COVER PAGE

Official Title:	A Phase 1, Blinded, Randomized, Placebo-controlled Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Doses of BIIB132 Administered Intrathecally to Adults with Spinocerebellar Ataxia 3
NCT Number:	NCT05160558
Document Date:	10 November 2023
Name of Sponsor/Company:	Biogen MA Inc./ Biogen Idec Research Limited
Name of Finish Product:	BIIB132
Name of Active Ingredient:	BIIB132
Study Indication:	Spinocerebellar Ataxia Type 3
Primary Investigator/ Coordinating investigators	Not Applicable

These Clinical Study Results are provided for informational purposes only.

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:

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Number of Study Sites and Countries:

Approximately 19 sites located in the United States, United Kingdom, and Europe participated in this study.

Study Period:	**Phase of Development:** 1
Date of first treatment: 15 March 2022 End of Study date: 25 July 2023	

Study Objective(s):

Primary Objective:

- To evaluate the safety and tolerability of multiple ascending doses of BIIB132 administered via intrathecal (IT) injection to participants with spinocerebellar ataxia 3 (SCA3)

Secondary Objective:

- To characterize the multiple-dose pharmacokinetics (PK) of BIIB132 administered via IT injection to participants with SCA3

[redacted]

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

Study Design:

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This was a Phase 1, randomized, blinded, placebo-controlled study to investigate the safety, tolerability, and PK of multiple doses of BIIB132 administered IT to 8 adult participants with SCA3.

The decision to terminate the program was announced on 24 April 2023 and was based on the assessment of the 41-week IT toxicity study in monkeys, insufficient clinical pharmacodynamic (PD) data, and the future development pathway for BIIB132. As of the end of the study, Cohort 1 completed and was comprised of 8 participants who were randomly assigned to treatment in a 6:2 ratio (BIIB132 at 10 mg: placebo). The frequency of study treatment administration was every 4 weeks (Q4W) (total of 4 doses).

Number of Participants (Planned and Analyzed):

Planned:

A total of 8 participants were planned to be enrolled and randomly assigned in a 6:2 ratio to BIIB132 10 mg: placebo, with 4 doses received with Q4W dosing frequency (Days 1, 29, 57, and 85).

Analyzed:

Eight participants were enrolled and received BIIB132 or placebo: 6 participants received BIIB132 10 mg and 2 participants received placebo.

Study Population:

This study was conducted in participants who met the following criteria:

- Age 18 to 70 years, inclusive, at the time of informed consent.
- Diagnosis of SCA3 with cytosine-adenine-guanine repeats ≥ 60 in ATXN3 gene.
- Symptomatic ataxia with a screening SARA score 3 to 15 (still ambulatory) and a minimum SARA gait subscore of 1.
- Able to ambulate 8 m independently without any assistive device.
- Treatment naïve or on a stable dose of symptomatic therapy for a minimum of 4 weeks prior to Screening.

Study Treatment, Dose, and Mode of Administration:

Participants received BIIB132 10 mg (6 participants) or placebo (2 participants).

Participants received 4 doses (at Days 1, 29, 57, and 85) in total, with dosing every 4 weeks.

For each participant, a review of all available safety and tolerability data was performed approximately 14 days after the first dose was administered and before the administration of the second dose on Day 29. This single-dose review was performed by the site's Principal Investigator and communicated to the Sponsor Medical Director and Global Medical Safety Physician. The Sponsor Medical Director and Safety Physician determined whether each participant could proceed with subsequent doses. The second dose could not be given until this review was completed.

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Duration of Treatment and Follow-Up:

The study duration for each participant was approximately 44 weeks:

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

Criteria for Evaluation:

Following is a description of all safety, PK, and efficacy assessments that were originally planned for this study.

Primary Safety Endpoint:

Incidence of adverse events (AEs) assessed from Day 1 to final study visit and serious adverse events (SAEs) assessed from Screening to final study visit.

Secondary Pharmacokinetics Endpoints:

Serum PK parameters including but not limited to, the following:

- AUC, AUC_{inf}, and AUC_{last}
- C_{max}
- T_{max}
- $t_{½}$

[redacted]

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[redacted]

Statistical Methods:

Analysis Populations:

The Safety Analysis Population (Safety Analysis Set) was defined as all participants who received at least 1 dose of study treatment.

The PK analysis set was defined as all randomized participants who receive at least 1 dose of BIIB132 and have at least 1 measurable BIIB132 concentration and at least 1 of the PK parameters of interest measured.

[redacted]

All participants receiving placebo were combined to form placebo control groups.

Methods of Analysis:

Safety, PK, [redacted] were summarized using descriptive statistics for each BIIB132 dose level and placebo. PK parameters were calculated for each participant. Additionally, changes from baseline in safety parameters, [redacted] were summarized. Further, the incidence of treatment-emergent AEs and SAEs was tabulated.

Sample Size Calculation:

The sample size of the study was considered adequate to characterize the multiple dose safety, tolerability, and PK of BIIB132 in a first-in-human study. The sample size was empirically determined and is not based on formal statistical considerations. However, calculations showed that, with a total of 36 BIIB132-dosed participants, there was an 85% probability of observing at least 1 AE that has an incidence of 5.2% or more. A fewer number of

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participants were planned for Cohorts 1 through 3 because of the reduced pharmacological activity of BIIB132 and thus, the reduced potential for AEs at lower doses.

Results:

Participant Accountability:

The first participant was randomized on 15 March 2022 and the last participant was randomized on 25 October 2022. The decision to terminate the study was announced on 24 April 2023.

A total of 8 participants were enrolled and 7 participants (1 participant received 3 doses of BIIB132) received 4 doses of study treatment (BIIB132 or placebo): 6 participants received 10 mg BIIB132, and 2 participants received placebo.

No participants who received BIIB132 discontinued study treatment or withdrew from the study. There was also no treatment discontinuation or study withdrawal due to a COVID-19-related reason.

All 8 participants received at least 1 dose of study treatment (BIIB132 or placebo) and were included in the Safety Analysis Population.

Demographics and Baseline Disease Characteristics:

Median ages for the placebo and treatment groups were 49.5 and 56 years, respectively. The majority of participants were White (75%), male (62.5%), and not Hispanic or Latino (87.5%). The median weight of participants was 78.8 kg in the BIIB132 group and 64.04 kg in the placebo group.

All participants reported at least one condition on medical history. The most frequent conditions (occurred to ≥ 2 participants) were: diplopia (100%) in placebo group; sinus bradycardia (33.3%), meniscus injury (33.3%), muscle spasms (33.3%), scoliosis (33.3%), spinal osteoarthritis (33.3%), anxiety (33.3%), and depression (33.3%) in the BIIB132 treatment group.

Efficacy, Pharmacokinetics, [redacted]:

No meaningful conclusions can be drawn based on the efficacy, PK, [redacted] parameters between participants who received BIIB132 and participants who received placebo.

Safety:

All participants experienced at least 1 AE during the study. The most frequently reported AEs were in the system organ class of Nervous system disorders. The most frequently observed AEs (≥50% for both placebo and BIIB132 treatment groups) were headache and fall.

Four participants (66.7%) who received BIIB132 10 mg experienced AEs that were assessed by the Investigators as related to study treatment. Headache, which occurred in 2 participants, was the most common BIIB132-related AE. All of these AEs were assessed to be mild or moderate in severity, and all were considered resolved except for the event of muscular weakness.

Overall, treatment with BIIB132 was not associated with any clinically meaningful shifts from baseline over time for hematology, blood chemistry, urinalysis, vital signs, and electrocardiogram.

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Conclusion(s): Multiple doses of BIIB132 at 10 mg were generally safe and well tolerated in adult participants with SCA3.		
Date of Report: 10 November 2023		
Version: 1.0		