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A study to evaluate the effects of multiple doses of itraconazole and carbamazepine on processing of giredestrant by the body in healthy female participants

Submission date
05/03/2024

Recruitment status
No longer recruiting

Registration date
14/03/2024

Overall study status
Completed

Last Edited
13/03/2024

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Cancer is a health condition where the body's cells start growing and multiplying in an uncontrolled and abnormal way. Instead of following the usual pattern of cell growth, these cells form a lump or mass called a tumor. Breast cancer is a health condition where cancer cells form in the breast. Despite how well the available treatments are working, the cancer ultimately returns in many patients after it improved for a while, or the cancer stops responding to the treatment. This study tests a medicine called giredestrant. It is being developed to treat breast cancer with estrogen receptors, which are little proteins found in the cancer cells. Giredestrant is an experimental medicine. This means health authorities (like the U.S. Food and Drug Administration and European Medicines Agency) have not approved giredestrant for the treatment of breast cancer. This study aims to test how much giredestrant reaches the bloodstream and how long the body takes to get rid of it when it is given along with itraconazole or carbamazepine to healthy female participants who are unable to become pregnant.

Who can participate?
Healthy females of 18-65 years of age with breast cancer, who could not become pregnant took part in the study. Patients treated with any drug that specifically works on the estrogen receptors, which are little proteins found in the cancer cells, are unable to take part in this study.

People who are pregnant, or breastfeeding are unable to take part in the 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 approximately 5 weeks before the start of treatment.

Everyone who joins this study will be split into two groups, Group A and Group B. Both groups receive two treatment periods, Periods 1 and 2. Participants are able to take part in only one group of the study.

In Group A, participants are given giredestrant, as a pill by mouth on Day 1 of Period 1 and then on Day 4 of Period 2 along with itraconazole given as an oral liquid. Participants are given itraconazole on Days 1 to 14 of Period 2.

In Group B participants are given giredestrant, as a pill by mouth on Day 1 of Period 1 and then on Day 15 of Period 2 along with carbamazepine, also given as a pill by mouth. Participants are given carbamazepine on Days 1 to 21 of 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 participants are confined at the study site for at least 26 days (Group A) or at least 31 days (Group B). Participants received a follow-up telephone call from the study doctor to check on their well-being after approximately 8 to 10 days of completing the study treatment. Total time of participation in the study was about 6 weeks for group A and 7 weeks for group B, excluding the 5 weeks of screening. Participants had the right to stop study treatment and leave the study at any time if they wished to do so.

What are the possible benefits and risks of participating?
Taking part in the study may or may not make participants feel better. However, the information collected in the study can help other people with similar health conditions in the future.

It may not have been fully known at the time of the study how safe and well the study treatment worked. The study involves some risks to the participants. However, these risks are generally not greater than those related to routine medical care or the natural progression of the health condition. People interested in taking part are informed about the risks and benefits, as well as any additional procedures or tests they may need to undergo. All details of the study are described in an informed consent document. This includes information about possible effects and other options for treatment.

Risks associated with the study drugs
Participants may have unwanted effects of the drugs used in this study. These unwanted effects can be mild to severe, even life-threatening, and vary from person to person. During this study, participants will have regular check-ups to see if there are any unwanted effects.

Giredestrant:
Participants are told about the known unwanted effects of giredestrant and possible unwanted effects based on human and laboratory studies or knowledge of similar medicines. Known unwanted effects include pain or stiffness in the joints (arthralgia), frequent watery stools (diarrhea), the feeling of spinning, being unsteady and losing balance (dizziness), tiredness, muscle or bone pain, queasy feeling in the stomach that gives the sensation of wanting to vomit (nausea).

Itraconazole:
Participants are told about the known unwanted effects of itraconazole. Known unwanted effects include shortness of breath, headache, the feeling of spinning, being unsteady and losing balance, heartburn, runny nose, a persistent feeling of sadness, and loss of interest that can affect daily functioning (depression), hair loss, and fever.

Carbamazepine:
Participants are told about the known unwanted effects of carbamazepine. Known unwanted effects include increased thoughts of suicide, liver damage feeling of spinning, being unsteady, and losing balance, frequent watery stools, heart failure, blurred vision, and fainting.

Where is the study run from?
Genentech

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

Who is funding the study?
Genentech

Who is the main contact?
rocheisrctn-mail@xogene.com

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Dr Clinical Trials

Contact details
Building 1, Grenzacherstrasse 124
Basel
Switzerland
CH-4070
+1 888-662-6728
global-roche-genentech-trials@gene.com

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
GP44001

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 giredestrant pharmacokinetics in healthy female subjects of non-childbearing potential

Study objectives
The main purpose of this study is to assess the effect of multiple oral doses of itraconazole (ITZ) and carbamazepine (CBZ) on the single-dose pharmacokinetics (PK) of giredestrant in healthy female participants of non-childbearing potential.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 24/02/2022, Salus IRB (2111 W. Braker Lane Suite 100, Austin, Texas, 78758, United States of America; +1 512-380-1244; salus@salusirb.com), ref: None provided

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

Primary study design
Interventional

Study type(s)
Other

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

Interventions
Participants will be assigned to either Part A or Part B of the study. Each part consisted of 2 periods.

Part A - Period 1: Participants received giredestrant, 10 mg, orally, on Day 1 of Period 1.

Part A - Period 2: Participants received itraconazole, 200 milligrams (mg), orally, twice daily (BID), on Day 1, and once daily (QD) on Days 2 to 14 of Period 2. Participants also received giredestrant, 200 mg, orally, along with itraconazole on Day 4 of Period 2.

There was a washout period of at least 10 days between the first giredestrant dose and the first ITZ dose.

Part B - Period 1: Participants received giredestrant, 30 mg, orally, on Day 1 of Period 1.

Part B - Period 2: Participants received carbamazepine, 100 mg, orally, BID, on Days 1 to 3, 200 mg on Days 4 to 6, 300 mg on Days 7 to 19, 200 mg on Day 20, and 100 mg on Day 21 of Period 2. Participants also received giredestrant, 30 mg, orally along with carbamazepine on Day 15 of Period 2.

There was a washout period of at least 10 days between the 2 giredestrant doses.

Intervention Type
Drug

Phase

Phase I

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

Primary outcome(s)
1. Part A: Maximum observed concentration (Cmax) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

2. Part A: Time to maximum observed concentration (tmax) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

3. Part A: Area under the concentration-time curve from hour 0 to last measurable concentration (AUC0-t) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

4. Part A: Area under the concentration-time curve extrapolated to infinity (AUC 0-∞) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

5. Part A: Apparent terminal elimination rate constant (λz) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

6. Part A: Apparent terminal elimination half-life (t1/2) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

7. Part A: Apparent total clearance (CL/F) of giredestrant determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

8. Part A: Apparent volume of distribution (Vz/F) of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

9. Part A: Percentage of AUC0-∞ extrapolated (%AUCextrap) of giredestrant in plasma measured determined using the non-compartmental analysis approach at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 4 up to Day 15 in Period 2 of Part A

10. Part B: Cmax of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

11. Part B: Tmax of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

12. Part B: AUC0-t of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

13. Part B: AUC 0-∞ of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

14. Part B: λz of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

15. Part B: T1/2 of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

16. Part B: CL/F of giredestrant determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

17. Part B: Vz/F of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

18. Part B: %AUCextrap of giredestrant in plasma determined using the non-compartmental analysis approach from samples collected at predose and multiple time points post-dose from Day 1 up to Day 8 in Period 1 and Day 15 up to Day 22 in Period 2 of Part B

Key secondary outcome(s))
1. Part A: Number of participants with adverse events (AEs) and severity of AEs determined according to National Cancer Institute Common Terminology Criteria For Adverse Events (NCI CTCAE) from Day 1 up to follow-up (up to approximately 35 days)

2. Part B: Number of participants with AEs and severity of AEs determined according to NCI CTCAE from Day 1 up to follow-up (up to approximately 40 days)

3. Part B: Number of participants with suicidal ideation or behavior, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) score from screening up to follow-up (up to approximately 75 days)

Completion date
25/05/2022

Eligibility

Key inclusion criteria

1. Females of non-childbearing potential and either postmenopausal and with a negative pregnancy test result at screening (serum test) and check-in (Day -1; urine test) of Period 1.
2. Females with body mass index (BMI) range 18.5 to 32.0 kilograms per meter square (kg/m2), inclusive, at screening.
3. Females in good health, determined by no clinically significant findings from medical history, 12-lead electrocardiogram (ECG), or vital signs.
4. Negative hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and negative human immunodeficiency virus (HIV) antibody screens.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
Female

Total final enrolment
33

Key exclusion criteria
1. Female participant with a 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. History of stomach or intestinal surgery (including cholecystectomy) or resection that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy and hernia repair were allowed (unless performed within 12 months prior to screening).
3. Malabsorption syndrome or other condition that would interfere with enteral absorption.
4. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance < 70 milliliters/minute (mL/min) using the Cockcroft-Gault equation.
5. History of active or latent tuberculosis (TB), regardless of treatment history, or positive QuantiFERON TB Gold test.
6. History of previous use of tamoxifen, aromatase inhibitors, giredestrant, or any other endocrine agent for the treatment of breast cancer.
7. The use of hormone replacement therapy or selective estrogen receptor (ER) modulators (selective estrogen receptor modulators (SERMs); e.g., raloxifene) within 1 year prior to Check-in (Day -1) or
8. The use of oral antibiotics within 4 weeks or intravenous (IV) antibiotics within 8 weeks prior to check-in (Day -1).

9. Use of any moderate or strong cytochrome P450 (CYP3A) inhibitor or inducer within 30 days or 5 half-lives, whichever is longer, prior to Check-in (Day-1).
10. The use or intent to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in (Day -1).
11. Female subject having a history of any malignancy, within 5 years prior to screening.
12. Positive for the human leukocyte antigen-B (HLA-B*1502) allele (Part B only).

Date of first enrolment
05/04/2022

Date of final enrolment
14/04/2022

Locations

Countries of recruitment
United States of America

Study participating centre
Clinical Pharmacology of Miami (CPMI)
Miami, Florida
United States of America
33014-3616

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