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

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Name of Finished Product: Cinpanemab (BIIB054)	**Name of Active Ingredient:** BIIB054	**Study Indication:** Parkinson's Disease

Title of Study:

A Multicenter, Blinded, Placebo-Controlled, Randomized, Single- and Multiple Ascending Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Japanese Subjects with Parkinson's Disease.

Number of Study Sites and Countries:

Nine investigators at 9 sites located in Japan participated (i.e., enrolled at least 1 participant) in the study.

Study Period:	**Phase of Development:** 1b
Date of first treatment: 12 March 2019 End of Study date: 23 April 2021	

Study Objective(s):

Primary Objective:

- To evaluate the safety and tolerability of a range of single and 13 repeated doses of BIIB054, administered as intravenous (IV) infusion, in Japanese participants with Parkinson's Disease (PD)Secondary Objectives:
- To assess the serum pharmacokinetic (PK) profile of BIIB054 after single- and multiple-dose administrationTo evaluate the immunogenicity of BIIB054Additional Objectives:
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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Study Design:

This was a randomized, blinded, placebo-controlled, single- and multiple ascending dose study to examine the safety, tolerability, PK, and pharmacodynamics of BIIB054 administered to Japanese participants with early PD. Cohorts of 8 participants were sequentially enrolled. Participants within each cohort were randomized to receive a single IV infusion, followed, after a 12 week outpatient monitoring period, by 13 IV infusions (1 IV infusion every 4 weeks for 48 weeks) of BIIB054 (250 mg, 1250 mg, 3500 mg) or placebo in a 6:2 ratio. Investigators, study site staff (except for a designated pharmacist/technician), and study participants remained blinded to the randomized study treatment assignments.

This study in Japanese participants was terminated early due to a lack of efficacy in Study 228PD201, which evaluated BIIB054 for the treatment of PD in a global participant population. At the time of this report, results from Study 228PD201 are in preparation and are expected to be published during Q4 2021.

Number of Participants (Planned and Analyzed):

Planned: A total of 24 participants were planned to be enrolled: 8 participants (6:2 ratio, BIIB054:placebo) in each of the BIIB054 250 mg, 1250 mg, and 3500 mg cohorts.

Analyzed: Twenty-four participants were enrolled and received BIIB054 or placebo: 6 participants each received BIIB054 250 mg, 1250 mg, 3500 mg, or placebo.

Study Population:

Main Inclusion Criteria:

To have been eligible to participate in this study, candidates must have met the following eligibility criteria at Screening, or at the timepoint specified in the individual eligibility criterion listed:

1. Was diagnosed with PD within a maximum of 3 years prior to Screening. Participants must have had 1 of the following:

- An asymmetric or bilateral presentation of one of the following:
  - Resting tremor and bradykinesia
  - Bradykinesia and rigidity
  - Rigidity and resting tremor

OR

- Either asymmetric resting tremor or asymmetric bradykinesia

2. No known or suspected cause of Parkinsonism other than neurodegenerative PD. Participants with drug-induced Parkinsonism (e.g., metoclopramide and flunarizine), metabolic-identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or Parkinson-Plus syndromes, other forms of atypical Parkinsonian syndromes (e.g.,

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progressive supranuclear palsy and multiple system atrophy), or Lewy body dementia were not allowed in the study.

3. Had not received levodopa or any other treatment for PD, herein referred to as symptomatic PD medication (including, but not limited to, dopamine agonists, amantadine, anticholinergics, MAO-B inhibitors, or safinamide; further guidance was provided by the study's Medical Monitor on a case-by-case basis) for at least 12 weeks prior to Day 1 and, in the opinion of the Investigator, was not expected to require PD treatment for at least 9 months following Day 1. Maximum total duration of prior PD regimens should not have exceeded 30 days.

4. Score of ≤ 2.5 on the Modified Hoehn and Yahr Scale.

5. Screening dopamine transporter/single-photon emission computed tomographyDaT]/single photon emission computed tomography [SPECT]) results demonstrating activity in the striatum was either asymmetric, absent in the putamen and/or one or both caudate nuclei, consistent with neurodegenerative Parkinsonism, as assessed with screening qualitative visual assessment. DaT/SPECT images were reviewed by a central reader to confirm eligibility.

Main exclusion criteria:

Medical History

1. Presence of freezing gait.

2. MoCA score < 23 or other significant cognitive impairment or clinical dementia that, in the opinion of the Investigator, would have interfered with study evaluation.

3. Unstable psychiatric illness, including psychosis, suicidal ideation, or untreated major depression within 90 days before Screening, as determined by the Investigator.

4. History or screening magnetic resonance imaging (MRI) results that showed 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 or might have prevented a satisfactory MRI assessment for safety monitoring. MRI results were reviewed by a central reader to confirm eligibility at Screening.

5. History of drug or alcohol abuse within the past 5 years (as defined by the Investigator), a positive urine drug test, or an unwillingness to abstain from these substances during clinic visit days. Participants who tested positive for cannabinoids due to occasional marijuana use, as determined by the Investigator, and who agreed to refrain from using marijuana for the duration of the study may have been enrolled at Investigator's discretion, after a consultation with the Sponsor.

6. History of any brain surgery for PD (e.g., pallidotomy, deep brain stimulation, or fetal tissue transplant).

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7. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., values of aspartate aminotransferase, alanine aminotransferase, or total bilirubin ≥ 2 times the upper limit of normal).

8. Indication of impaired renal function at Screening (estimated glomerular filtration rate < 60 mL/min).

9. Participants with contraindications to lumbar punctures (LPs). Contraindications included the following characteristics but were not limited to:

- Any history of lumbar surgery for any reason (e.g., herniated disc) that, in the opinion of the Investigator, would have interfered with or posed risks to the LP procedure.
- Low platelet count (below 50,000 cells/μL), or screening values of international normalized ratio, prothrombin time, or activated partial thromboplastin time that were not within normal ranges.
- Anticipated need for antiplatelet medication (e.g., aspirin > 81 mg daily, clopidogrel, or nonsteroidal anti-inflammatory drugs) within 7 days prior to the planned LP or anticipated need for antiplatelet medication within 48 hours after an LP.
- Use of anticoagulant medication (warfarin, heparinoids, and direct coagulation factor inhibitors, e.g., apixaban, dabigatran, rivaroxaban) within 90 days before Day 1.
- X-ray, MRI, or myelographic evidence of significant lumbar spine abnormalities or other anatomical factors at or near the LP site that might have interfered with performance of LP.

Treatment History

10. Participation in any passive or active immunotherapy study targeting α-syn or other PD related protein.

Study Treatment, Dose, and Mode of Administration:

Cohorts of 8 participants were sequentially enrolled. Participants within each cohort were randomized to a single IV infusion followed, after a 12-week outpatient monitoring period, by 13 IV infusions (1 IV infusion every 4 weeks for 48 weeks) of BIIB054 or placebo in a 6:2 ratio.

Three dose cohorts were administered as follows:

- Cohort 1: BIIB054 250 mg or placebo
- Cohort 2: BIIB054 1250 mg or placebo
- Cohort 3: BIIB054 3500 mg or placebo

BIIB054 was supplied as a liquid drug product in 5-mL vials containing 250 mg of BIIB054 per vial. Commercially available saline, provided by the site, was used as placebo.

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Duration of Treatment and Follow-Up:

Total duration for each participant was approximately 77 weeks, consisting of the following:

- A Screening Visit within 5 weeks before study drug administration
- A single dosing day with an inpatient dosing/monitoring period through at least 8 hours after dosing
- An outpatient monitoring period of 12 weeks after the single dose
- A multiple dosing period of 48 weeks with an inpatient observation period through at least 1 hour after each administration
- A follow-up period of 12 weeks after the last administration of the study drug

Criteria for Evaluation:

Following is a description of all efficacy and safety assessments that were originally planned for this study.Primary Safety Endpoint:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)

Secondary Pharmacokinetics Endpoint:

- Serum BIIB054 PK parameters calculated after the first and fourth doses including the following:
  - Area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf})
  - Area under the concentration-time curve from time 0 to time tau over a dosing interval (AUC_{tau})
  - Maximum observed concentration (C_{max})
  - Time to reach C_{max} (T_{max})
  - Half-life ($t_{½}$)
  - Clearance (CL)
  - Volume of distribution at steady state (V_{ss})
  - Accumulation ratio (R)
  - Observed concentration at the end of dosing interval (C_{trough})

Secondary Immunogenicity Endpoint:

- Incidence of anti-BIIB054 antibodies in serum

[redacted]

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

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Statistical Methods:

Primary Safety Endpoint:

The safety population was defined as all participants who received at least 1 dose of study treatment (BIIB054 or placebo).

All safety data were summarized for the overall study period. In addition, it was planned to summarize overall summary of adverse events, and AEs by system organ class and preferred term for the single dose period; however, due to early termination of the study this was not provided.

All AEs and SAEs, clinical laboratory abnormalities, vital sign measurements, physical and neurological examination findings, 12 lead electrocardiogram (ECG) readings, disease activity by brain MRI metrics, body weight and Columbia Suicide Severity Rating Scale (C-SSRS) scores were evaluated for safety. Unless mentioned otherwise, all safety data, regardless if it was collected before or after PD medication, were summarized by treatment group and overall active group by visit, as appropriate.

Adverse events: The incidence of AEs was summarized using the primary system organ class or preferred term, or both, sorted by decreasing frequency of the overall active group. Within each system organ class or/and preferred term, the same participant was counted only once. Under the same system organ class or/and preferred term, the occurrence of the AE with the greatest severity was used in the calculation of incidence by severity. The incidence of AEs by maximum Common Toxicity Criteria for Adverse Events grade, SAEs, study drug related AEs, lumbar puncture-related AEs, radioligand-related AEs, AEs that led to study drug discontinuation, and AEs that led to study withdrawal by system organ class, preferred term, and treatment group were presented. The incidence of AEs within 2 hours from start of infusion was summarized by preferred term and visit for each treatment group.

Quantitative laboratory analyses: for numeric laboratory parameters, actual values, change and percent change from baseline were summarized by visit. Number of evaluable participants, mean, standard deviation, median, Q1, Q3, and minimum and maximum values were presented at each visit.

Qualitative laboratory and safety analyses: data from laboratory, MRI, and ECG findings were summarized using shift tables where appropriate. For hematology, blood chemistry and urinalysis, the number of participants with potentially clinically significant laboratory abnormalities postbaseline were summarized for select parameters.

Sample Size Calculations:

The sample size was not based on statistical considerations. A cohort of 8 participants (6:2 ratio, BIIB054:placebo) for Cohorts 1, 2, and 3 was considered adequate to characterize the safety, tolerability, and PK profile of a range of a single and 13 repeated doses of BIIB054. Participants who withdrew from the study prior to completing the Final Visit may have been replaced at the discretion of the Sponsor. A replacement participant received the same study

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treatment and dosage as the participant who discontinued treatment. A minimum number of 6 participants completing the Week 24 visit was required to complete each cohort.

Results:

Participant Accountability:

The first participant was randomized on 12 March 2019 and the last participant was randomized on 18 February 2020.

A total of 24 participants were enrolled and all received at least 1 dose of study treatment (BIIB054 or placebo): 6 participants each who received BIIB054 250 mg, 1250 mg, or 3500 mg, and 6 participants who received placebo.

A total of 17 participants completed the study treatment, and 16 participants completed the study. Treatment discontinuations and study withdrawals occurred at a similar rate in participants who received placebo, BIIB054 1250 mg, or BIIB054 3500 mg. There was no treatment discontinuation or study withdrawal in participants who received BIIB054 250 mg. There was no treatment discontinuation or study withdrawal due to a COVID-19 pandemic-related reason. Of the 8 participants (33.3%) who withdrew from the study, the most common reason was withdrawal by participant (4 participants [16.7%]), followed by study terminated by Sponsor (3 participants [12.5%]). There was one withdrawal (4.2%) due to an AE in a participant who received BIIB054 1250 mg.

All 24 participants received at least 1 dose of study treatment (BIIB054 or placebo) and were included in the Safety Population.

Demographics and Baseline Disease Characteristics:

Demographics in the Safety Population were typically similar among the treatment groups.

All participants were Asian. A higher proportion of male participants received placebo, BIIB054 250 mg, and BIIB054 1250 mg, with 66.7%, 83.3%, and 66.7% of male participants, respectively. In contrast, a higher proportion of female participants received BIIB054 3500 mg, with 66.6% of female participants. The average participant body mass index was similar between the treatment groups, with an overall mean (SD) of 23.78 (3.926) kg/m^2. Participant ages ranged from 45 to 78 years; participants who received placebo were slightly younger than the BIIB054-treated participants, with a mean (SD) age of 59.8 (12.95) years in participants who received placebo versus 63.6 (10.46) years old in BIIB054-treated participants. Other demographic characteristics were similar between the treatment groups.

[redacted]

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[redacted]

Immunogenicity:

Treatment with BIIB054 was not associated with production of anti-BIIB054 antibodies; none of the participants were positive for anti-BIIB054 antibodies at baseline or post-treatment.

Pharmacokinetics:

Measured serum concentrations of BIIB054 were proportional to the dose administered. After the first infusion of BIIB054, measured serum concentrations peaked at a median T_{max} ranging between 2.10 and 3.09 hours (across all doses) after the end of the infusion, and the mean CL was 0.01 L/h for all BIIB054 doses. Across all BIIB054 dose levels, mean AUC_{inf} after the first infusion was similar to the mean AUC_{tau} after repeated infusions; however, mean C_{max} after the first infusion was lower than mean C_{max} after repeated infusions. After repeated infusions, C_{max} normalized by dose was similar for each dose level (0.62, 0.48, and 0.54 in participants who received BIIB054 250 mg, 1250 mg, and 3500 mg, respectively). There was little accumulation following repeated infusions, with a mean R for C_{max} ranging between 1.36 and 1.60 between infusion 4 and infusion 1. The predose serum concentrations measured up to infusion 14 were consistent with C_{trough} described for infusion 4.

[redacted]

Safety:

Overall, BIIB054 was generally well tolerated at doses of 250 mg, 1250 mg, or 3500 mg. The safety profile was consistent with the results from Study 228PD201 and previously completed studies. There were no evident differences in tolerability of the different dose levels of BIIB054 used in this study.

There were no fatal events reported during the study, and only 2 participants (8.3% overall) experienced SAEs: [redacted] and [redacted] fracture in 1 participant, and acute cholecystitis in 1 participant. These SAEs were considered to be not related to the study drug, the LP, or the radioligand. Other than these SAEs, no other events of ≥ Grade 3 severity were reported. Treatment emergent adverse events (TEAEs) leading to discontinuation of study treatment and withdrawal from the study were experienced by 1 participant (4.2% overall), who experienced the TEAE of glossitis which was assessed by the Investigator to be related to the study drug.

All of the participants who received BIIB054, and the majority (83.3%) of the participants who received placebo, experienced at least 1 TEAE during the study. The profile of TEAEs experienced by participants during the study were typical of a population with PD who had undergone an LP procedure. The most common TEAE was

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worsening of PD, followed by back pain, insomnia, arthralgia, constipation, headache, hypertension, and postlumbar puncture syndrome. There were no meaningful differences in the incidence or profile of TEAEs experienced by participants who received different doses of BIIB054 compared with participants who received placebo. No participant experienced any COVID-19-related TEAE during the study.

Four participants (16.7% overall) who received BIIB054 experienced TEAEs assessed by the Investigator to be related to the study drug: 1 participant who received BIIB054 250 mg had urticaria, 1 participant who received BIIB054 1250 mg had gastritis and glossitis (3 TEAEs), and 2 participants who received BIIB054 3500 mg had events of diarrhea and decreased neutrophil count (1 participant) and headache (1 participant). These TEAEs were considered to be mild or moderate in severity, and all resolved by the end of the study. TEAEs considered to be related to the LP were experienced by 6 participants (25.0%); all of these TEAEs were considered to be mild in severity and all resolved.

Overall, treatment with BIIB054 was not associated with any clinically meaningful shifts from baseline over time for hematology, serum chemistry, urinalysis, vital sign, ECG, C-SSRS, or MRI parameters. One participant who received BIIB054 3500 mg experienced a TEAE of CTCAE Grade 1 decreased neutrophil count which was considered to be related to the study drug; no other laboratory results, vital signs, or physical examination findings met the definition of an AE.

Conclusion: BIIB054 is generally safe and tolerable up to 3500 mg in Japanese participants with early PD.

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Version: 1