Randomized phase I trials of the safety/tolerability of anti-LINGO-1 monoclonal antibody BIIB033

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ABSTRACT

Objective: To evaluate the safety, tolerability, and pharmacokinetics (PK) of BIIB033 (anti-LINGO-1 monoclonal antibody) in healthy volunteers and participants with multiple sclerosis (MS).

Methods: In 2 separate randomized, placebo-controlled studies, single ascending doses (SAD; 0.1–100 mg/kg) of BIIB033 or placebo were administered via IV infusion or subcutaneous injection to 72 healthy volunteers, and multiple ascending doses (MAD; 0.3–100 mg/kg; 2 doses separated by 14 days) of BIIB033 or placebo were administered via IV infusion to 47 participants with relapsing-remitting or secondary progressive MS. Safety assessments included adverse event (AE) monitoring, neurologic examinations, conventional and nonconventional MRI, EEG, optical coherence tomography, retinal examinations, and evoked potentials. Serum and CSF PK as well as the immunogenicity of BIIB033 were also evaluated.

Results: All 72 healthy volunteers and 47 participants with MS were included in the safety analyses. BIIB033 infusions were well tolerated. The frequency of AEs was similar between BIIB033 and placebo. There were no serious AEs or deaths. No clinically significant changes in any of the safety measures were observed. BIIB033 PK was similar between healthy volunteers and participants with MS. Doses of ≥10 mg/kg resulted in BIIB033 concentrations similar to or higher than the concentration associated with 90% of the maximum remyelination effect in rat remyelination studies. The incidence of anti-drug antibody production was low.

Conclusions: The emerging safety, tolerability, and PK of BIIB033 support advancing BIIB033 into phase II clinical development as a potential treatment for CNS demyelination disorders.

Classification of evidence: This study provides Class I evidence that BIIB033 is well tolerated and safe (serious adverse event rate 0%, 95% confidence interval 0–7.6%). *Neurol Neuroimmunol Neuroinflammation* 2014;1:e18; doi: 10.1212/NXI.0000000000000018

GLOSSARY

AE = adverse event; **AUC** = area under the time-concentration curve; **C_{max}** = maximum serum concentration; **DTI** = diffusion tensor imaging; **Gd** = gadolinium; **Ig** = immunoglobulin; **mAb** = monoclonal antibody; **MAD** = multiple ascending dose; **MS** = multiple sclerosis; **MT** = magnetization transfer; **MTR** = magnetization transfer ratio; **NAWM** = normal-appearing white matter; **PK** = pharmacokinetics; **RRMS** = relapsing-remitting MS; **SAD** = single ascending dose; **SC** = subcutaneous; **SPMS** = secondary progressive MS; **SSEP** = somatosensory evoked potential; **$t_{1/2}$** = half-life; **T_{max}** = time to maximum serum concentration; **VEP** = visual evoked potential; **V_{SS}** = steady-state volume of distribution.

Currently available therapies for multiple sclerosis (MS) do not facilitate remyelination or axonal repair in the CNS. These processes are hypothesized to be actively suppressed by signaling pathways that are potential targets for pharmacologic interventions.[1] One such signaling pathway involves leucine-rich repeat and immunoglobulin (Ig) domain-containing neurite outgrowth inhibitor Nogo receptor-interacting protein-1 (LINGO-1), a glycoprotein selectively expressed in neurons and oligodendrocyte progenitor cells in the CNS.[2–4] LINGO-1 negatively regulates myelination through distinct mechanisms involving activation of RhoA-GTPase[5] as well as

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Supplemental data
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nerve growth factor and the tyrosine kinase A receptor.[6] Blockade of LINGO-1 has been shown to result in remyelination in various animal models of CNS demyelination.[4,7]

BIIB033 is a human aglycosyl IgG1 monoclonal antibody (mAb) that binds LINGO-1 with high affinity and specificity and is being developed as an investigational product to lead to remyelination and axonal protection and/or repair in patients with MS.[4] Although CNS penetration of anti-LINGO-1 mAbs is limited,[8] the CNS-specific expression of LINGO-1 created an opportunity to deliver efficacious concentrations of BIIB033 by giving high doses systemically. We conducted the first-in-human studies to evaluate the safety and tolerability of BIIB033 in healthy volunteers and participants with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS). Serum and CSF pharmacokinetics (PK) as well as immunogenicity of BIIB033 were also evaluated in both studies. Finally, conventional and nonconventional MRI (magnetization transfer [MT] and diffusion tensor imaging [DTI][9]) was used to evaluate the safety of BIIB033 in both studies and as a pilot exploratory efficacy endpoint for preexisting brain lesions in the multiple ascending dose (MAD) study.

METHODS **Study designs.** Two randomized, blind, placebo-controlled phase I studies were conducted: the single ascending dose (SAD) study in healthy volunteers (ClinicalTrials.gov identifier NCT01052506) and the MAD study in participants with RRMS or SPMS (ClinicalTrials.gov identifier NCT01244139). In the SAD study, eligible healthy adult participants were randomized 3:1 to receive single doses of BIIB033 (IV: 0.1, 0.3, 1.0, 3.0, 10, 30, 60, or 100 mg/kg; subcutaneous [SC]: 3.0 mg/kg; n = 6 each, total N = 54) or IV placebo (0.9% saline; total N = 18). In the MAD study, eligible adult participants with MS were randomized 2:1 to receive IV BIIB033 (n = 4 each at 0.3, 1.0, 3.0, 10, 30, 60, and 100 mg/kg; total N = 28) or placebo (total N = 14); the 2 doses were given 12–14 days apart. A single-dose group (n = 5; 4 BIIB033 and 1 placebo) was added to assess the tolerability of 100 mg/kg at a faster infusion rate (80 minutes instead of 2.75 hours). Both studies were conducted in a staggered fashion in which available safety and PK data from the SAD study were evaluated prior to dose escalation in the MAD study.

In both studies, participants and study site personnel were blinded to treatment assignment. An unblinded study pharmacist prepared study treatments and randomized participants according to a randomization code developed by Biogen Idec but was not involved in assessments.

Participants. The SAD study was conducted at one site in the Netherlands and one site in the United States. Eligible participants (aged 25–55 years) were healthy and had a body mass index of 18–30 kg/m². Male participants were required to practice contraception for ≥6 months from the first study medication dose;

females of childbearing potential were not eligible. Key exclusion criteria included history of any clinically significant systemic disease; abnormal laboratory tests or ECGs; history or positive test for HIV, hepatitis C, or hepatitis B virus; treatment with any prescription medication (<28 days before screening) or over-the-counter products (14 days before screening); history of alcohol or substance abuse; and regular use of any tobacco product within 3 months of screening.

The MAD study was conducted at one site in the United States. Eligible participants (aged 18–60 years; body mass index of 18–30 kg/m²) were diagnosed with RRMS or SPMS (revised 2005 McDonald criteria[10]) and had an Expanded Disability Status Scale[11] score between 1.0 and 6.0 at screening. Male and female participants of childbearing potential were required to practice contraception during the study and for ≥6 months after the last study medication dose. In addition to the key exclusion criteria listed above for the SAD study, participants were ineligible if they had any of the following: a relapse that had not resolved within 30 days of screening; allergy or intolerance for gadolinium (Gd) contrast agents; prior treatment with total lymphoid irradiation, T cell or T-cell receptor vaccination, alemtuzumab, mitoxantrone, cyclophosphamide, cladribine, rituximab, or fingolimod; treatment within 12 months with one of the following: natalizumab, daclizumab, azathioprine, methotrexate, IV Ig, plasmapheresis, or mycophenolate mofetil; or treatment within 1 month with high-dose oral or IV steroids.

Standard protocol approvals, registrations, and patient consents. The SAD and MAD study protocols were reviewed and approved by the local institutional review boards. The studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the European Union Clinical Trial Directive 2001/20/EC, and the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Safety and tolerability assessments. In both studies, evaluation of the safety and tolerability of BIIB033 was the primary objective (Class I evidence). Clinical safety measures included physical and neurologic examinations, vital signs, ECGs, and treatment-emergent adverse events (AEs). Laboratory measures included hematology, blood chemistry, and urinalysis. In the SAD study, brain MRI scans with MT ratio (MTR) were performed at weeks 4 and 8. The MTR was used to measure the integrity of the cerebral white matter in 6 regions of normal-appearing white matter (NAWM). To test for any potential neurologic effects in the SAD study, visual evoked potentials (VEPs), somatosensory evoked potentials (SSEPs; performed in one leg and one arm), EEGs, and retinal examination with optical coherence tomography and photography were also assessed (see appendix e-1 at Neurology.org/nn). In the MAD study, conventional brain MRI (T1-weighted with and without Gd enhancement, T2-weighted), and quantitative MRI sequences (MTR and DTI) were performed at weeks 8 and 16. The MTR and DTI of preexisting lesions and nonlesional NAWM were used as exploratory endpoints to assess short-term treatment safety and efficacy. Changes in brain volume were also analyzed. Detailed information on MRI methods is provided in appendix e-1.

For VEPs and SSEPs, abnormalities signifying pathology are typically regarded as values falling 2.5–3 SD above values for age-matched control samples from the normal population. However, for the purposes of the current study, this was considered insufficiently sensitive to detect presymptomatic changes. Therefore, a more appropriate basis was used based on protocols applied to intraoperative monitoring in which an increase of ≥10% in the latency of the evoked potential or a decrease of ≥50% in its
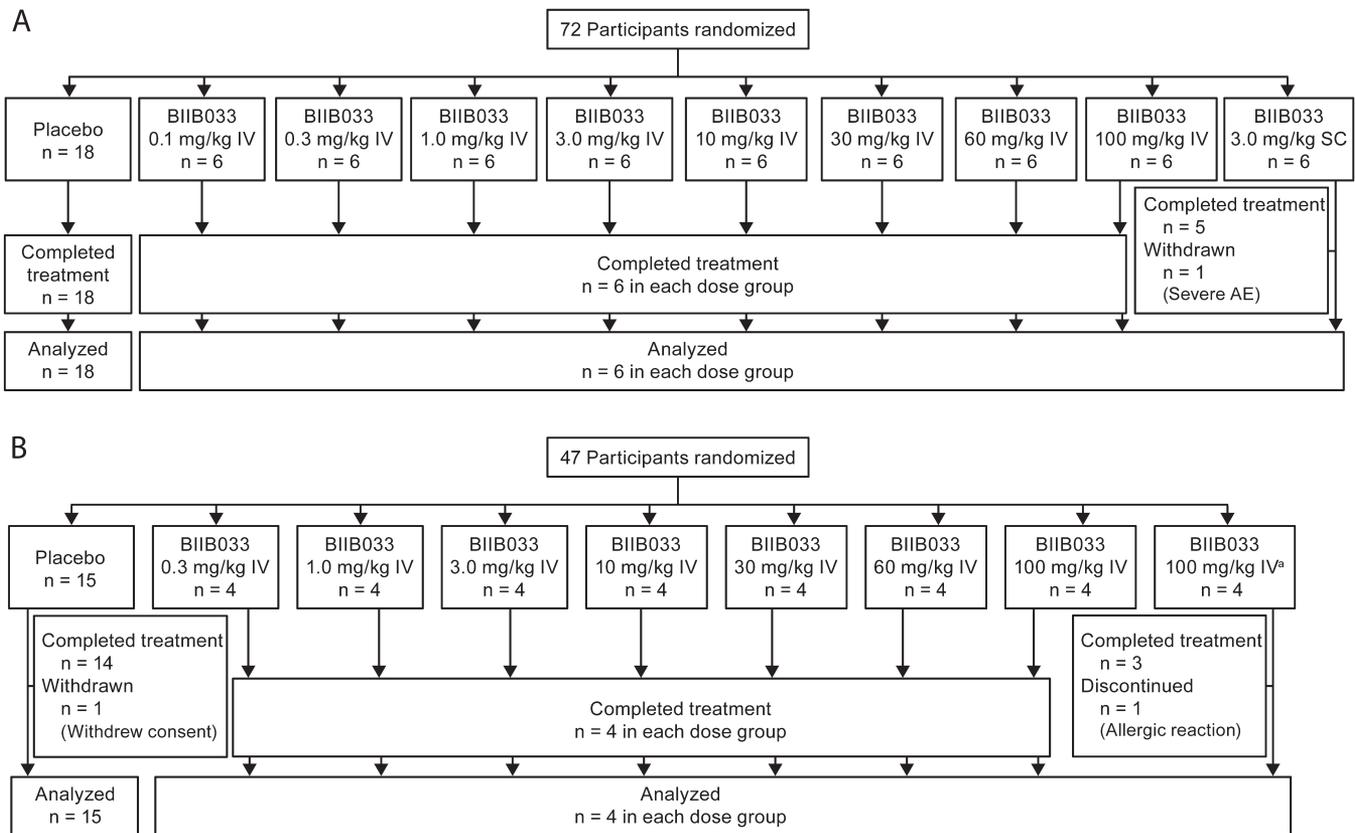
(A) Single ascending dose study and (B) multiple ascending dose study. Abbreviations: AE = adverse event; SC = subcutaneous. [a] 80-minute infusion time.

amplitude was considered "abnormal." Determinations of abnormalities for results of EEG, brain MRI, and retinal examinations were each made by expert interpretation of specialists (EEG: neurologist/electrophyisologist; brain MRI: neuroradiologist; retinal examination: neuro-ophthalmologist).

Immunogenicity. In both studies, immunogenicity (a secondary endpoint) was tested by analyzing serum anti-BIIB033 antibody levels using biotin- and digoxigenin-labeled BIIB033 in an ELISA of blood samples collected at baseline (predose), at various times during the treatment period, and at the end of treatment or discontinuation (Assay Services Laboratory [Biogen Idec], Cambridge, MA). In predose testing, this assay had a 5% false-positive rate.

PK assessments. Evaluation of serum and CSF PK was a secondary objective in both studies. Serial PK blood samples for the measurement of serum BIIB033 concentration were collected for up to 16 weeks after dosing. Serum concentrations were determined with an ELISA using anti-BIIB033 2H09 (performed by Assay Services Laboratory). Serum PK values were estimated using noncompartmental analysis (Phoenix WinNonlin 6.2.1, Pharsight, St. Louis, MO) and included maximum serum concentration (C_{max}), time to maximum serum concentration (T_{max}), area under the time-concentration curve from time extrapolated to infinity (AUC_{inf}) for the SAD study or AUC over a dosing interval (AUC_{tau}) for the MAD study, terminal elimination half-life ($t_{1/2}$), clearance, and steady-state volume of distribution (V_{ss}).

The CSF samples for the measurement of BIIB033 concentration were collected by lumbar puncture at baseline and 2 weeks postdose in the SAD study in healthy volunteers (for doses between 10 mg/kg

and 100 mg/kg IV and 3 mg/kg SC) or 2 weeks after the second/last dose in the MAD study in participants with MS (for all dose levels). Concentrations of BIIB033 in CSF were determined using immuno-PCR (Imperacer, Chimera Biotec, Dortmund, Germany).

Statistical analyses. All safety analyses were performed on the safety population, defined as all participants who were randomized and dosed with study medication. All AEs, serious AEs, clinical laboratory abnormalities, vital signs, physical and neurologic examinations, ECG and continuous cardiac monitoring, VEPs, SSEPs, EEG, retinal examinations, and brain MRI in each group were evaluated and compared with those given placebo. Data from participants on placebo were counted as a single group in each study. All PK analyses were performed on the PK population, which included all randomized participants who received study medication and had measurable BIIB033 concentrations.

RESULTS Demographics and participant disposition. Of the 72 healthy volunteers enrolled, randomized, and dosed in the SAD study between January 2010 and October 2011, 71 completed the study (figure 1). One participant in the 3.0-mg/kg SC group was withdrawn owing to severe AEs (affective disorder and toxicity) after consuming amphetamines and alcohol (protocol violation). Of the 47 participants with MS who were dosed in the MAD study between October 2010 and April 2012, 46 completed the study. One

Table 1   Adverse events

Variable	Placebo (N = 18)	SAD study, BIIB033 dose, mg/kg									Total BIIB033 (N = 54)
		0.1 (n = 6)	0.3 (n = 6)	1.0 (n = 6)	3.0 (n = 6)	10 (n = 6)	30 (n = 6)	60 (n = 6)	100 (n = 6)	3.0[a] (n = 6)	
Any AE, n (%)	14 (78)	6 (100)	5 (83)	4 (67)	4 (67)	3 (50)	2 (33)	4 (67)	3 (50)	3 (50)	34 (63)
Most frequent AEs,[b] n (%)											
Headache	4 (22)	4 (67)	2 (33)	2 (33)	0	2 (33)	0	0	0	0	10 (19)
URTI	4 (22)	0	0	0	1 (17)	1 (17)	0	2 (33)	1 (17)	1 (17)	6 (11)
Nasopharyngitis	0	2 (33)	1 (17)	1 (17)	0	0	0	0	0	0	4 (7)
Gastroenteritis	0	0	2 (33)	0	0	0	0	0	0	1 (17)	3 (6)
Dizziness	2 (11)	0	0	0	0	0	0	0	0	0	0
Variable	Placebo (N = 15)	MAD study, BIIB033 dose, mg/kg									Total BIIB033 (N = 32)
		0.3 (n = 4)	1.0 (n = 4)	3.0 (n = 4)	10 (n = 4)	30 (n = 4)	60 (n = 4)	100 (n = 4)	100[c] (n = 4)		
Any AE, n (%)	10 (67)	4 (100)	3 (75)	3 (75)	1 (25)	3 (75)	4 (100)	2 (50)	2 (50)		22 (69)
Most frequent AEs,[b] n (%)											
Urinary tract infection	2 (13)	3 (75)	0	0	0	1 (25)	0	1 (25)	0		5 (16)
Headache	2 (13)	1 (25)	2 (50)	1 (25)	0	0	0	0	1 (25)		5 (16)
URTI	3 (20)	0	3 (75)	0	0	0	0	0	0		3 (9)
MRI, n (%)											
New Gd+ lesions at end of study	1 (7)	0	1 (25)	0	0	1 (25)	0	0	0		2 (6)
New T2 hyperintense lesions at end of study	2 (13)	0	0	0	0	2 (50)	0	0	0		2 (6)

Abbreviations: AE = adverse event; Gd+ = gadolinium enhancing; MAD = multiple ascending dose; SAD = single ascending dose; URTI = upper respiratory tract infection.

[a] Subcutaneous dose.

[b] Occurring in ≥2 participants in any dose group within each study.

[c] Single dose, shorter infusion time (80 minutes).

participant in the placebo group withdrew consent (relocated). Overall, SAD participants were about 10 years younger (mean ± SD, 36.7 ± 9.6 years) than MAD participants (mean ± SD, 47.7 ± 8.8 years). A notably larger percentage of participants were female in the MAD vs SAD studies (77% vs 10%) due to exclusion of females of childbearing potential from the SAD study. Other baseline demographic and clinical characteristics for SAD and MAD participants are presented in table e-1.

Clinical safety. About two-thirds of participants experienced ≥1 AE during the course of the SAD and MAD studies (table 1). There were no serious AEs or deaths during either study. The most commonly reported AEs in both studies were headache, upper respiratory tract infection, nasopharyngitis, gastroenteritis, and urinary tract infection. In the MAD study, 1 participant in the single-dose 100-mg/kg group with shorter infusion time discontinued treatment due to an allergic reaction. This reaction fully resolved within 1 hour; the participant was treated with antihistamines and completed the study.

For both studies, there were no clinically significant changes in physical examination findings, vital signs, or ECGs. Results from laboratory tests showed that, although there were some sporadic shifts in hematology, blood chemistry (table e-2), and urinalysis results, none were considered to be an AE or clinically significant, and there were no differences in clinical and laboratory safety results for BIIB033- vs placebo-treated participants.

In the SAD study, occasional shifts to abnormal were noted for neurologic examinations, VEPs, SSEPs, EEG, brain MRI, and retinal examinations (table e-3), although none were considered clinically significant and none were considered an AE. Shifts to abnormal for neurologic examinations were as follows: BIIB033-treated participants, motor (n = 2, 4%), coordination (n = 1, 2%), sensory (n = 1, 2%); placebo-treated participants, sensory (n = 1, 6%).

Immunogenicity. In the SAD study, 3 participants tested positive for anti-BIIB033 antibodies: 1 in the BIIB033 3.0-mg/kg IV group (week 4 only), 1 in the BIIB033 100-mg/kg IV group (day 0 only), and 1 in the placebo group (week 4 and end of study). In the MAD study, 1 placebo-treated participant had positive results for anti-BIIB033 antibodies at days 0 and 14.

Serum pharmacokinetics. After IV infusion, serum BIIB033 concentration-time profiles in the PK population of both the SAD study (n = 53) and MAD study (n = 31) showed a multi-exponential decrease (figure 2, A and B). The PK values were similar between healthy adults (table 2) and participants with MS (tables 3 and e-4). In both studies, serum BIIB033 exposure (AUC, C_{max}) increased in an approximately dose-proportional manner and mean $t_{1/2}$ values spanned from 15 to 24 days (tables 2 and 3). The mean estimated values for V_{ss} and mean values for clearance were both low. In the MAD study, serum BIIB033 PK was not detectably affected by concomitant treatment with interferon-β (n = 12) or glatiramer acetate (n = 14; table e-5). The C_{max} and T_{max} values for 100 mg/kg at the faster IV infusion rate (80 minutes) were similar to those observed for the 2.75-hour infusion, indicating that the PK was not affected by the duration of infusion.

Figure 2 Mean serum concentrations of BIIB033 vs time
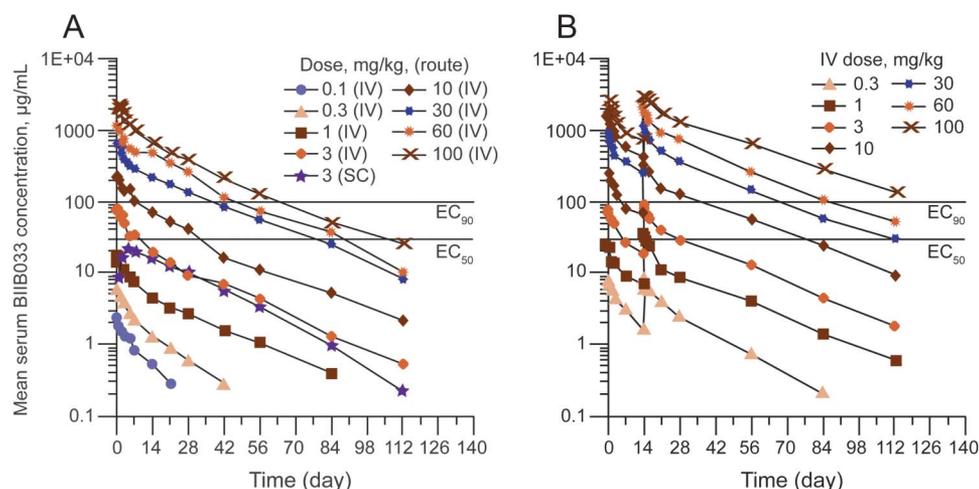
(A) Single ascending dose study and (B) multiple ascending dose study. EC_{50} and EC_{90} values determined in rat lysolecithin-induced demyelination spinal cord model; values adjusted for 0.1% brain penetration. Abbreviations: EC_{50} and EC_{90} = 50% and 90% maximal effective concentrations; SC = subcutaneous.

Table 2 Serum pharmacokinetic measures of noncompartmental analysis by dose for the SAD study[a]

	BIIB033 dose, mg/kg								
	0.1	0.3	1.0	3.0	10	30	60	100	3.0[b]
C_{max}, μg/mL	2.49 (0.52)	7.13 (0.89)	18.41 (3.79)	95.10 (15.61)	270.06 (73.62)	723.11 (128.17)	1,240.77 (150.12)	2,245.72 (325.87)	21.81 (2.95)
T_{max}, h	3.50 (1.02–7.00)	3.00 (1.00–7.00)	2.08 (1.00–3.00)	5.30 (2.00–13.00)	2.54 (1.07–25.00)	4.25 (2.82–26.75)	4.75 (2.82–14.75)	2.82 (2.82–4.75)	120.55 (71.48–194.08)
AUC_{inf}, d × μg/mL	21.07 (3.12)	61.45 (12.54)	221.22 (89.45)	1,020.52 (175.13)	3,279.55 (427.82)	11,482.65 (2,355.52)	19,317.85 (2,131.20)	32,943.73 (2,775.00)	665.30 (50.75)
CL, L/d	0.39 (0.08)	0.41 (0.06)	0.34 (0.14)	0.25 (0.06)	0.23 (0.06)	0.20 (0.06)	0.22 (0.04)	0.25 (0.02)	0.34 (0.04)
$t_{1/2}$, d	8.91 (1.91)	9.78 (2.12)	14.84 (5.03)	15.36 (4.80)	21.65 (2.94)	20.76 (4.18)	19.03 (4.79)	21.77 (2.31)	14.73 (1.28)
V_{ss}, L	4.75 (0.95)	5.49 (0.66)	6.56 (1.31)	5.32 (1.13)	5.41 (0.94)	5.61 (1.36)	5.57 (1.16)	6.49 (0.78)	—

Abbreviations: AUC_{inf} = area under the time-concentration curve extrapolated to infinity; CL = clearance; C_{max} = maximum concentration; SAD = single ascending dose; $t_{1/2}$ = half-life; T_{max} = time of occurrence of C_{max}; V_{ss} = volume of distribution at steady state.
[a] Data are geometric means and SDs except for T_{max} (median, range).
[b] Subcutaneous dose.

After SC administration, absorption of BIIB033 was slow, with a median T_{max} of 121 hours (~5 days). However, the mean terminal $t_{1/2}$ was about 15 days, which is comparable to that observed after IV dosing. The absolute bioavailability of the 3.0-mg/kg SC dose was estimated to be 65%. In the only participant who was found to have anti-drug antibodies during treatment with BIIB033 (SAD study, week 4), no effects on serum PK were evident.

CSF pharmacokinetics. The CSF-to-serum BIIB033 concentration ratios obtained at 2 weeks postdose were highly variable, with interparticipant variability ranging between 43% and 76% in healthy volunteers and between 24% and 54% in participants with MS (table e-6). In healthy volunteers, the mean CSF/serum BIIB033 concentration ratios ranged between 0.032% and 0.079%, with no evidence of dose dependency. Similarly, the mean CSF/serum BIIB033 concentration ratios in participants with MS 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 was not consistent with the trend from other dose levels and was primarily due to the high ratios in 3 participants (>0.2% and <0.3%). The reason for the higher CSF/serum ratios in these participants is not known. Disease status (i.e., RRMS or SPMS) did not account for this observation because these 3 participants had RRMS (like most other participants in the study). Excluding the high CSF/serum ratios in the 3 participants in the 10-mg/kg dose group, CSF/serum BIIB033 concentration ratios appeared to increase in a dose-dependent manner, with the mean CSF/serum ratios reaching a plateau at approximately 0.1%.

MRI findings. In the SAD study (N = 72), there were no structural abnormalities, hemorrhage, or infarction among participants, although incidental findings of mucosal thickening in the maxillary sinuses (n = 2) and small venous angioma (n = 1) were noted in 3 BIIB033-treated participants (table e-2). In the MAD study (N = 47), MRI showed no new unexpected findings or increase in T2 lesions (included all participants) or Gd^{+} lesions (participants with Gd^{+} lesions at baseline: BIIB033, n = 5; placebo, n = 0) in the drug vs placebo group. Overall, slightly smaller percentages of participants in the BIIB033 treatment groups developed new T2 hyperintense lesions or Gd^{+} lesions at the end of the study compared with the placebo groups (table 1). No change in NAWM MTR was observed in either study vs baseline (figure e-1 and data not shown). Results of an exploratory efficacy analysis of change from baseline to week 16 of preexisting T2 and T1 brain lesions on MTR and fractional anisotropy in the MAD study by dose group are shown in figure e-2. Some increase in MTR and fractional anisotropy was

Table 3 Serum pharmacokinetic measures by dose for the MAD study[a]

	BIIB033 dose, mg/kg							
	0.3		1.0		3.0		10	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
C_{max}, µg/mL	7.6 (1.3)	8.8 (1.9)	26.7 (0.3)	35.3 (6.3)	77.3 (10.3)	77.9 (19.2)	262.3 (60.5)	356.2 (51.0)
T_{max}, h	2.0 (1.0, 6.9)	4.8 (1.1, 6.9)	2.0 (1.1, 3.0)	2.0 (1.9, 3.0)	4.0 (1.1, 7.0)	1.9 (1.9, 2.0)	2.1 (1.0, 25.0)	13.6 (2.0, 47.7)
AUC_{tau}, µg·d/mL	46.3 (5.8)	57.0 (6.5)	138.0 (35.3)	200.8 (59.6)	449.2 (62.8)	590.2 (107.1)	1,401.4 (86.0)	2,438.9 (161.6)

	30		60		100		100[b]	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
C_{max}, µg/mL	868.5 (138.3)	1,110.9 (101.7)	1,680.3 (264.6)	2,130.2 (416.6)	2,673.4 (719.3)	3,119.9 (541.4)	2,447.5 (209.8)	NA
T_{max}, h	3.3 (2.8, 4.8)	4.1 (3.6, 4.7)	2.8 (2.8, 3.7)	3.7 (2.8, 8.7)	2.8 (2.8, 4.8)	8.7 (2.8, 26.2)	3.2 (2.3, 7.2)	NA
AUC_{tau}, µg·d/mL	5,383.9 (395.4)	7,375.5 (900.6)	9,233.9 (504.4)	14,109.8 (1,772.7)	15,766.0 (1,988.4)	25,030.5 (1,007.8)	ND	NA

Abbreviations: AUC_{tau} = area under the time-concentration curve over a treatment period; C_{max} = maximum concentration; MAD = multiple ascending dose; NA = not applicable; ND = not determined; T_{max} = time of occurrence of C_{max}; V_{ss} = volume of distribution at steady state.
[a] Data are geometric means and SDs except for T_{max} (median, range).
[b] Single dose, shorter infusion time (80 minutes; n = 3).

apparent in preexisting T2 lesions but not preexisting T1 hypointense lesions for the highest dose groups. In contrast, no significant change in whole brain volume was observed following administration of BIIB033 or placebo at weeks 8 or 16 in the MAD study, and transient changes (week 8 only) in ventricular volume were observed in only the 3.0-mg/kg and 30-mg/kg BIIB033 treatment groups (table e-7).

DISCUSSION In these studies evaluating the emerging safety and tolerability of BIIB033 in healthy volunteers and participants with MS, 1 and 2 doses up to 100 mg/kg were well tolerated. There were no serious AEs in either of the 2 studies. In both studies, the incidence of AEs was similar between the BIIB033- and placebo-treated groups. Most AEs were mild to moderate in severity and not related to study treatment. Development of anti-drug antibodies following administration of BIIB033 was observed in only 1 participant transiently, and it did not have any detectable effect on PK levels or AEs. Among healthy volunteers in the SAD study, no clinically significant findings were observed in the neurologic examinations, brain MRI with MTR, VEPs, SSEPs, EEG, and retinal examination with optical coherence tomography and photography. Together, these results indicate that administration of BIIB033 up to the highest dose of 100 mg/kg did not have a negative effect on the general health or on the CNS or peripheral nervous system function, including neurons, axons, and their myelin, in either healthy volunteers or participants with RRMS or SPMS.

The BIIB033 serum PK profiles among healthy volunteers and participants with MS were similar and showed linear PK with exposure increasing dose proportionally over the studied dose range of 0.1 mg/kg to 100 mg/kg. The small volume of distribution indicates that significant target density does not appear to exist within the BIIB033 distribution volume. The low systemic clearance indicates that BIIB033 is not subject to significant target-mediated clearance. These properties are consistent with those reported for other IgG antibodies.[12] The BIIB033 CSF/serum ratio was also similar to the reported values of approximately 0.1%–1% for other IgG mAb drugs.[13,14]

In rats, CNS penetration for BIIB033 was reported to be low, with brain and CSF exposure approximately 0.16% and 0.075% of that in serum, respectively.[8] Although it is not possible to directly measure levels of BIIB033 in the human brain or spinal cord, based on the similar CSF/serum BIIB033 ratios found in humans from the phase I studies and rats,[8] it is likely that the brain and spinal cord to plasma ratios of BIIB033 in humans are approximately 0.1%. In the rat lysolecithin-induced demyelination spinal cord model, a relationship between anti-LINGO-1 mAb dose (0.1–100 mg/kg) and response at the target tissue (extent of spinal cord remyelination detectable by histology) was observed.[8] The CSF concentrations of anti-LINGO-1 mAb associated with 50% (EC_{50}) and 90% (EC_{90}) of maximum remyelinating spinal cord response were approximately 30 ng/mL and 100 ng/mL, respectively.[8] These CSF EC_{50} and EC_{90} values would correspond to serum EC_{50} and EC_{90} values of 30 µg/mL and 100 µg/mL, respectively, assuming 0.1% penetration into the CSF. As illustrated in figure 2, IV doses >3 mg/kg and >10 mg/kg in participants with MS resulted in mean BIIB033 serum concentrations higher than serum EC_{50} and serum EC_{90}, suggesting that these doses would be expected to result in pharmacologic activity.

The pilot exploratory efficacy analysis of BIIB033 effects on preexisting brain MRI lesions by MTR and DTI did not reveal any clear treatment effects on preexisting T2 or T1 lesions (figure e-2). However, the sample size was too small and the duration of treatment too short to allow any firm conclusions to be drawn. Larger and longer studies are necessary to investigate whether MTR and DTI are sensitive enough to detect treatment effects of candidate treatments for CNS repair such as BIIB033.

The findings from these 2 phase I studies of BIIB033 showed that the doses up to 100 mg/kg were well tolerated and had low immunogenicity. Moreover, the highest doses are expected to result in pharmacologic activity. Thus, the emerging safety, tolerability, and PK profiles of BIIB033 in both healthy volunteers and participants with MS support advancing its clinical development into proof-of-concept phase II studies. A placebo-controlled phase II study in 396 participants with MS commenced in August 2013.

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