experimental drug being developed for the treatment of certain types of cancer. Belvarafenib being an experimental drug is not yet approved by the health authorities. This study will be conducted in two parts. The purpose of this study is:

Part 1: This part of the study will compare the amount of study drug that enters the circulation of the body (to have an active effect), and how long it takes for the body to get rid of it when given as the original reference tablet formulation (belvarafenib di-hydrochloride salt [HCl]) compared to a new tablet formulation (belvarafenib bis-methanesulfonic acid salt [MSA] formulation), as well as the new tablet formulation given at different doses. Both formulations will be given with a low-fat meal.

Part 2: Food Effect: Part 2 of this study aims to evaluate the effect of food on the absorption of the new tablet formulation of the study drug, and to collect information on any side effects that may occur when the study drug (new tablet formulation) is taken with and without food.

Part 2: pH Effect: The purpose of this part of the study is to assess the effect of rabeprazole (an approved medication that changes the pH in the stomach) on the amount of study drug (new tablet formulation) that reaches the bloodstream, and how long the body takes to get rid of it, when given with a low-fat meal.

Both Part 1 & Part 2: The safety and tolerability of the study drug will be evaluated in both parts of the study.

Who can participate?
Healthy people aged between 18 to 65 years old

What does the study involve?
The study includes the following parts: Part 1, Part 2 (food effect), and Part 2 (pH effect). Participants will be enrolled in any one part of the study i.e., Part 1, Part 2 (food effect), and Part 2 (pH effect). Both parts of this study have 3 stages:

1. Screening: To see if participants are eligible for the study. Participants will have one clinic visit for screening which will be done 35 days before the first dose of the study drug.
2. Dosing/Confinement: Participants will receive study drugs during this period.

Part 1: Participants will be randomly assigned to one of the two groups, each having two dosing periods. The order in which the participants receive each dosing will be determined by chance.

Group 1a: Participants will receive a single dose of belvarafenib new formulation and original formulation by mouth, after a low-fat breakfast, on Day 1 of Period 1 and Day 1 of Period 2 in one of the two sequences:
Sequence I: Belvarafenib new formulation in Period 1 and belvarafenib original formulation in Period 2
Sequence II: Belvarafenib original formulation in Period 1 and Belvarafenib new formulation in Period 2

Group 1b: Participants will receive a single dose of 50 mg and 200 mg belvarafenib tablets (new formulation) by mouth, after a low-fat breakfast on Day 1 of Periods 1 and 2 in one of the two sequences:
Sequence I: Belvarafenib 50 mg, in Period 1 and belvarafenib 200 mg in Period 2
Sequence II: Belvarafenib 200 mg in Period 1 and belvarafenib 50 mg in Period 2

Part 2: Food effect: Participants will receive a single dose of belvarafenib new formulation by mouth on Day 1 of Period 1 and 2, in one of the two sequences. The order in which the participants receive each dosing will be determined by chance.

Sequence I: Belvarafenib with high-fat breakfast in Period 1 and belvarafenib without breakfast in Period 2.
Sequence II: Belvarafenib without breakfast in Period 1 and belvarafenib with high-fat breakfast in Period 2

Part 2: pH effect: Participants will receive a single dose of belvarafenib new formulation by mouth on Day 1 of Period 1. In Period 2, participants will receive a rabeprazole tablet by mouth on Days 1 to 5 and belvarafenib new formulation on Day 1 after a low-fat breakfast.

During this study, each dose of the medicines will be given in the morning after an overnight fast of at least 8 hours.
Participants will have to be a part of this study for 8 weeks (Part 1) and 7 weeks (Part 2: Food effect and pH effect), not including the screening visit. Participants will have to check in to the study site one day prior to belvarafenib dosing for both parts. There will be 2 clinic confinements visits for each part are as follows:
- Part 1: Clinic confinements of 11 days/10 nights
- Part 2 food effect: Clinic confinements of 11 days/10 nights
- Part 2 pH effect: One confinement lasting 11 days/10 nights; One clinic confinement lasting 15 days/14 night
There will be at least 18 days between each dosing in all the parts of the study.

3. Follow-up: To check on the participants after dosing is finished. Participants will have one outpatient visit 21 to 27 days after the last dose of the study drug for both Part 1 and Part 2 (food and pH effect). A follow-up phone call will be done only if the outpatient visit occurs between 21 and 27 days after the last dose of the study drug.

What are the possible benefits and risks of participating?
Participants will not receive any health benefits from participating in this study, but the information that is learned may help people with cancer in the future.
Participants may have side effects from the drugs used in this study. The known side effects of this drug, as well as potential side effects, are listed below.

Risks associated with belvarafenib:
1. Known Side Effects: Skin changes including different types of rashes and itching
2. Potential Side effects: Injury to the digestive tract, decreased heart function, abnormal electrical conduction within the heart, sensitivity to sunlight, acne, hair loss, constipation, nausea, or the urge to vomit, vomiting, heartburn, fatigue or tiredness, fever, loss of appetite, muscle pain, high blood pressure, severe skin or mucosal reactions, nerve injury, liver injury, kidney injury

Risks Associated with Rabeprazole: Abdominal pain, sore throat, gas, increased chance of infections, constipation

There may be a risk in exposing an unborn child to study the drug, and all risks are not known at this time. Women who are pregnant, become pregnant, or are currently breastfeeding, cannot participate in this study.

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

When is the study starting and how long is it expected to run for?
June 2022 to June 2023

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

Who is the main contact?
global-roche-genentech-trials@gene.com

# Contact information

### Type(s)
Public

### Contact name
Mr Clinical Trials

### Contact details
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# Additional identifiers

### EudraCT/CTIS number
Nil known

### IRAS number

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
GP44112

# Study information

### Scientific Title
A phase I, single-dose, randomized, crossover, relative bioavailability and food-effect study and phase I, single-dose, fixed-sequence, crossover, pH-effect study of belvarafenib (GDC-5573) in healthy subjects

### Study objectives
The purpose of this study is:
Cohort 1a: To evaluate the influence of a formulation change on belvarafenib exposure by determining the relative bioavailability of belvarafenib following administration of the MSA formulation tablet (test) relative to the HCl formulation tablet (reference) in the fed state (low-fat meal)
Cohort 1b: To evaluate the dose proportionality of belvarafenib exposure following different doses of the MSA tablet formulation administered in the fed (low-fat meal) state
Cohort 2a: To evaluate the influence of food on belvarafenib exposure by determining the exposure of the MSA tablet formulation when administered with a high-fat meal versus the fasted state
Cohort 2b: To evaluate the influence of a proton pump inhibitor on belvarafenib exposure following administration of the MSA tablet formulation in the fed state (low-fat meal) in combination with rabeprazole versus alone

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 13/07/2022, Salus IRB (2111, W. Braker Lane, Suite 100, Austin, Texas, 78758, USA; +1 (0)512 380 1244; salus@salusirb.com), ref: None available

### Study design
Single-centre two-part single-dose open-label randomized crossover fixed-sequence relative-bioavailability food-effect pH-effect study

### Primary study design

Interventional

## Secondary study design
Randomised cross over trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

## Health condition(s) or problem(s) studied
Healthy participants

## Interventions
1. Part 1: Cohort 1a, Sequence I: Participants will first receive a single dose of belvarafenib bis-methanesulfonic acid salt (MSA) formulation, 400 milligrams (mg), orally, after a low-fat meal, on Day 1, Period 1. Following an 18-day washout period, participants will then receive a single dose of belvarafenib di-hydrochloride salt (HCl) formulation, 400 mg, orally, after a low-fat meal on Day 1, Period 2.
2. Part 1: Cohort 1a, Sequence II: Participants will first receive a single dose of belvarafenib HCl formulation, 400 mg, orally after a low-fat meal on Day 1, Period 1. Following an 18-day washout period, participants will then receive a single dose of belvarafenib MSA formulation, 400 mg, orally, after a low-fat meal on Day 1, Period 2.
3. Part 1: Cohort 1b, Sequence I: Participants will first receive a single dose of belvarafenib MSA formulation, 50 mg, orally, after a low-fat meal on Day 1, Period 1. Following an 18-day washout period, participants will then receive a single dose of belvarafenib MSA formulation, 200 mg, orally, after a low-fat meal on Day 1, Period 2.
4. Part 1: Cohort 1b, Sequence II: Participants will first receive a single dose of belvarafenib MSA formulation, 200 mg, orally, after a low-fat meal on Day 1, Period 2. Following an 18-day washout period, participants will then receive a single dose of belvarafenib MSA formulation, 50 mg, orally, after a low-fat meal on Day 1, Period 2.
5. Part 2: Cohort 2a, Sequence I: Participants will first receive a single dose oral of belvarafenib MSA formulation, at dose determined in Part 1, following a high-fat meal, on Day 1, Period 1. Following an 18-day washout period, participants will then receive a single oral dose of belvarafenib MSA formulation, at dose determined in Part 1, in a fasted state on Day 1, Period 2.
6. Part 2: Cohort 2a, Sequence II: Participants will first receive a single oral dose of belvarafenib MSA formulation, at dose determined in Part 1, in a fasted state on Day 1, Period 1. Following an 18-day washout period, participants will then receive a single oral dose of belvarafenib MSA formulation, at dose determined in Part 1, following a high-fat meal on Day 1, Period 2.
7. Part 2: Cohort 2b: Participants will first receive a single oral dose of belvarafenib MSA formulation, at dose determined in Part 1, following a low-fat meal on Day 1, Period 1. Following an 18-day washout period, participants will then receive Rabeprazole, 20 mg, orally, after an 8-hour fast, on Days 1 to 5 of Period 2, followed by single oral dose of belvarafenib MSA formulation, at dose determined in Part 1, following a low-fat meal on Day 5, Period 2.

## Intervention Type

Drug

### Phase
Phase I

### Drug/device/biological/vaccine name(s)
Belvarafenib (GDC-5573)

### Primary outcome measure
1. Cohort 1a: The geometric mean ratio (GMR) and associated 90% confidence intervals (CIs) of maximum observed plasma concentration (Cmax), concentration versus time curve from time zero extrapolated to infinity (AUC0-∞), and AUC from hour 0 to the last measurable concentration (AUC0-t) following administration of belvarafenib HCl and belvarafenib MSA formulation after low-fat meal
2. Cohort 1b: Dose-normalized Cmax, AUC0-∞, and AUC0-t following administration of different dose levels of belvarafenib MSA formulation after low-fat meal
3. Cohort 2a: The GMR and associated 90% CIs of Cmax, AUC0-∞, and AUC0-t following administration of belvarafenib MSA formulation after high-fat meal and in the fasted state
4. Cohort 2b: The GMR and associated 90% CIs of Cmax, AUC0-∞, and AUC0-t following administration of belvarafenib MSA formulation alone and co-administered with rabeprazole after low-fat meal

Timeframe: PK outcomes measured using blood samples collected from Day 1 up to Day 14

### Secondary outcome measures
1. Cohort 1a: Time to Cmax (tmax), apparent terminal elimination rate constant (Λz), terminal half-life (t1/2), apparent systemic clearance (CL/F), and apparent volume of distribution during the terminal phase (Vz/F) following administration of belvarafenib HCl and belvarafenib MSA formulation after low-fat meal
2. Cohort 1b: tmax, Λz, t1/2, CL/F, and Vz/F following administration of different dose levels of belvarafenib MSA formulation after low-fat meal
3. Cohort 2a: tmax, Λz, t1/2, CL/F, and Vz/F following administration of belvarafenib MSA formulation after high-fat meal and in the fasted state
4. Cohort 2b: tmax, Λz, t1/2, CL/F, and Vz/F following administration of belvarafenib MSA formulation alone and coadministered with rabeprazole after low-fat meal

Timeframe: PK outcomes measured using blood samples collected from Day 1 up to Day 14

5. Incidence and severity of adverse events (AEs), incidence of abnormalities in clinical laboratory evaluations, 12-lead ECGs, and vital signs measurements (up to approximately 84 Days)

### Overall study start date
01/06/2022

### Completion date
23/06/2023

## Eligibility

### Key inclusion criteria

1. Males or females of non-childbearing potential, between 18 and 65 years of age, inclusive
2. Within body mass index (BMI) range 18 to 32 kilograms per square meter (kg/m^2), inclusive, at Screening
3. Females will not be pregnant or breastfeeding and must be either postmenopausal or surgically sterile. For all females, the pregnancy test result must be negative at Screening and Period 1 Check-in (Day -1)
4. Negative screening test for latent Mycobacterium tuberculosis (TB) infection by QuantiFERON® TB Gold. Indeterminate results may be confirmed by repeat or by a purified protein derivative (PPD) skin test

## Participant type(s)
Healthy volunteer

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
66

## Key exclusion criteria
1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder
2. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs except that uncomplicated appendectomy and hernia repair will be allowed
3. History of acute gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, heartburn) as determined by the investigator (or designee) at Screening or Period 1 Check-in (Day -1)
4. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 5 half-lives or 90 days, whichever is longer, prior to study entry
5. Treatment with intravenous antibiotics within 8 weeks or oral antibiotics within 4 weeks prior to Screening or during the entire study duration
6. Use of any drugs known to be moderate or strong inhibitors or inducers of CYP3A, and for Cohort 2b CYP2C19, within 30 days prior to Period 1 Check-in (Day -1) and during the entire study duration
7. Poor peripheral venous access
8. History of malignancy within 5 years prior to enrollment

## Date of first enrolment
20/09/2022

## Date of final enrolment
19/05/2023

# Locations

**Countries of recruitment**
United States of America

**Study participating centre**
**Labcorp Drug Development**
1900 Mason Avenue
Suite 140
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# Sponsor information

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**Sponsor type**
Industry

**Website**
www.roche.com/about_roche/roche_worldwide.htm

# Funder(s)

**Funder type**
Industry

**Funder Name**
F. Hoffmann-La Roche Ltd

# Results and Publications

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

### Intention to publish date
10/03/2024

### 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