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A study to evaluate the effect of itraconazole and carbamazepine on the processing of fenebrutinib by the body in healthy participants

Submission date 03/05/2024	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 20/06/2024	**Overall study status** Completed	
Last Edited 17/06/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
Multiple sclerosis is a health condition in which the body's natural defense (immune system) attacks the protective covering of nerve fibers in the brain and spinal cord. This leads to communication problems between the brain and the rest of the body. This study is testing a medicine called fenebrutinib. It is being developed to treat multiple sclerosis. Fenebrutinib is an experimental medicine. This means health authorities (like the U.S. Food and Drug Administration, European Medicines Agency, and the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]) have not approved fenebrutinib for the treatment of multiple sclerosis. This study aims to test the safety of fenebrutinib. Also, it aims to understand how fenebrutinib gets to different parts of the body, and how the body changes and gets rid of it when given along with medicines called itraconazole or carbamazepine.

Who can participate?
Healthy people 18 to 60 years of age with multiple sclerosis can take part in the study. People with a history of stomach or intestinal surgery may not be able to take part in this study.

What does the study involve?
Participants will be screened to check if they can participate in the study. The screening period will take place up to 28 days before the start of treatment. Everyone who joins this study will be either enrolled in Part 1 or Part 2 of the study. In both parts, participants will receive treatment in two periods (Periods 1 and 2).

In Part 1, participants will be given fenebrutinib, as a pill by mouth, on Day 1 of Period 1 and Day 8 of Period 2. Participants will also be given itraconazole, as a pill by mouth, from Days 4 to 10 during Period 2.

In Part 2, participants will be given fenebrutinib, as a pill by mouth, on Day 1 of Period 1 and Day 18 of Period 2. Participants will also be given multiple doses of carbamazepine, as a pill by mouth from Days 4 to 20 during Period 2.

This is an open-label study. This means everyone involved, including the participant and the study doctor, will know the study treatment the participant has been given.

During this study, the doctor will see the participants regularly during their stays at the clinic (13 days in Part 1 and 22 days in Part 2). They will see how well the treatment is working and any unwanted effects participants may have. Participants will receive a follow-up telephone call from the study doctor to check on their well-being after 8-10 days of completing the study treatment. The total time of participation in the study will be about 7 weeks for Part 1 and 8 weeks for Part 2. Participants have the right to stop study treatment and leave the study at any time if they wish to do so.

What are the possible benefits and risks of participating?
Fenebrutinib is an experimental drug and is being given purely for research purposes, it is not intended that participants will receive any benefit from this study. However, the information collected in the study can help other people with multiple sclerosis in the future. The study involves some risks to the participants.

People interested in taking part will be informed about the risks and benefits, as well as any additional procedures or tests they may need to undergo. All details of the study will be described in an informed consent document.

Risks associated with the study
Participants may have side effects of the medicines used in this study. These side effects can be mild to severe, even life-threatening, and vary from person to person. All volunteers will be closely monitored during the study and safety assessments will be performed at regular intervals.

Fenebrutinib
Full information on risks associated with fenebrutinib is provided to volunteers in the Informed Consent Form. When investigating new medicines there is also a risk of unexpected side effects and occasionally allergic reactions. Known unwanted effects include the risk of liver injury. Fenebrutinib may be harmful to an unborn baby, and not all potential risks are 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 the study.

Itraconazole
Known unwanted effects include headache, dizziness, and runny nose.

Carbamazepine
Known unwanted effects include increased thoughts of suicide, liver damage, dizziness, drowsiness, unsteadiness, nausea, vomiting, abdominal pain, and frequent watery stools.

Where is the study run from?
Genentech Inc. (USA)

When is the study starting and how long is it expected to run for?
April 2024 to September 2024

Who is funding the study?
Genentech Inc. (USA)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
1009824

Protocol serial number
GP45241

Study information

Scientific Title
A Phase I, open-label, single-dose, fixed-sequence, two-part study to evaluate the effect of itraconazole and carbamazepine on fenebrutinib pharmacokinetics in healthy subjects

Study objectives
The main purpose of this study is to determine the effect of multiple oral doses of itraconazole and carbamazepine on the single-dose pharmacokinetics (PK) of fenebrutinib in healthy participants.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 14/06/2024, London - Brent Research Ethics Committee (80 London Road Skipton House, London, SE1 6LH, United Kingdom; +44 (0)20 7972 2561; brent.rec@hra.nhs.uk), ref: 24/LO/0307

Primary study design
Interventional

Study design
Phase 1 open-label single-dose fixed-sequence two-part drug-drug interaction (DDI) study

Study type(s)
Other

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
Part 1: Participants will receive a single dose of fenebrutinib 100 milligrams (mg), orally, on Day 1 of Period 1. After a washout period of 3 days, participants will receive itraconazole 200 mg, orally, twice daily (BID) on Day 4, and once daily (QD) from Days 5 to 10 of Period 2. Participants will also receive a single dose of fenebrutinib 100 mg, orally, along with itraconazole on Day 8 of Period 2.

Part 2: Participants will receive a single dose of fenebrutinib 200 mg, orally, on Day 1 of Period 1. After a washout period of 3 days, participants will receive carbamazepine 100 mg, orally, BID from Days 4 to 6, 200 mg, BID from Days 7 to 9, and 300 mg, BID from Days 10 to 20 of Period 2. Participants will also receive a single dose of fenebrutinib 200 mg, orally, along with carbamazepine, on Day 18 of Period 2.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Fenebrutinib, Itraconazole, Carbamazepine

Primary outcome(s)
1. Parts 1 and 2: Maximum observed plasma concentration (Cmax) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
2. Parts 1 and 2: Time to maximum observed plasma concentration (tmax) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
3. Parts 1 and 2: Area under the concentration-time curve (AUC) from time zero to the last measurable concentration (AUC0-t) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
4. Parts 1 and 2: Area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC0-∞) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
5. Parts 1 and 2: Apparent terminal elimination rate constant (λz) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
6. Parts 1 and 2: Apparent terminal elimination half-life (t1/2) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-

dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
7. Parts 1 and 2: Apparent systemic clearance (CL/F) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
8. Parts 1 and 2: Apparent volume of distribution during the terminal elimination phase (Vz/F) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2
9. Parts 1 and 2: Percentage of AUC0-∞ extrapolated (%AUCextrap) of fenebrutinib determined using a model-independent approach from samples collected at pre-dose and multiple time-points post-dose from Day 1 up to Day 11 in Part 1 and Day 1 up to Day 21 in Part 2

Key secondary outcome(s)
1. Parts 1 and 2: Number of participants with adverse events (AEs) and severity of AEs determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) from screening to end of treatment (approximately 50 days for Part 1 and 60 days for Part 2)

Completion date
03/09/2024

Eligibility

Key inclusion criteria
1. Body weight ≥45 kilograms (kg), within the body mass index range of 18 to 32 kilograms per metre squared (kg/m2).
2. Participants in good health, determined by no clinically significant findings from medical history, 12-lead electrocardiogram (ECG), and vital signs.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
All

Key exclusion criteria
1. Part 2 only: Participants that test positive for human leukocyte antigen-B (HLA-B)*1502 allele and/or HLA-A 3101 allele

2. Participants who are pregnant or breastfeeding or intending to become pregnant during the study or within 28 days after the final dose of the study drug
3. Evidence of any infectious, metabolic (except well-controlled/stable hypothyroidism), allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal (GI), neurological, or psychiatric disorder that would preclude subject participation
4. Any acute or chronic liver disease, e.g., hepatitis, cirrhosis (Child-Pugh Class A, B, or C), or Gilbert's Syndrome
5. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs, except that appendectomy and hernia repair will be allowed
6. History of pancreatitis, cholecystectomy or gallstones, or clinically significant GI ulcer or bleeding
7. History of malignancy, except for appropriately treated carcinoma in situ of the cervix or non-melanoma skin carcinoma with 5-year disease-free follow-up
8. Use of any moderate or strong CYP3A inhibitor or inducer within 30 days or 5 half-lives, whichever is longer, before Check-in (Period 1 Day -1)
9. Participants vaccinated with live, attenuated vaccines within 6 weeks before first dosing (Period 1 Day 1)
10. Dyspepsia, gastroesophageal reflux disease, ulcer, or GI symptoms for which the participant has recently taken (within 14 days before Check-in [Period 1 Day -1]) prescription or over-the-counter proton-pump inhibitors (PPIs), H2 blockers, or antacids for the control of gastric acidity

Date of first enrolment
24/07/2024

Date of final enrolment
06/08/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Fortrea Clinical Research Unit (Drapers Yard)
Drapers Yard, Marshall St, Holbeck
Leeds
United Kingdom
LS11 9EH

Sponsor information

Organisation
Genentech

ROR
https://ror.org/04gndp242

Funder(s)

Funder type
Industry

Funder Name
Genentech

Alternative Name(s)
Genentech, Inc., Genentech USA, Inc., Genentech USA

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

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