COVER PAGE

Official Title:	A Phase 1, 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
NCT Number:	NCT03864614
Document Date:	25 Jun 2024
Name of Sponsor/Company:	Biogen
Name of Finish Product:	BIIB113
Name of Active Ingredient:	BIIB113
Study Indication:	Alzheimer's Disease

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The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen MA Inc./Biogen Idec Research Limited	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
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Title of Study:

A Phase 1, 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

Principal Investigator:

[redacted]
Manchester United Kingdom M23 9QZ

Study Period:	**Phase of Development**:
Date of first treatment: 26 September 2023 End of Study Date: 28 December 2023	1

Study Objectives:

Primary Objectives:

- Part A: To evaluate the effect of itraconazole (a strong cytochrome P450 [CYP]3A inhibitor) on the single-dose pharmacokinetics (PK) of BIIB113 in healthy participants
- Part B: To evaluate the effect of phenytoin (a strong CYP3A inducer) on the single-dose PK of BIIB113 in healthy participants
- Part C: To evaluate the effect of BIIB113 on the PK of midazolam (a sensitive CYP3A substrate) in healthy participants

Secondary Objectives:

- Part A
  - To assess the safety and tolerability of BIIB113 when coadministered with a strong CYP3A inhibitor
  - To further assess the effect of itraconazole on secondary PK parameters of single-dose BIIB113
- Part B
  - To assess the safety and tolerability of BIIB113 when coadministered with a strong CYP3A inducer
  - To further assess the effect of phenytoin on secondary PK parameters of single-dose BIIB113
- Part C
  - To assess the safety and tolerability of BIIB113 when coadministered with a CYP3A substrate
  - To further assess the effect of BIIB113 on secondary PK parameters of single-dose midazolam
  - To evaluate the effect of BIIB113 on 1-hydroxymidazolam after single-dose midazolam

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Study Design:

This was a Phase 1, open-label, fixed-sequence, crossover study in healthy participants to investigate the effect of itraconazole (a strong CYP3A inhibitor) and phenytoin (a strong CYP3A inducer) on BIIB113 and the effect of BIIB113 on midazolam (a sensitive CYP3A substrate). This study comprised 3 parts: Part A (itraconazole), Part B (phenytoin), and Part C (midazolam).

Part A (Itraconazole):

Part A investigated the effect of itraconazole (a strong CYP3A inhibitor) on the PK of BIIB113 in healthy participants aged 18 to 65 years (inclusive). Approximately 24 participants were to be enrolled into Part A to complete with 20 evaluable participants for PK assessments.

Part B (Phenytoin):

Part B investigated the effect of phenytoin (a strong CYP3A inducer) on the PK of BIIB113 in healthy participants aged 18 to 65 years (inclusive). Approximately 24 participants were to be enrolled into Part B to complete with 20 evaluable participants for PK assessments.

Part C (Midazolam):

Participants in Parts A and B may have enrolled in Part C provided they met the relevant inclusion and exclusion criteria. Participants in Part A should have had a washout period of at least 14 days after the last dose of itraconazole before participating in Part C. Participants in Part B should have had a washout period of at least 35 days after the last dose of phenytoin before participating in Part C.

Part C investigated the effect of BIIB113 (a potential CYP3A inducer) on midazolam (a sensitive CYP3A substrate) in healthy participants aged 18 to 65 years (inclusive). Approximately 22 participants were to be enrolled into Part C to complete with 18 evaluable participants for PK assessments.

Number of Participants (Planned and Analyzed):

Planned**:**

- Part A (itraconazole): approximately 24 participants
- Part B (phenytoin): approximately 24 participants
- Part C (midazolam): approximately 22 participants

Analyzed:

- Part A (itraconazole): 24 participants
- Part B (phenytoin): 18 participants
- Part C (midazolam): 22 participants

Study Population:

Main Inclusion Criteria:

- In good health as determined by the Investigator, based on medical history and screening evaluations, with a body mass index (BMI) between 18 and 30 kg/m^2, inclusive, at the time of informed consent.
- Females or infertile/vasectomized males aged 18 to 65 years, inclusive, at the time of informed consent. All participants of childbearing potential must practice contraception.

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- Negative severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) test result within 5 days of Day -1.

Main Exclusion Criteria:

- 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.
- History of any clinically significant cardiac disease as determined by the Investigator.
- Clinically significant (as determined by the Investigator) 12-lead electrocardiogram (ECG) abnormalities.
- Use of any hormonal oral contraceptives, systemically acting hormone-releasing contraceptive implants (excluding intrauterine devices), and hormone replacement medication.
- 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-metabolizing 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.

Study Treatment, Dose, Mode of Administration:

Participants received oral doses of BIIB113 and either concomitant itraconazole, phenytoin, or midazolam (Part A, Part B, or Part C, respectively). A total of 2 lots of BIIB113 were used during this study.

Part A (Itraconazole):

On Day 1, participants received a single oral dose of BIIB113 [redacted]. Participants fasted overnight for approximately 8 hours before and for approximately 2 hours after dosing with BIIB113.

On Days 7 to 16, participants received single oral doses of itraconazole 200 mg once daily in the morning. From Days 7 to 10 and Days 12 to 16, no food was allowed 2 hours before and 2 hours after itraconazole dosing.

On Day 11, a single oral dose of BIIB113 [redacted] was coadministered with a single oral dose of itraconazole 200 mg. Participants fasted overnight for approximately 8 hours prior to the administration of BIIB113 dose and for approximately 2 hours postdose.

Part B (Phenytoin):

On Day 1, participants received a single oral dose of BIIB113 [redacted]. Participants fasted overnight for approximately 8 hours before and for approximately 2 hours after BIIB113 dosing.

On Days 7 to 20, participants received phenytoin 100 mg oral capsules 3 times daily. From Days 7 to 14 and Days 16 to 20, no food was allowed 2 hours before and 2 hours after phenytoin dosing.

On Day 15, a single oral dose of BIIB113 [redacted] was coadministered with the first morning dose of phenytoin 100 mg. Participants fasted overnight for approximately 8 hours prior to the administration of BIIB113 dose and for approximately 2 hours postdose.

Part C (Midazolam):

On Day 1, participants received a single oral dose of midazolam 2.5 mg. Participants fasted overnight for approximately 8 hours before and for approximately 2 hours after midazolam dosing.

On Days 2 to 15, participants received oral doses of BIIB113 [redacted] once daily. From Days 2 to 14, no food was allowed 2 hours before and 2 hours after BIIB113 dosing.

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On Day 15, a single oral dose of midazolam 2.5 mg was coadministered with a single oral dose of BIIB113 [redacted]. Participants fasted overnight for approximately 8 hours prior to the administration of BIIB113 dose and for approximately 2 hours postdose.

Duration of Treatment and Follow-Up:

Part A (Itraconazole):

The total study duration for each participant was up to 52 days:

- Screening Period of up to 28 days
- Inpatient clinic stay of a total of 17 days
    - Check in: Day -1 (1 day)
    - Inpatient treatment and observation period:
        - Period 1 (BIIB113): Days 1 to 6
        - Period 2 (itraconazole): Days 7 to 10
        - Period 3 (BIIB113 and itraconazole coadministration): Days 11 to 17
- Outpatient Follow-Up/End of Study (EOS) Visit: Day 23 ± 1 day

Part B (Phenytoin):

The total study duration for each participant was up to 54 days.

- Screening Period of up to 28 days
- Inpatient clinic stay of a total of 21 days
    - Check in: Day -1 (1 day)
    - Inpatient treatment and observation period:
        - Period 1 (BIIB113): Days 1 to 6
        - Period 2 (phenytoin): Days 7 to 14 (before BIIB113 administration)
        - Period 3 (BIIB113 and phenytoin coadministration): Days 15 to 21
- Outpatient Follow-Up/EOS Visit: Day 25 ± 1 day

Part C (Midazolam):

The total study duration for each participant was up to 51 days.

- Screening Period of up to 28 days
- Inpatient clinic stay of 16 days
    - Check in: Day -1 (1 day)
    - Inpatient treatment and observation period:
        - Period 1 (midazolam): Day 1
        - Period 2 (BIIB113): Days 2 to 14
        - Period 3 (midazolam and BIIB113 coadministration): Days 15 to 16
- Outpatient Follow-Up/EOS Visit: Day 22 ± 1 day

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Criteria for Evaluation:

The following is a description of all PK and safety assessments that were originally planned for this study.

Pharmacokinetics:

Part A (itraconazole):

- The following plasma PK parameters of BIIB113:
  - Maximum observed concentration (C_{max}), area under the concentration-time curve from time 0 to time of the last measurable concentration (AUC_{last}), and area under the concentration-time curve from time 0 to infinity (AUC_{inf})
  - Terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), time to reach maximum observed concentration (T_{max}), apparent volume of distribution during the terminal elimination phase (V_z/F), elimination rate constant (λ_z), time of the last measurable observed concentration (T_{last}), and last measurable concentration (C_{last})

Part B (phenytoin):

- The following plasma PK parameters of BIIB113:
  - C_{max}, AUC_{last}, and AUC_{inf}
  - $t_{1/2}$, CL/F, T_{max}, V_z/F, λ_z, T_{last}, and C_{last}

Part C (midazolam):

- The following plasma PK parameters of midazolam:
  - C_{max}, AUC_{last}, and AUC_{inf}
  - $t_{1/2}$, CL/F, T_{max}, V_z/F, λ_z, T_{last}, and C_{last}
- The following plasma PK parameters of 1-hydroxymidzolam:
  - C_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, T_{max}, λ_z, T_{last}, C_{last}, ratio of the C_{max} for the metabolite to the C_{max} for the parent drug (MPC_{max}), and ratio of the AUC_{inf} for the metabolite to the AUC_{inf} for the parent drug ($MPAUC_{inf}$)

Safety:

Part A (itraconazole), Part B (phenytoin), and Part C (midazolam):

- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Changes in laboratory parameters, vital signs, 12-lead ECGs, and Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Methods:

The main statistical methods are as follows:

Primary Endpoints:

- Part A (itraconazole) and Part B (phenytoin): plasma PK parameters of BIIB113 (C_{max}, AUC_{last}, and AUC_{inf})
- Part C (midazolam): plasma PK parameters of midazolam (C_{max}, AUC_{last}, and AUC_{inf})

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Plasma concentrations of BIIB113 and midazolam were summarized by study treatment and timepoint using descriptive statistics and graphical display.

For Part A (itraconazole) and Part B (phenytoin), the PK parameters C_{max}, AUC_{last}, and AUC_{inf} for BIIB113 were statistically analyzed by a mixed-effect analysis of variance (ANOVA) model to assess the effect of itraconazole and phenytoin on the PK of BIIB113.

For Part C (midazolam), the PK parameters C_{max}, AUC_{last}, and AUC_{inf} for midazolam were statistically analyzed by a mixed-effect ANOVA model to assess the effect of BIIB113 on the PK of midazolam.

Secondary Endpoints:

- Part A (itraconazole), Part B (phenytoin), and Part C (midazolam): incidence of AEs and SAEs and changes in laboratory parameters, vital signs, 12-lead ECGs, and C-SSRS

All AEs, SAEs, shift in clinical laboratory values, postbaseline vital signs abnormalities, C-SSRS, and shift in 12-lead ECG and postbaseline ECG outlier data were summarized by study treatment and overall.

Secondary Endpoints:

- Part A (itraconazole) and Part B (phenytoin): plasma PK parameters of BIIB113 ($t_{1/2}$, CL/F, T_{max}, V_z/F, λ_z, T_{last}, and C_{last})
- Part C (midazolam): plasma PK parameters of midazolam ($t_{1/2}$, CL/F, T_{max}, V_z/F, λ_z, T_{last}, and C_{last}) and of 1-hydroxymidazolam (C_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, T_{max}, λ_z, T_{last}, C_{last}, MPC_{max}, and $MPAUC_{inf}$)

The PK parameters for BIIB113, midazolam, and 1-hydroxymidazolam were listed and summarized by study treatment using descriptive statistics. Trough concentrations of itraconazole (Part A), phenytoin (Part B), and BIIB113 (Part C) were summarized using descriptive statistics by study day.

For Part A (itraconazole) and Part B (phenytoin), the PK parameters C_{max}, AUC_{last}, and AUC_{inf} for BIIB113 were statistically analyzed to assess the effect of itraconazole and phenytoin on the PK of BIIB113.

For Part C (midazolam), the PK parameters C_{max}, AUC_{last}, and AUC_{inf} for midazolam and 1-hydroxymidazolam were statistically analyzed to assess the effect of BIIB113 on the PK of midazolam. The magnitude change for 1-hydroxymidazolam PK parameters was explored.

For a detailed description of the planned analyses and determination of sample size, refer to the final version of the statistical analysis plan (SAP; Appendix 16.1.9, SAP Version 1.0).

Results:

Participant Accountability: Part A (Itraconazole):

The first participant was enrolled and received study treatment on 26 September 2023. The EOS date for all study parts (Parts A, B, and C) was 28 December 2023. A total of 24 participants were enrolled at 1 site in the United Kingdom (UK). Of the 24 participants, 23 participants (95.8%) completed study treatment. One participant (4.2%) discontinued study treatment and withdrew from the study due to study visit burden and scheduling conflicts.

Participant Accountability: Part B (Phenytoin):

The first participant was enrolled and received study treatment on 26 September 2023. A total of 18 participants were enrolled at 1 site in the UK. Of the 18 participants, 4 participants (22.2%) completed study treatment, and 14 participants (77.8%) discontinued study treatment (5 due to AEs and 9 at the Investigator's discretion after an increased incidence of AEs with phenytoin administration in Part B was noted by the Investigator). Of the 18 participants, 1 participant (4.2%) withdrew from the study due to a non-AE-related reason.

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Participant Accountability: Part C (Midazolam):

The first participant was enrolled and received study treatment on 26 October 2023. A total of 22 participants were screened and enrolled at 1 site in the UK. Of the 22 participants, 19 participants (86.4%) completed study treatment. Three participants (13.6%) discontinued study treatment and withdrew from the study due to AEs.

Demographics and Baseline Disease Characteristics: Part A (Itraconazole):

The median age (range) was 47 years (18 to 64 years). Of the 24 participants who received study treatment, all participants were female. The median BMI (range) was 22.45 kg/m^2 (19.7 to 30.0 kg/m^2). Overall, the participants were predominantly White (18 participants [75.0%]) and Not Hispanic or Latino (22 participants [91.7%]).

Of the 24 participants, 15 participants (62.5%) reported medical history. The most commonly reported medical history were urinary tract infection and depression (2 participants [8.3%] each). There was no clinically concerning medical history in any participant.

Demographics and Baseline Disease Characteristics: Part B (Phenytoin):

The median age (range) was 45 years (19 to 61 years). Of the 18 participants who received study treatment, 15 participants (83.3%) were female. The median BMI (range) was 23.15 kg/m^2 (20.6 to 27.7 kg/m^2). Overall, the participants were predominantly White (14 participants [77.8%]). All participants (100%) were Not Hispanic or Latino.

Of the 18 participants, 15 participants (83.3%) reported medical history. The most commonly reported medical history were coronavirus disease 19 (COVID-19) (4 participants [22.2%]) and dysmenorrhea and vasectomy (3 participants [16.7%] each). There was no clinically concerning medical history in any participant.

Demographics and Baseline Disease Characteristics: Part C (Midazolam):

The median age (range) was 44 years (27 to 64 years). Of the 22 participants who received study treatment, 16 participants (72.7%) were female. The median BMI (range) was 24.10 kg/m^2 (20.4 to 30.3 kg/m^2). Overall, the participants were predominantly White (15 participants [68.2%]) and Not Hispanic or Latino (21 participants [95.5%]).

Of the 22 participants, 20 participants (90.9%) reported medical history. The most commonly reported medical history were COVID-19 (9 participants [40.9%]) and vasectomy (6 participants [27.3%]). There was no clinically concerning medical history in any participant.

Pharmacokinetics:

- After concomitant administration with a strong CYP3A inhibitor, systemic exposure (area under the concentration-time curve [AUC]) to BIIB113 was increased by less than 2-fold, CL/F was decreased, and $t_{1/2}$ was increased.
- After concomitant administration with a strong CYP3A inducer, systemic exposure (AUC) to BIIB113 was decreased by approximately 65%, CL/F was increased, and $t_{1/2}$ was decreased.
- BIIB113 had no effect on CYP3A-mediated metabolism.

Safety: Part A (Itraconazole):

- BIIB113 was generally well tolerated in the presence of itraconazole, a strong CYP3A inhibitor.
- Eleven participants (45.8%) who received study treatment experienced at least 1 AE.
- The most frequently reported (> 2 participants during any treatment period) AE was headache (0 participants in Period 1, 4 participants [16.7%] in Period 2, and 1 participant [4.2%] in Period 3).

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- All AEs were mild or moderate in severity. No severe AEs were observed.
- No BIIB113-related AEs were reported. Three participants (12.5%) experienced itraconazole-related AEs.
- No participants discontinued study treatment or withdrew from the study due to AEs.
- No deaths or SAEs were reported.
- No clinically significant trends in clinical laboratory results, vital signs, ECGs, or C-SSRS results were observed.

Safety: Part B (Phenytoin):

- BIIB113 was generally well tolerated in the presence of phenytoin, a strong CYP3A inducer.
- Sixteen participants (88.9%) who received study treatment experienced at least 1 AE.
- The most frequently reported (> 2 participants during any treatment period) AEs included headache (0 participants in Period 1, 4 participants [22.2%] in Period 2, and 2 participants [11.1%] in Period 3), lethargy (0 participants in Period 1, 3 participants [16.7%] in Period 2, and 1 participant [5.6%] in Period 3), and pyrexia (0 participants in Periods 1 and 2 and 3 participants [16.7%] in Period 3).
- Most AEs were mild or moderate in severity. One severe AE of pulmonary embolism was observed.
- Five participants (27.8%) experienced BIIB113-related AEs. Seven participants (38.9%) experienced phenytoin-related AEs. All BIIB113-related AEs were also assessed as related to phenytoin.
- Five participants (27.8%) experienced AEs that led to discontinuation of study treatment.
- No participants withdrew from the study due to AEs.
- No deaths were reported. One SAE of pulmonary embolism was reported, which was assessed by the Investigator as not related to BIIB113 or phenytoin.
- Some participants experienced transient changes in hematology parameters and liver function tests, which were not unexpected given the known adverse drug reactions of phenytoin. No clinically significant trends were observed for any other laboratory parameters, vital signs, ECGs, or C-SSRS results.

Safety: Part C (Midazolam):

- BIIB113 was generally well tolerated in the presence of midazolam, a strong CYP3A substrate.
- There were no clinically meaningful effects of BIIB113 on the safety of midazolam.
- Nineteen participants (86.4%) who received study treatment experienced at least 1 AE.
- The most frequently reported (> 2 participants during any treatment period) AEs included headache (0 participants in Period 1, 6 participants [27.3%] in Period 2, and 1 participant [4.5%] in Period 3), tremor (0 participants in Period 1, 3 participants [13.6%] in Period 2, and 4 participants [18.2%] in Period 3), abnormal dreams (0 participants in Period 1, 3 participants [13.6%] in Period 2, and 1 participant [4.5%] in Period 3), insomnia (0 participants in Period 1, 4 participants [18.2%] in Period 2, and 0 participants in Period 3), and medical device site rash (0 participants in Period 1, 3 participants [13.6%] in Period 2, and 0 participants in Period 3).
- Most AEs were mild or moderate in severity. One severe AE of acute stress disorder was observed.
- Six participants (27.3%) experienced BIIB113-related AEs. One participant (4.5%) experienced midazolam-related AEs.

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- Three participants (13.6%) experienced AEs that led to discontinuation of study treatment.
- Three participants (13.6%) experienced AEs that led to withdrawal from the study.
- No deaths were reported. One SAE of acute stress disorder was reported, which was assessed by the Investigator as related to BIIB113.
- No clinically significant trends in clinical laboratory results, vital signs, ECGs, or C-SSRS results were observed.

Conclusions:

- Systemic exposure to BIIB113 was increased by less than 2-fold after concomitant administration with a strong CYP3A inhibitor (itraconazole) and decreased by approximately65% after concomitant administration with a strong CYP3A inducer (phenytoin).
- After concomitant administration with a strong CYP3A inhibitor (itraconazole), CL/F was decreased and $t_{1/2}$ was increased.
- After concomitant administration with a strong CYP3A inducer (phenytoin), CL/F was increased and $t_{1/2}$ was decreased.
- BIIB113 had no effect on CYP3A-mediated metabolism.
- BIIB113 was generally well tolerated in healthy participants in the presence of a CYP3A inhibitor (itraconazole), CYP3A inducer (phenytoin), or CYP3A substrate (midazolam).
- There were no clinically meaningful effects of BIIB113 on the safety of midazolam.

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