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 Idec Inc.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Anti-LINGO-1 antibody (BIIB033)	**Name of Active Ingredient:** Anti-LINGO-1 antibody (BIIB033)	**Study Indication:** Multiple sclerosis

Title of Study:

A Randomized, Blinded, Placebo-Controlled, Serial-Cohort, Multiple Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of BIIB033 in Subjects With Multiple Sclerosis

Principal Investigator:

[redacted], MD
[redacted]
USA

Study Period:	**Phase of Development:**
Date of first treatment: 22 October 2010 End of Study Date: 25 April 2013	Phase 1

Study Objectives:

Primary objective:

- The primary objective of the study was to evaluate the safety and tolerability profile of 2 intravenous (IV) infusions of BIIB033 in patients with multiple sclerosis (MS).

Secondary objectives:

- Assess the repeated dose serum pharmacokinetic (PK) profile of BIIB033.
- Assess the repeated dose immunogenicity of BIIB033.
- Measure the concentration of BIIB033 in the cerebrospinal fluid (CSF).
- Explore potential biomarkers of BIIB033 activity in the periphery and in the central nervous system (CNS).
- Assess the tolerability of faster infusion rates at the highest tolerated dose established in the multiple-ascending dose (MAD) cohorts (if the highest tolerated dose was ≥30 mg/kg).

Study Design:

This was a Phase 1, randomized, blinded, placebo-controlled, MAD escalation study of 2 IV infusions of BIIB033 administered 2 weeks apart in MS subjects. This study included 7 MAD cohorts composed of 6 subjects each

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(4 BIIB033-treated subjects and 2 placebo-treated subjects). In addition, a single-dose cohort composed of 4 subjects (3 BIIB033-treated subjects and 1 placebo-treated subject) was used to test the tolerability of faster IV infusion at the highest tolerated dose tested in the MAD cohorts, if the highest tolerated dose was ≥30 mg/kg (the ≥30 mg/kg doses in the MAD cohorts were infused over 2 hr 45 min).

Doses administered to the MAD cohorts were as follows: Cohort 1, BIIB033 0.3 mg/kg or placebo; Cohort 2, BIIB0331.0 mg/kg or placebo; Cohort 3, BIIB033 3.0 mg/kg or placebo; Cohort 4, BIIB033 10 mg/kg or placebo; Cohort 5, BIIB033 30 mg/kg or placebo; Cohort 6, BIIB033 60 mg/kg or placebo; and Cohort 7, BIIB033 100 mg/kg or placebo.

Dose escalation in the MAD study progressed only after at least 1 cohort in the SAD study (215HV101) had received a dose of equivalent or greater exposure than the anticipated cumulative 2-dose exposure to be administered in the MAD study, or the SAD study had reached its highest dose at 100 mg/kg. Prior to each MAD dose escalation, a comprehensive safety and PK review from prior and current cohorts in the SAD (215HV101) and MAD studies was conducted to ensure the predicted MAD exposure did not exceed that observed in the SAD study.

The dose for the single-dose, faster infusion cohort was the highest tolerated dose established in the SAD study (215HV101) and the MAD cohorts of this study. Dosing for the single-dose, faster infusion cohort was initiated only after the tolerability of the 2 hr 45 min infusion for the highest dose in both the SAD and MAD studies was established. This was determined to be BIIB033 100 mg/kg.

The first 2 subjects within each MAD cohort were assigned to receive either active or placebo, and they were both dosed on the first day. The remaining subjects were dosed at least 2 hours apart to allow review of safety assessments conducted up to 2 hours postdose. No more than 2 subjects were dosed per day.

To allow review of safety assessments of 1 subject treated with active study treatment in the BIIB033 100.0 mg/kg single-dose, faster infusion cohort before the other 2 were dosed and to maintain the blind, the 4 subjects randomized in the single-dose cohort were dosed over 3 days as follows: the first subject randomized was dosed first, the second subject randomized was dosed the next day, and the third and fourth subjects randomized were dosed the subsequent day.

Number of Subjects (Planned and Analyzed):

Approximately 46 MS subjects were planned to be enrolled in the study; 47 subjects were enrolled and received at least 1 dose of study treatment and were analyzed as the safety population. Forty-six subjects completed the study. Twenty-eight subjects from the BIIB033-treated MAD cohorts and 3 subjects in the BIIB033 100 mg/kg single dose cohort were analyzed as the PK population. Fourteen placebo-treated subjects and 28 BIIB033-treated subjects in the MAD cohorts were evaluated for CSF biomarkers; 46 subjects (14 placebo, and 4 subjects each from the BIIB033-treated MAD cohorts and the BIIB033 100 mg/kg single-dose, faster infusion cohort) were evaluated for imaging biomarkers.

Study Population:

Main inclusion criteria:

- Aged 18 to 60 years old, inclusive, at the time of informed consent.
- Diagnosed with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) as defined by the

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revised McDonald Committee criteria ([Polman 2005]. Note: Treatment with any IFN -beta OR glatiramer acetate (GA) was allowed to continue during the study as long as the initiation of treatment was at least 3 months prior to study entry.

- Expanded Disability Status Score (EDSS) between 1.0 and 6.0, inclusive.
- Body mass index (BMI) of 18 to 30 kg/m^2, inclusive.

Main exclusion criteria:

- Diagnosis of primary progressive MS (as defined by the revised McDonald's criteria).
- An MS relapse that had not resolved within 30 days prior to screening.
- Any condition or circumstance that, in the opinion of the Investigator, contraindicated MRI scans or lumbar puncture (LP). Note: All screening LP symptoms were required to be resolved prior to randomization.
- History of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic (except MS), dermatologic, psychiatric, renal, severe allergic or anaphylactic reactions, or other major disease, as determined by the Investigator.
- Had a laboratory value at Screening or Day -1 that was outside the normal range, unless it was judged by the Investigator as not clinically significant after appropriate evaluation.
- Clinically significant (as determined by the Investigator) 12-lead electrocardiogram (ECG) abnormalities, including corrected QT interval using Bazett's correction method (QTcB) of >450 msec for males and >470 msec for females.

Study Treatment, Dose, Mode of Administration, Lot Numbers:

BIIB033 was supplied as a liquid drug in vials of 5 mL, with an extractable dose of 250 mg BIIB033 per vial. BIIB033 contained 50 mg/mL BIIB033 (anti-LINGO-1 IgG1 mAbs of approximately 144.4 kDa), 10 mM sodium citrate, 160 mM L arginine hydrochloride, and 0.03% (w/v) polysorbate 80, at pH 6.5.

The label included conditions for storage, lot number, and other pertinent information such as manufacturer, lot number, and caution statement. BIIB033 was not to be used after the expiration date. The lot numbers of BIIB033 used in this study were 34-10-033, 34-10-042, 34-11-120, and 45-10-018.

The placebo (control agent) used in this study was sterile normal saline (0.9% w/v of sodium chloride), supplied by the investigational site. The manufacturer's directions for material storage and handling were followed, as are standard clinical practices for ensuring sterility of the material.

Duration of Treatment and Follow-Up:

Treatment period:

Subjects in the MAD cohorts participated in the study for up to 20 weeks, including a 4-week screening period and a 2-week treatment period during which 2 doses of BIIB033 or placebo were administered. Subjects in the BIIB 100 mg/kg single-dose cohort had a treatment period consisting of a single dose administration (at an increased infusion rate) of BIIB033/placebo followed by a 48-hour postdosing inpatient observation period.

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Follow-up period:

For the MAD cohorts, after completing inpatient follow-up after the first (Day 2) and the second (Day 16) doses, subjects had evaluations performed in the outpatient setting at Day 7 and at specified intervals from Week 3 through Week 16 or Week 20 (or longer), depending on the dose. During this time, the subjects were required to return periodically to the clinic for tests and assessments.

For the single-dose, faster infusion cohort, after completing inpatient follow-up after the single dose (Day 2), subjects had evaluations performed in the outpatient setting at Day 7 and at specified intervals from Day 13 through Week 16 or Week 20 (or longer), depending on the follow-up schedule determined for the MAD cohort of the established highest dose. During the follow-up period, subjects were required to return periodically to the clinic for tests and assessments.

Based on review of emerging safety data, a serum BIIB033 $t_{½}$ of approximately 2 to 3 weeks determined in Study 215HV101, and from PK data accrued during this MAD study, the follow-up period was shortened from 24 weeks to 16 weeks after the last dose.

Criteria for Evaluation:

Safety

Criteria for evaluation of safety including the following:

- Incidence and types of adverse events (AEs)
- Incidence of serious adverse events (SAEs)
- Changes from baseline in clinical laboratory assessments and vital signs
- Changes from baseline in other safety measures: physical and neurological examinations, brain magnetic resonance imaging (MRI; change in combined unique lesions defined as the number of new and enlarging T2 lesions), and electrocardiograms (ECGs).

Pharmacokinetics (PK)

The following PK parameters were determined from serum concentrations of BIIB033 using noncompartmental analysis:

- Area under the concentration curve for a dosing interval (AUC_{tau})
- Area under the concentration curve from time extrapolated to infinity (AUC_{inf}) for total doses
- Maximum observed concentration (C_{max})
- Time to reach maximum observed concentration (T_{max})
- Terminal elimination half -life ($t_{½}$)
- Clearance (CL) for total doses
- Volume of distribution at steady state (V_{ss}) for total doses

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Immunogenicity

Incidence of anti-BIIB033 serum antibodies was determined for evaluation of potential immunogenicity for repeat-dose BIIB033.

Pharmacodynamics (PD)

Exploratory molecular biomarkers evaluated from CSF in the MAD cohorts included neurofilament-light, total soluble LINGO-1, and free soluble LINGO-1.

Exploratory axonal and myelin imaging was measured by MRI, which included magnetic transfer ratio (MTR) and diffusion tensor imaging (DTI). Change in brain volumes was also analyzed.

Statistical Methods:

Descriptive statistics were used for summaries of subject accountability, demographics, baseline disease characteristics, baseline MRI measurements, and concomitant treatments; these results were summarized by treatment group. The subjects on placebo in each cohort were combined and counted as a single group.

All treatment emergent AEs and SAEs, clinical laboratory abnormalities, vital signs, physical and neurological examinations, ECG and continuous cardiac monitoring, and brain MRI were evaluated for safety and compared with placebo. The data from the subjects on placebo were accumulated and counted as a single group. The incidence of treatment emergent AEs, SAEs, discontinuations of study treatment due to an AE, and withdrawal from study due to an AE were summarized by treatment group (placebo, and BIIB033 [each dosing group and total]), by severity, and by relationship to study treatment. Shift tables were used to evaluate changes in clinical laboratory parameters and ECGs. Summary statistics were applied to abnormalities relative to baseline for vital signs and physical examination findings. Immunogenicity data and the number of new Gd-enhancing T1 lesions, and new and enlarging T2 lesions by treatment group were provided as subject listings.

Summary statistics were presented for serum BIIB033 PK parameters by treatment group. The individual and mean serum BIIB033 concentration values were plotted over time in both linear and semilogarithmic scales.

Because of the scope and the small sample size of this study, all potential biomarkers (molecular and imaging) were considered exploratory. Although the data were not necessarily normally distributed, for an exploratory purpose, Student's t-test was used to compare the treatment difference between placebo and a BIIB033 dose group. If there were <3 subjects in any comparison group, there was no statistical test, and only the summary statistics were presented. For exploratory molecular biomarkers, summary statistics of net change (postdose minus baseline) and fold change (postdose/baseline) were presented by treatment group. For imaging biomarkers, summary statistics of net change (postdose minus baseline) and fold change (postdose/baseline) of multiple potential imaging biomarkers were presented by treatment group. The measurement at the Screening Visit was considered as baseline.

Results:

Subject disposition:

Forty-seven subjects were enrolled in the study and randomized to 7 MAD dosing cohorts and 1 single-dose, faster infusion cohort. All 47 subjects were dosed with study treatment, which comprised the safety population. Of the 47 subjects enrolled, randomized and dosed, 46 subjects completed the study. One placebo-treated subject

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withdrew consent and did not complete the study, and 1 subject from the BIIB033 100.0 mg/kg single dose, faster infusion cohort discontinued study treatment due to an AE of hypersensitivity.

- The safety population comprised 47 subjects.
- The PK population comprised 28 subjects from the BIIB033-treated MAD cohorts and 3 subjects in the BIIB033 100 mg/kg single dose cohort.
- Molecular biomarkers in the CSF were evaluated in 14 placebo-treated subjects and 28 BIIB033-treated subjects in the MAD cohorts.
- Imaging biomarkers were evaluated in 46 subjects (14 placebo, and 4 subjects each from the BIIB033-treated MAD cohort and the BIIB033 100.0 mg/kg single-dose, faster infusion cohort).

Demographics and baseline disease characteristics:

- The subjects were predominantly female (77%) and white (94%).
- The median age was 50 years (range, 24.0 to 60.0 years, inclusive).
- Median height, weight, and body mass index were 170.00 cm (range, 156.0 to 190.0 cm), 67.80 kg (range, 48.4 to 102.3 kg), and 27.77 kg/m^2 (range, 21.9 to 29.8 kg/m^2), respectively.
- Most subjects (83%) had RRMS whereas 8 subjects (17%) had SPMS.
- Most subjects (77%) at screening had no relapses during the past 12 months; 11 subjects (23%) at screening had 1 relapse during the past 12 months.
- The median time since the last relapse at Screening was 131.6 weeks (range, 10.7 to 859.0 weeks).
- The median EDSS score at screening was 3.00 (range, 1.0 to 6.0).
- Most subjects (85%) had EDSS walking distance of ≥500 meters.
- Most subjects had no T1 Gd-enhancing lesions (89%).

Pharmacokinetics:

- Serum BIIB033 exposure increased in an approximately dose-proportional manner with the percent coefficients of variation (%CV) for AUC_{tau} and C_{max} ranged between 1% and 29%. The mean $t_{1/2}$ values ranged from 15 to 24 days. The mean estimated V_{ss} values ranged from 5.44 to 7.84 L, suggesting that BIIB033 may be largely confined to the vascular and interstitial spaces and that significant target density does not appear to exist within the BIIB033 distribution volume. The mean CL values were approximately 0.14 to 0.26 L/day. Both V_{ss} and CL values for BIIB033 are similar to the estimated population V_{ss} and CL values for other IgG monoclonal antibody drugs.
- The mean CSF/serum BIIB033 concentration ratios ranged between 0.030% and 0.13%, with the exception of a mean ratio of 0.22% at the 10 mg/kg dose level, which is not consistent with the trend from other dose levels.
- Doses ≥3 mg/kg or ≥10 mg/kg resulted in mean serum BIIB033 concentrations greater than or equal to the estimated serum concentrations of anti-LINGO-1 mAb associated with 50% (EC_{50}) and 90% (EC_{90}),

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respectively, of maximum remyelinating response in the rat lysolecithin-induced demyelination spinal cord model.

- No apparent effect of either IFN-beta or GA was observed on serum BIIB033 PK.

Pharmacodynamics:

- Neurofilament-light levels in the CSF of BIIB033-treated subjects remained unchanged relative to those of placebo-treated subjects.
- At BIIB033 doses ≥10 mg/kg, total soluble LINGO-1 levels in the CSF, measured 2 weeks after the second dose, increased significantly relative to baseline, suggesting target engagement.
- No differences or trends in any of the imaging biomarkers were observed for BIIB033-treated subjects compared with placebo-treated subjects.

Results (continued):

Safety:

- BIIB033, given as 2 IV ascending doses of 0.3 mg/kg to 100 mg/kg or as a single, faster infusion dose of 100.0 mg/kg, was well tolerated by subjects with RRMS or SPMS.
- There were no SAEs and no deaths reported during the study.
- One subject in the BIIB033 100 mg/kg single-dose, faster infusion cohort discontinued study treatment due to an AE of hypersensitivity, considered moderate in severity and related to study treatment.
- The safety profile was comparable between the BIIB033- and placebo-treated cohorts (overall incidence of AEs, 69% and 67%, respectively). The incidence of AEs showed no dose-dependent response.
- The incidence of AEs by SOC and PT was comparable between BIIB033- and placebo-treated subjects.
- The majority of AEs were considered mild or moderate in severity and not related to study treatment. Only 1 AE (migraine, BIIB033 30 mg/kg) was considered severe, but not related to study treatment.
- Analysis of other safety parameters showed no abnormalities in clinical laboratory evaluations, vital signs, physical examinations, and ECGs that were considered clinically significant or reported as AEs.
- No significant immune response was raised in the presence of BIIB033.

- **Conclusions:** BIIB033, administered by IV twice at doses from 0.3 mg/kg to 100 mg/kg and as a single dose of 100 mg/kg at a faster infusion rate, was well tolerated by subjects with RRMS and SPMS. The safety profile was similar to that observed in a previous study in healthy volunteers.
- BIIB033 pharmacokinetics were linear, with typical low target-mediated disposition IgG values that included a small volume of distribution, minimal apparent target-mediated clearance, and a terminal elimination half-life of approximately 2 to 3 weeks.
- Although brain penetration of BIIB033 in humans is expected to be low (~0.1%), IV infusion of doses ≥ 3

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mg/kg in MS subjects yielded serum concentrations anticipated to result in pharmacological activity.

- At BIIB033 doses ≥10 mg/kg, total soluble LINGO-1 levels in the CSF increased significantly relative to baseline, suggesting target engagement.

Publication(s) Based on the Study: Not applicable.

Date of Report: 10 May 2013