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A two-part study to evaluate the safety, tolerability, and processing by the body (pharmacokinetics) of fenebrutinib (part A) and to evaluate the effect of fenebrutinib on the heartbeat (QT/QTC interval) (part B) in healthy subjects

Submission date 21/04/2021	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 29/05/2021	**Overall study status** Completed	
Last Edited 01/08/2022	**Condition category** Other	

Plain English summary of protocol

Background and study aims
This is a two-part study of an investigational drug called fenebrutinib that will be performed in healthy volunteers. Part A will evaluate the safety and drug levels in the blood of single doses of fenebrutinib. This information will help with the selection of the doses to test in part B. Part B of the study will primarily evaluate whether fenebrutinib has any effect on the electrocardiogram, a measurement of the heart's electrical activity.

Who can participate?
Healthy volunteers

What does the study involve?
In part A of the study, a single dose of oral fenebrutinib or placebo will be given to volunteers to evaluate the safety and drug levels in the blood. This information will help with the selection of the doses to test in part B. In part B of the study, on different days volunteers will be given a single dose of fenebrutinib (at two different dose levels), moxifloxacin (an antibiotic), and placebo. The objective of part B is to evaluate whether fenebrutinib has any effect on the electrocardiogram, a measurement of the heart's electrical activity. Part B will also evaluate the safety and blood levels of fenebrutinib. Volunteers will participate in either part A or B, but not both.

What are the possible benefits and risks of participating?
Study volunteers will not receive any medical benefit. They will be compensated for their time. One identified risk of fenebrutinib is potential increased blood level of liver enzymes. Other risks that have not been observed but are theoretically possible include infection, change in

levels of certain cells in the blood, liver injury, effect on vaccinations, bleeding, nausea, vomiting, diarrhea, abnormal heart rhythm, inflammation (swelling or redness) of blood vessels, ability to fight cancer, birth defects, or rash.

Where is the study run from?
Genentech (USA)

When is the study starting and how long is it expected to run for?
November 2020 to August 2022

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

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Protocol serial number
GP42654

Study information

Scientific Title
A two-part, phase 1, randomized, double-blind, single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of fenebrutinib in healthy subjects (part A) and a randomized, single-dose, placebo- and positive-controlled, crossover phase 1 study to evaluate the effect of fenebrutinib on the QT/QTC interval in healthy subjects (part B)

Study objectives
To evaluate the safety, tolerability and clinical activity of fenebrutinib in healthy subjects

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/03/2021, Salus IRB (2111 West Braker Lane, Suite 100, Austin, TX, USA; +1 512-380-1244; salus@salusirb.com), ref: 8441772

Study design
Single center phase I double-blinded two-part interventional study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Safety, tolerability and clinical activity of fenebrutinib in healthy subjects

Interventions
Part A: Single Ascending Dose Study
Participants will enroll in three sequential cohorts (A1, A2, and A3) that will test single ascending doses. In cohort A1, participants will receive a single dose of fenebrutinib or placebo, administered orally. Dosing of subsequent cohorts A2 and A3 will be contingent upon available preliminary fenebrutinib safety, tolerability, and PK data from the preceding dose. Participants in cohorts A2 and A3 will also receive a single dose of oral fenebrutinib or placebo; the dose will be determined based on analysis of the data from the prior cohort.
Duration: 1 day of treatment, 7 days of follow-up.

Part B: Thorough QT Interval Study
The fenebrutinib therapeutic dose and supratherapeutic dose in Part B will be selected based on PK and safety data from Part A. Each participant will receive a single dose of the following treatments:
1. Fenebrutinib therapeutic dose
2. Fenebrutinib supratherapeutic dose
3. Positive control, moxifloxacin 400-mg tablet
4. Placebo
Duration: Approximately 24 days of treatment and 7 days of follow-up.

The randomization is done using a randomization list and unblinded pharmacist since there is only one site for this study. In Part A of the study participants are randomized 3:1 to active drug or placebo. In part B, participants are randomized 1:1:1:1 to one of four sequences of receiving the study drugs.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
fenebrutinib, RO7010939

Primary outcome(s)
Part A:
1. Incidence and severity of AEs and incidence of abnormalities measured using clinical laboratory evaluations, 12-lead ECGs, vital signs measurements, and physical examinations throughout the study
2. Pharmacokinetics measured using Cmax, tmax, AUC0-∞ and/or AUC0-t, and t1/2 of fenebrutinib on days 1 and 2
Part B
1. Placebo-adjusted change from predose-averaged baseline QTcF (ΔΔQTcF) of fenebrutinib measured using ECG on days 1 and 2

Key secondary outcome(s))
Part B:
1. Incidence and severity of AEs and incidence of abnormalities measured using clinical laboratory evaluations, 12-lead ECGs, vital signs measurements, and physical examinations throughout the study
2. Pharmacokinetics measured using Cmax, tmax, AUC0-∞ and/or AUC0-t, and t1/2 of fenebrutinib and moxifloxacin on days 1 and 2
3. Absolute and change from baseline in heart rate and PR, RR, QRS, QT, and QTcB intervals; and change from baseline T-wave morphology and U-wave presence measured using ECG on days 1 and 2
4. ΔΔQTcF of moxifloxacin measured using ... at 1, 1.5, 2, 3, and 4 hours postdose
5. Change from baseline QTcF (ΔQTcF) at the individual tmax for each treatment (ΔQTcF, tmax) measured using ECG

Completion date
21/08/2022

Eligibility

Key inclusion criteria
1. Males or females of non-childbearing potential, between 18 and 60 years of age, inclusive;
2. Within body mass index (BMI) range 18 to 31 kg/m², inclusive, with a bodyweight >45 kg;
3. In good health, determined by no clinically significant findings from medical history, 12-lead ECG, and vital signs;
4. Clinical laboratory evaluations (including chemistry panel [fasted at least 10 hours], complete blood count [CBC], coagulation [prothrombin time {PT}, international normalized ratio {INR}, and activated partial thromboplastin time {aPTT}], and urinalysis [UA] with complete microscopic analysis) within the reference range for the test laboratory, unless deemed not clinically significant by the investigator;
5. Negative test for selected drugs of abuse and cotinine at Screening (does not include alcohol) and at Check-in (Day -1 for Part A, Period 1 Day -1 for Part B; does include alcohol);
6. Negative hepatitis panel (hepatitis B virus core antibody, hepatitis B surface antigen, and hepatitis C virus antibody) and negative human immunodeficiency virus (HIV) antibody screens;
7. Females will not be pregnant or breastfeeding, and must be either postmenopausal (at least 12 months without a period [i.e., amenorrhea]; in a woman at least 50 years of age and documented by a serum follicle-stimulating hormone [FSH] level consistent with postmenopausal status [i.e., ≥40 IU/L] in the absence of a reversible medical iatrogenic cause) or surgically sterile (e.g., tubal ligation, bilateral salpingectomy, or hysterectomy) for at least 90 days. For all females, the pregnancy test result must be negative at Screening and Check-in (Day -1 for Part A, Period 1 Day -1 for Part B).

8. Males with partners of childbearing potential will either be sterile (confirmed by documentation in addition to agreeing to using a condom from Check-in [Day -1 for Part A, Period 1 Day -1 for Part B] until 90 days following study completion) or agree to use from Check-in (Day -1 for Part A, Period 1 Day -1 for Part B) until 90 days following study completion, one of the following approved methods of contraception: male condom with spermicide; sterile sexual partner; use by female sexual partner of an intrauterine device with spermicide; a female condom with spermicide; a contraceptive sponge with spermicide; an intravaginal system [e.g., NuvaRing®]; a diaphragm with spermicide; a cervical cap with spermicide; or oral, implantable, transdermal, or injectable contraceptives. Subjects will refrain from sperm donation from Check-in (Day -1 for Part A, Period 1 Day -1 for Part B) until 90 days or 5 half-lives plus 74 days (a spermatogenesis cycle), whichever is longer, following study completion. Male subjects (including men who have had vasectomies) whose partners are currently pregnant should use a barrier method for the duration of the study and for 90 days or 5 half-lives plus 74 days (a spermatogenesis cycle), whichever is longer, after the study completion. This is to ensure that the fetus is not exposed to the drug in the ejaculate;
9. Receive an explanation of the mandatory WGS component of the study; 10. Able to comprehend and willing to sign an Informed Consent Form (ICF); 11. Able to comply with the study restrictions.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal (GI), neurological, or psychiatric disorder (as determined by the investigator)
2. Evidence of active infection (with the exception of fungal nail infections or oral herpes); history of recurrent bacterial, viral, mycobacterial, or fungal infections (defined as >2 similar episodes requiring anti-microbial treatment within the previous 12 months), with the exception of recurrent oral or genital herpes (herpes simplex virus 1/herpes simplex virus 2) or uncomplicated urinary tract infections in females; or history of infection requiring hospitalization within 8 weeks prior to Screening
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator
4. Any personal or family history of bleeding disorders and any personal use of drugs known to affect blood clotting within 30 days prior to dosing
5. Family history of intracranial bleed (berry aneurysm, hemorrhagic stroke) or recent personal history of head trauma
6. History of vasculitis

7. Having one or more of the following clinical laboratory evaluations at Screening:
• Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² as calculated using the Cockcroft-Gault or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (may be repeated if 45 to 59 mL/min/1.73 m²
• ALT or AST >2 × ULN (may be repeated if 2 to 3 × ULN)
• Total bilirubin >1.5 × ULN (may be repeated if 1.6 to 3 × ULN)
• Abnormalities in hepatic synthetic function tests (e.g., PT, INR, aPTT, albumin) judged by the investigator to be clinically significant
8. Sustained (i.e., three consecutive occasions of assessments) systolic blood pressure measurements <85 or >140 mmHg or diastolic blood pressure measurements <45 or >90 mmHg at Screening
9. Sustained (i.e., confirmed upon repeat) pulse >100 or <45 beats per minute at Screening
10. Personal or family history of congenital long QT syndrome or family history of sudden death
11. History or presence of an abnormal ECG (including marked mean QTcF prolongation ≥450 msec) at Screening or Check-in (Day -1 for Part A, Period 1 Day -1 for Part B) that, in the investigator's opinion, is clinically significant
12. Short QTc (mean QTcF <300 msec) at Screening or Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
13. Subject had dyspepsia for which he/she had recently taken (within 2 weeks prior to Check-in [Day -1 Part A, Period 1 Day -1 for Part B]) prescription and/or over-the-counter medicinal products for the control of gastric acidity (e.g., proton-pump inhibitors, H2 blockers, antacids)
14. History of stomach or intestinal surgery or resection or any GI disorder that would potentially alter absorption and/or excretion of orally administered drugs, except that appendectomy, hernia repair, and/or cholecystectomy will be allowed
15. History of alcoholism or drug addiction within 1 year prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
16. History of tuberculosis (TB) or treatment with TB prophylaxis within 12 months prior to study enrollment
17. Use of oral antibiotics within 4 weeks or IV antibiotics within 8 weeks prior to the Screening evaluation
18. Any vaccination within 6 weeks prior to dosing
19. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 30 days or 5 half-lives, whichever is longer, prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
20. Use of any moderate or strong CYP3A inhibitor or inducer within 30 days or 5 half-lives, whichever is longer, prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
21. Use of any prescription medications/products within 14 days or 5 half-lives, whichever is longer, prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B), unless deemed acceptable by the investigator
22. Use of acetaminophen within 24 hours prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
23. Use of any over-the-counter, non-prescription preparations (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) within 14 days or 5 half-lives, whichever is longer, prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B), unless deemed acceptable by the investigator
24. Use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
25. Use of grapefruit-containing foods or beverages within 7 days prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B), unless deemed acceptable by the investigator
26. Strenuous exercise from 7 days prior to Check-in (Day -1 Part A, Period 1 Day -1 for Part B)
27. Use of alcohol- or caffeine-containing foods or beverages within 48 hours prior to Check-in

(Day -1 for Part A, Period 1 Day -1 for Part B), unless deemed acceptable by the investigator
28. Poor peripheral venous access
29. History of malignancy, except for appropriately treated carcinoma in situ of the cervix or non-melanoma skin carcinoma with 3-year disease-free follow-up
30. Donation or loss of blood in excess of approximately 450 mL from 30 days prior to Screening through study completion, inclusive, or of plasma from 2 weeks prior to Screening through study completion, inclusive
31. Receipt of blood products within 2 months prior to Check-in (Day -1 for Part A, Period 1 Day -1 for Part B)
32. Any acute or chronic condition that, in the opinion of the investigator, would limit the subject' s ability to complete and/or participate in this clinical study.

Date of first enrolment
27/04/2021

Date of final enrolment
18/07/2022

Locations

Countries of recruitment
United States of America

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

Sponsor information

Organisation
Roche (United States)

ROR
https://ror.org/011qkaj49

Funder(s)

Funder type
Industry

Funder Name
Roche

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co., Roche Holdings, Inc.

Funding Body Type
Government 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 this not being a regulatory requirement.

IPD sharing plan summary
Not expected to be made available