ISRCTN48011192 https://doi.org/10.1186/ISRCTN48011192

A study to assess the effect of itraconazole and phenytoin on BIIB113 and the effect of BIIB113 on midazolam in healthy participants

Submission date 10/05/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 29/06/2023	**Overall study status** Completed	
Last Edited 12/09/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
This study is testing a drug called BIIB113, which is being developed to treat Alzheimer's disease (AD). Alzheimer's disease is a progressive illness, which means it slowly gets worse. People with Alzheimer's disease have memory loss and eventually lose their ability to think clearly and carry on their daily activities.
BIIB113 is an experimental drug, which means health authorities have not approved BIIB113 for the treatment of AD or any other disease. BIIB113 along with other approved drugs, itraconazole, phenytoin, and midazolam will be tested in this study. The aim of this study is to determine how the study drug, BIIB113 interacts with these approved drugs.

Who can participate?
Healthy participants aged 18 to 65 years

What does the study involve?
The study includes three parts: Part A (Itraconazole), Part B (Phenytoin), and Part C (Midazolam). Participants will be enrolled in any one part of the study i.e., Part A, Part B, or Part C. Participants from Part A and Part B can enroll in Part C. Participants may be asked to be in the study for a maximum of 54 days.
All parts of this study will have three periods:
1. Screening Period: Participants will undergo certain screening tests and/or procedures to make sure that they are eligible to take part in this study. Participants will have one clinic visit during the screening period which will be done 28 days before the first dose of the study drug.
2. Dosing/Clinic Stay: Participants will receive study drugs during this period. They will be admitted to the clinical site one day (Day -1) before the study drug is administered and they will have to stay in the clinic for a stipulated period. The length of the dosing period will vary based on the part of the study the participants enrol in.
3. Follow-up Visit: Participants will have one check-up visit with the study doctor at the clinic.
The three parts of the study are:
Part A:
Participants will receive BIIB113 by mouth on Days 1 and 11 after an overnight fast of 8 hours.

They will also receive itraconazole by mouth on Days 7 to 16 after a fast of 2 hours. Participants will be discharged from the clinic on Day 17 and will have to return to the clinic 6 to 8 days after the last dose of itraconazole for a final check-up.
Part B:
Participants will receive BIIB113 by mouth on Days 1 and 15 after an overnight fast of 8 hours. They will also receive phenytoin by mouth on Days 7 to 20, after a fast of 2 hours. Participants will be discharged from the clinic on Day 21. Participants will have to return to the clinic 4 to 6 days after the last dose of phenytoin for a final check-up.
Part C:
Participants enrolling in Part C will receive midazolam by mouth on Days 1 and 15, after an overnight fast of 8 hours. They will also receive BIIB113 by mouth on Days 2 to 15 after a fast of 2 hours. Participants will be discharged from the clinic on Day 16. Participants will have to return to the clinic 6 to 8 days after the last dose of study medicines for a final check-up. Eligible participants from Part A and Part B who wish to enrol in Part C will have to wait for a period of 14 and 35 days respectively during which no study drug will be administered to them (wash-out period) before participating in Part C.

What are the possible benefits and risks of participating?
Participants will be healthy adults and not expected to receive any benefit from participating in this study (beyond that of an assessment of their medical status), but the information that is learned may help further in the clinical development of BIIB113 and for the treatment of people with AD in the future.
The risks of participation are primarily those associated with possible side effects from the treatments or procedures and discomfort from the collection of blood samples and other study procedures in this study. This study is designed to address and mitigate the potential risks to participants. Information about potential risks will be provided to the participants in the informed consent form.

Where is the study run from?
Biogen (UK)

When is the study starting and how long is it expected to run for?
April 2023 to December 2023

Who is funding the study?
Biogen Idec (USA)

Who is the main contact?
Dr Shruthi Ramesh, SRamesh@meu.org.uk

Contact information

Type(s)
Principal investigator

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Dr Shruthi Ramesh

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1007834

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
276HV103, IRAS 1007834

Study information

Scientific Title
A Phase I, open-label, fixed-sequence, crossover study to investigate the effect of itraconazole (CYP3A inhibitor) and phenytoin (CYP3A inducer) on BIIB113 and the effect of BIIB113 on midazolam (CYP3A substrate) in healthy participants

Study objectives
The purpose of this study is to evaluate the effect of itraconazole and phenytoin on the pharmacokinetics (PK) of BIIB113 and the effect of BIIB113 on the PK of midazolam.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/08/2023, North West - Greater Manchester Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)207 1048 007; gmcentral.rec@hra.nhs.uk), ref: 23/NW/0118

Study design
Multi-centre Phase I interventional open-label fixed-sequence crossover study

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Experimental: Part A (Itraconazole)
Participants will receive BIIB113, orally, once daily (OD), on Days 1 and 11 along with itraconazole, orally, OD, from Days 7 to 16.

Experimental: Part B (Phenytoin)
Participants will receive BIIB113, orally, OD, on Days 1 and 15 along with phenytoin, orally, thrice daily (TDS), from Days 7 to 20.

Experimental: Part C (Midazolam)
Participants will receive midazolam, orally, OD, on Days 1 and 15, along with BIIB113, orally, OD, from Days 2 to 15. Participants from Parts A and B may be eligible to enroll into Part C, after a wash-out period of 14 and 35 days respectively.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Itraconazole, phenytoin, midazolam, BIIB113

Primary outcome(s)
1. Parts A and B: Maximum observed concentration (Cmax) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
2. Part C: Cmax of midazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
3. Parts A and B: Area under the concentration-time curve from time zero to time of the last measurable concentration (AUClast) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21(Part B)
4. Part C: AUClast of midazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
5. Part A and B: Area under the concentration-time curve from time zero to infinity (AUC0-inf) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
6. Part C: AUC0-inf of midazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16

Key secondary outcome(s))
1. Parts A, B, and C: Number of participants with adverse events (AEs) as assessed using data recorded on the electronic case report forms (eCRFs) from Day 1 up to the end of study (up to approximately 26 days)
2. Parts A, B, and C: Number of participants with serious adverse events (SAEs) assessed using data recorded on the SAE form from signing of informed consent up to the end of study (up to approximately 54 days)
3. Parts A, B, and C: Number of participants with clinically significant change from baseline in clinical laboratory parameters, vital signs, 12-lead electrocardiogram (ECG), and Columbia

Suicide Severity Rating Scale (C-SSRS) score as assessed by the investigator from screening to end of study (up to approximately 54 days)
4. Parts A and B: Terminal elimination half-life (t½) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
5. Part C: t½ of midazolam and 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
6. Parts A and B: Apparent total body clearance (CL/F) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
7. Part C: CL/F of midazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
8. Parts A and B: Time to maximum observed concentration (Tmax) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
9. Part C: Tmax of midazolam and 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
10. Parts A and B: Apparent volume of distribution during the terminal elimination phase (Vz/F) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
11. Part C: Vz/F of midazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
12. Parts A and B: Elimination rate constant (λz) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
13. Part C: λz of midazolam and 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
14. Parts A and B: Time of last measurable observed concentration (Tlast) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
15. Part C: Tlast of midazolam and 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
16. Parts A and B: Last measurable concentration (Clast) of BIIB113 assessed using blood samples at predose and multiple timepoints postdose up to Day 17 (Part A) and at predose and multiple timepoints postdose up to Day 21 (Part B)
17. Part C: Clast of midazolam and 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
18. Part C: Cmax of 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
19. Part C: AUClast of 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
20. Part C: AUC0-inf of 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
21. Part C: Ratio of the Cmax for the metabolite to the Cmax for the parent drug (MPCmax) of 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16
22. Part C: Ratio of the AUCinf for the metabolite to the AUCinf for the parent drug (MPAUCinf) of 1-hydroxymidazolam assessed using blood samples at predose and multiple timepoints postdose up to Day 16

Completion date

Eligibility

Key inclusion criteria
1. Body mass index (BMI) between 18 and 30 kilograms per square meter (kg/m^2) inclusive
2. Weight ≥50 kg at Screening
3. Negative severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) test result within 5 days of Day -1 prior to randomisation
4. Infertile males as defined by Clinical Trials Facilitation and Coordination Group (CTFG) guidelines:
4.1. Permanently sterile by bilateral orchidectomy
4.2. Vasectomised males defined as follows:
4.2.1. Minimum of 12 weeks after successful vasectomy surgical procedure, and
4.2.2. Documentation of confirmation of successful vasectomy by postvasectomy semen analysis – information collected at least 12 weeks after the surgery
5. All females of childbearing potential must practice contraception

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Key exclusion criteria
1. Suicidal ideation, per the Investigator’s clinical judgement, with some intent to act within 6 months prior to the start of Screening, per the Investigator’s clinical judgement or based on the C-SSRS, corresponding to a response of ‘Yes’ on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behaviour within 1 year prior to the start of Screening. Participants reporting suicidal ideation with intent to act or suicidal behaviour prior to the Day 1 visit should be excluded.
2. History of systemic hypersensitivity reaction to BIIB113, itraconazole (Part A), phenytoin (Part B), midazolam (Part C), other related drugs, or the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.
3. Any vaccination within 10 days prior to Day -1 or intention to be vaccinated within 10 days after the last dose of study treatment.
4. Use of any hormonal oral contraceptives, systemically acting hormone-releasing

contraceptive implants (excluding intrauterine devices), and hormone-replacement medication.
5. Use of any prescription medication, over-the-counter oral medication (excluding acetaminophen [≤ 2 g/day]) or dietary and herbal supplements that are not inducers or inhibitors of drug metabolising enzymes or drug transporters within 7 days prior to Day -1, and an unwillingness or inability to refrain from this use during study participation, unless specifically permitted elsewhere within the protocol.
6. Use of any prescription medication, over-the-counter oral medication, or dietary and herbal supplements (e.g., St. John's wort) that are a known inducer or inhibitor of drug metabolising enzymes (including but not limited to CYP3A) or drug transporters within 28 days of Day -1 and an unwillingness to refrain from use during study participation.

NOTE: Other protocol-defined inclusion/exclusion criteria may apply.

Date of first enrolment
07/09/2023

Date of final enrolment
04/12/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Medicines Evaluation Unit Ltd (MEU)
The Langley Building
Southmoor Road
Manchester
United Kingdom
M23 9QZ

Study participating centre
Hammersmith Medicines Research Limited
Cumberland Avenue
London
United Kingdom
NW10 7EW

Sponsor information

Organisation

Biogen (United Kingdom)

ROR
https://ror.org/00rd36p16

Funder(s)

Funder type
Industry

Funder Name
Biogen Idec

Alternative Name(s)

Funding Body Type
Private sector 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 will be stored in a publicly available repository (in accordance with Biogen's Clinical Trial Transparency and Data Sharing Policy on https://www.biogentrialtransparency.com/).

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other unpublished results	version 1	25/06/2024	12/09/2024	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes