COVER PAGE

Official Title:	A Phase 1 Single- and Multiple-Ascending-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB094 Administered Intrathecally to Adults With Parkinson's Disease
NCT Number:	NCT03976349
Document Date:	30 January 2025
Name of Sponsor/Company:	Biogen MA Inc./Biogen Idec Research Limited
Name of Finished Product	BIIB094
Name of Active Ingredient:	BIIB094
Study Indication:	Parkinson’s Disease

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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 Single- and Multiple-Ascending-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB094 Administered Intrathecally to Adults With Parkinson's Disease

Number of Study Sites and Countries:

18 sites globally (among 18 sites, 16 sites screened participants).

Study Period:	**Phase of Development:**
Date of first treatment: 27 August 2019 End of Study date: 12 August 2024	1

Study Objectives:

Primary Objective:

- To evaluate the safety and tolerability of single and multiple doses of BIIB094 administered via intrathecal (IT) injection to participants with PD

Secondary Objective:

- To evaluate the PK profile of BIIB094

[redacted]

- [redacted]
- [redacted]
- [redacted]

Study Design:

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

This was a Phase 1, randomized, blinded, placebo-controlled, 2-part dose escalation study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of BIIB094 in adult participants diagnosed with Parkinson's disease (PD). BIIB094 was administered via IT injection to participants with PD. Part A included 40 participants in a single ascending dose (SAD) study of up to 6 dose levels of BIIB094. Part B included 42 participants in a multiple ascending dose (MAD) study of up to 3 dose levels of BIIB094 administered up to 4 times over a period of approximately 3 months.

Part A (SAD)

Forty diagnosed PD participants were enrolled in up to 6 cohorts. The 6 cohorts included Cohorts 1 through 6, who were randomly assigned to a single dose of study treatment in a 3:1 ratio (active: placebo). A sentinel dosing strategy and safety monitoring throughout study were implemented in Part A (SAD). Those in Part A may enroll in Part B after a 20-week washout period, provided they met eligibility criteria and have completed Part A through Day 85.

Part B (MAD)

Forty-two diagnosed PD participants were to be enrolled in 5 cohorts with specific enrollment criteria:

Cohort 7: Enrolled all eligible PD participants regardless of genetic status.

Cohorts 8a and 9a: Enrolled PD participants without pathogenic leucine-rich repeat kinase 2 (LRRK2) variants.

Cohorts 8b and 9b: Enrolled PD participants with pathogenic LRRK2 variants.

Each cohort followed a randomized, placebo-controlled design with varying ratios of active treatment to placebo. Cohort 7 had an 8:2 ratio, while the others had a 6:2 ratio. The study employed a sentinel dosing strategy, where the first two participants in each cohort (one placebo, one BIIB094) were dosed initially. A 72-hour safety review of these sentinel participants was conducted before dosing the remaining cohort members. Subsequent participants were dosed 24 hours apart to allow for ongoing safety monitoring.

Number of Participants:

Planned:

- Part A (SAD): 40 participants (6 cohorts)
- Part B (MAD): 42 participants (5 cohorts)

Analyzed:

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

- Part A (SAD): 40 participants (6 cohorts and 1 pooled placebo group)
- Part B (MAD): 42 participants (5 cohorts and 1 pooled placebo group)

Study Population:

Main inclusion criteria:

- Aged 35 to 80 years, inclusive, at the time of informed consent.
- Diagnosed with PD within 7 years at the time of initial enrollment
- For Part B (MAD):
  - Cohort 7: Enrolled all eligible PD participants regardless of genetic status.
  - Cohorts 8a and 9a: Enrolled PD participants without pathogenic LRRK2 variants
  - Cohorts 8b and 9b: Enrolled PD participants with pathogenic LRRK2 variants.

Main exclusion criteria:

- Montreal Cognitive Assessment score < 23, dementia, or other significant cognitive impairment that, in the opinion of the Investigator, would interfere with study evaluation.
- History of any brain surgery for PD (e.g., pallidotomy, deep brain stimulation, or fetal tissue transplant) or history of focused ultrasound treatment at any time; or history of neuromodulation procedures, including, but not limited to, transcranial magnetic stimulation, transcranial direct or alternating current stimulation that have been performed within 90 days of screening.
- Known or suspected cause of parkinsonism other than neurodegenerative PD: participants with atypical parkinsonian syndromes (e.g., Lewy body dementia, progressive supranuclear palsy, or multiple system atrophy, presence of drug-induced parkinsonism (e.g., neuroleptics, metoclopramide, flunarizine, and so on), metabolic identified neurogenetic disorders (e.g., Wilson's disease), or encephalitis.

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

- Any contraindications to having a brain magnetic resonance imaging (MRI) [e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed without requiring general anesthesia, etc.].
- Any contraindication to lumbar puncture procedures
- Unstable psychiatric illness, including psychosis, suicidal ideation, or untreated major depression within 90 days before Screening, as determined by the Investigator.
- History or screening MRI results showing evidence of structural abnormalities that could have contributed to the participant's clinical state or any finding that might have posed a risk to the participant.

Study Treatment, Dose, and Mode of Administration:

Part A (SAD):

Participants received a single dose of BIIB094 [redacted] (Cohort 1), [redacted] (Cohort 2), [redacted] (Cohort 3), [redacted] (Cohort 4), [redacted] (Cohort 5), or [redacted](Cohort 6) administered intrathecally.

Part B (MAD):

Four doses of BIIB094 were administered on Days 1, 29, 57, and 85 for each cohort at the following planned dose levels:

- Cohort 7: [redacted]
- Cohort 8a: [redacted]
- Cohort 8b: [redacted]
- Cohort 9a: [redacted]
- Cohort 9b: [redacted]

Control Drug and Mode of Administration:

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

For Part A (SAD) and Part B (MAD), matching placebos were administered intrathecally to each cohort following the same dosing regimen as BIIB094.

Duration of Treatment and Follow-Up:

Study duration for each participant in Part A was approximately 18 weeks:

- 6-week screening period
- 12-week follow-up period

Study duration for each participant in Part B was up to 47 weeks:

- 11-week screening period
- 12-week treatment period
- 24-week follow-up period

For participants enrolling in both Part A (SAD) and Part B (MAD), study duration was a minimum of 62 weeks:

- 6-week screening period of Part A
- Minimum of 20 weeks total washout between the Day 1 dosing visit of Part A and the first dosing visit of Part B
- 12-week treatment period of Part B
- 24-week follow-up period of Part B

Criteria for Evaluation:

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

Pharmacokinetics:

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

The following PK parameters were calculated to assess the PK of BIIB094 in serum, when feasible:

- C_{max}
- T_{max}
- AUC_{∞}
- $AUC_{0\text{-last}}$
- $t_{½}$

Safety:

The following clinical assessments were performed to evaluate the safety profile of BIIB094:

- Adverse event (AE) and serious AE (SAE) recording.
- Physical examinations.
- Neurological examinations (assessed by a trained specialist).
- Vital sign measurements.
- Weight, height, and body mass index measurements.
- Triplicate 12-lead electrocardiograms (ECGs) were obtained at each specified timepoint after the participant had been resting in a supine position for at least 10 minutes
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Concomitant therapy and procedure recording.
- Medical history.

Statistical Methods:

Analysis populations were defined as follows:

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

- The safety analysis population was defined as all participants who received at least 1 administration of study drug (BIIB094 or placebo).
- The PK, [redacted] analysis populations included the participants from the safety analysis population who had at least 1 postbaseline measurement.
- All placebo treated participants within/across each patient population were combined to form a placebo control group for Part A or Part B. A separate statistical analysis was performed for Parts A and B.
- For Part B, data from the LRRK2-PD and the Non-LRRK2 PD/All PD groups were summarized separately for each dose level/cohort and pooled.

Methods of Analysis:

Safety, PK, [redacted] data were summarized using descriptive statistics for each BIIB094 dose level and placebo. Additionally, changes from baseline in safety parameters, [redacted] were summarized. Further, the incidences of treatment-emergent AEs and SAEs were tabulated.

The sample size of the study was considered adequate to characterize the initial single- and multiple-dose safety, tolerability, and PK profile of BIIB094.

Results:

Participant Accountability, Part A (SAD): A total of 40 participants were enrolled and randomized. Thirty-one participants received BIIB094, and 9 participants received the placebo. Forty participants completed Part A.

Participant Accountability, Part B (MAD): A total of 42 participants were enrolled and randomized. A total of 42 participants were dosed. Thirty-three participants received BIIB094, and 9 participants received the placebo. A total of 39 participants completed the study treatment. A total of 4 participants did not complete the study. One participant in Cohort 8a (BIIB094 [redacted]) withdrew from the study due to an adverse event, and one participant in Cohort 9b (BIIB094 [redacted]) withdrew from the study due to other reasons. Two participants from the pooled placebo did not complete the study (due to withdrawal by the participant and unable to get lumbar puncture, respectively).

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

Demographics and Baseline Disease Characteristics, Part A (SAD): Most of the participants were male (27[67.5%]), white (39 [97.5%]) and not Hispanic or Latino (36 [90%]). The median age of participants was 61 years. By age group, 20 participants (50%) were 60 to <70 years old, and 12 participants (30%) were 50 to <60 years old. The median height and weight of the participants were 167.6 cm and 77.1 kg, respectively. The median BMI (kg/m2) for the participants was 26.6.

Thirty-one out of 40 participants (77.5%) tested negative for the LKKR2 gene. One participant (2.5%) had an indeterminate result, and the remaining 8 participants (20.0%) tested positive. Fifteen out of 40 participants (37.5%) in this group had a family history of Parkinson's disease. Most participants experienced the symptoms of tremor (31 [77.5%]), rigidity (22 [55.0%]), and bradykinesia (24 [60.0%]) at PD diagnosis. Only 3 out of 40 participants (7.5%) experienced posture instability.

Demographics and Baseline Disease Characteristics, Part B (MAD): Most of the participants were male (25 [59.5%]), White (41 [97.6%]), and Not Hispanic or Latino (41 [97.6%]). The median age of participants was 62 years. By age group, 16 (38.1%) participants were 60 to <70 years old, and 14 participants (33.3%) were 50 to <60 years old. The median height and weight of the participants were 168.5 cm and 77.8 kg, respectively. The median BMI (kg/m2) for the participants was 25.5.

Twenty-four out of 42 participants (57.1%) tested negative for the LKKR2 gene. One participant (2.4%) had an indeterminate result, and the remaining 17 participants (40.5%) tested negative. Sixteen out of 42 participants (38.1%) in this group had a family history of Parkinson's disease. Most participants (31/42) experienced the symptoms of tremor (31 [73.8%]), rigidity (18 [42.9%]), and bradykinesia (31 [73.8%]) at PD diagnosis. Two out of 40 participants (4.8%) experienced posture instability.

Pharmacokinetics: Part A (SAD):

BIIB094 reached peak serum concentrations 1 to 6 hours after intrathecal administration, consistent with typical antisense oligonucleotide behavior. Concentrations generally increased with dose, though Cohort 5 [redacted] showed unexpectedly higher mean peak levels than Cohort 6 [redacted] due to one participant's notably high concentrations. Serum levels approached or fell below quantification limits by 168 hours postdose.

Serum PK parameters (C_{max}, $AUC_{0\text{-}last}$, and AUC_{∞}) remained below the NOAEL values established in nonhuman primate studies. These parameters showed a dose-related increase across the [redacted] range, with Cohort 5's geometric mean higher than expected due to one participant's elevated exposures.

Geometric mean half-life ($t_{1/2}$) ranged from 3.57 to 20.03 hours, increasing with dose. This trend suggests that $t_{1/2}$ may not have been accurately characterized at lower doses due to assay sensitivity limitations in the terminal phase.

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

Pharmacokinetics: Part B (MAD):

Peak concentrations were observed 2-6 hours postdose (median T_{max}), with dose-dependent increases in mean concentrations.

Individual and mean C_{max} and AUC values remained below the NOAEL established in nonhuman primate studies. The study revealed dose-related increases in C_{max} and $AUC_{0\text{-}tau}$ across the evaluated dose range. Importantly, no substantial drug accumulation was observed with multiple dosing.

The geometric mean half-life (t1/2) ranged from 4.01 to 14.11 hours, increasing with dose.

Safety: Part A (SAD):

Overall, single doses of BIIB094 at [redacted] were generally safe and tolerable.

- There were no fatal events or SAEs reported during the study. No TEAEs led to discontinuation of study treatment or withdrawal from the study.
- Five of the 9 participants in the pooled placebo group and most participants in the total active SAD groups experienced ≥ 1 TEAE. The most common TEAEs (reported in >1 participant) were postlumbar puncture syndrome, procedural pain, and headache.
- All the TEAEs were mild or moderate in severity (Grade 1 or 2).
- There were 2 TEAEs that were evaluated as study-drug related by Investigator: pleocytosis (1 participant in Cohort 4 [redacted]) and headache (1 participant in Cohort 6 [redacted])
- Eighteen out of 40 participants experienced TEAEs related to lumbar puncture as assessed by the Investigator. Procedural pain and postlumbar puncture syndrome were the most common TEAEs related to lumbar puncture.
- Treatment with single doses of BIIB094 was not associated with any clinically meaningful trends for clinical laboratory results, vital sign measurements, ECG findings, and C-SSRS assessments. Seventy-five percent of participants in Cohort 6 [redacted] and 50% of participants in Cohort 4 [redacted] experienced a shift to high in CSF leukocytes. A TEAE of pleocytosis was reported in Cohort 4 [redacted],

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

Safety: Part B (MAD):

BIIB094 administered in multiple doses of [redacted] to PD participants, both carriers and non-carriers of the LRRK2 gene mutation, demonstrated a generally safe and tolerable profile.

- Three SAEs were reported during the study. An SAE (intraductal proliferative breast lesion) with pretreatment onset was reported for a participant in Cohort 8a ([redacted] [non-LRRK2]) and led to the discontinuation of the treatment and withdrawal from the study. An SAE of atrial fibrillation was also reported in Cohort 8a ([redacted] [non-LRRK2]), and 1 SAE (post-lumbar puncture syndrome) was reported in Cohort 8b ([redacted] [LRRK2]). None of the SAE was assessed as related to the study treatment.

- All participants in the pooled placebo group and most participants in the total active MAD group experienced ≥ 1 TEAE. Post-lumbar puncture syndrome and procedural pain are most common TEAEs in each Cohort of active MAD group.

- Most TEAEs were mild or moderate in severity (Grade 1 or 2).

- Four participants who were treated with BIIB094 had at least 1 TEAE that was considered to be related to the study treatment: one participant each in Cohort 7 [redacted] and Cohort 8a ([redacted] [Non-LRRK2]) and 2 participants in Cohort 9b ([redacted] [LRRK2]).

- Thirty out of 42 participants (71.4%) experienced TEAEs related to lumbar puncture assessed by the Investigator. Post-lumbar puncture syndrome and procedural pain were the most common TEAEs related to lumbar puncture.

- Treatment with multiple doses of BIIB094 was not associated with any clinically significant trends in hematology, coagulation, serum chemistry, or urinalysis parameters. Sixty-seven percent of participants in Cohorts 8a ([redacted] [Non-LRRK2]) and 80% of participants in Cohort 9b ([redacted] [LRRk2]) experienced a shift to high in CSF leukocyte count. A TEAE of pleocytosis and a TEAE of CSF white blood cell count increased were reported in Cohort 9b ([redacted] [LRRK2])

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)***
Name of Finished Product:	**Name of Active Ingredient:** BIIB094	**Study Indication:** Parkinson's Disease

- Treatment with multiple doses of BIIB094 was not associated with any clinically significant trends in vital sign measurements, ECG findings, or C-SSRS assessments.

Conclusions:

- Regarding the primary objectives of this study, BIIB094 was generally safe and well tolerated at single doses (SAD) and multiple doses (MAD) tested in the study.
- The secondary objective of the study was to evaluate the PK profile of BIIB094. Serum BIIB094 concentrations peaked within 1 to 6 hours after single IT dosing and decreased to BLQ or near-BLQ levels by 168 hours postdose. BIIB094 exposures (C_{max} and AUC parameters) increased in a dose-related manner following both single and multiple doses. The PK exposures in this study did not exceed the NOAEL exposures established in the nonhuman primate toxicology studies. No substantial accumulation of BIIB094 was observed with multiple dosing.

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