COVER PAGE

Official Title:	A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration
NCT Number:	NCT03689972
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Name of Sponsor/Company:	Biogen MA/ Inc/ Biogen Idec Research Limited
Name of Finish Product:	Natalizumab
Name of Active Ingredient:	Natalizumab (BG00002; Tysabri)
Study Indication:	Relapsing-Remitting Multiple Sclerosis

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2. STUDY SYNOPSIS

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Principal Investigator/Coordinating Investigator:

[redacted], MD ([redacted] USA) was the Coordinating Investigator for this study

Study Period:	**Phase of Development:** 3b
Date of first treatment: 26 December 2018 End of Part 1 of the Study (Week 84): 12 April 2021	

Study Objectives:

Primary Objectives:

- To evaluate the efficacy of natalizumab every 6 weeks (Q6W) in participants who had previously been treated with natalizumab every 4 weeks (Q4W) for at least 12 months, in relation to continued Q4W treatment, with the goal of estimating the difference between Q4W and Q6W, with high precision and a narrow 95% confidence interval (CI), to support the treatment decision based on individualized benefit/risk assessments

Secondary Objectives:

- To evaluate additional relapse-based clinical efficacy measures of natalizumab Q6W in participants who had previously been treated with natalizumab Q4W for at least 12 months, in relation to continued Q4W treatment
- To evaluate disability worsening of natalizumab Q6W in participants who had previously been treated with natalizumab Q4W for at least 12 months, in relation to continued Q4W treatment
- To evaluate additional magnetic resonance imaging (MRI)-lesion efficacy measures of natalizumab Q6W in participants who had previously been treated with natalizumab Q4W for at least 12 months, in relation to continued Q4W treatment

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- To evaluate the safety of natalizumab Q6W in participants who had previously been treated with natalizumab Q4W for at least 12 months in relation to continued Q4W treatment

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Study Design: Part 1 was a prospective, randomized, interventional, controlled, open-label, rater-blinded, Phase 3b study in participants with relapsing-remitting multiple sclerosis (RRMS) where natalizumab IV infusion was administered in 2 treatment groups, natalizumab Q4W or natalizumab Q6W. All participants had received natalizumab Q4W for at least 12 months without relapses in the last 12 months prior to randomization in this study. All MRI scans were read at a central facility with raters blinded to participant assignment.

Randomization was stratified by country/region (North America [included United States and Canada], United Kingdom, Europe [included Belgium, France, Germany, Italy, Netherlands, and Spain], Israel, and Australia), body weight (≤ 80 kg versus > 80 kg), and duration of natalizumab exposure (≤ 3 years versus > 3 years). Participants received open-label natalizumab at their assigned frequency throughout the 72 weeks of the study.

Number of Participants (Planned and Analyzed):

Planned: For Part 1, approximately 100 sites in North America, the United Kingdom, the European Union, Israel, and Australia were planned to enroll approximately 480 participants with approximately 240 participants per treatment group (Q4W and Q6W).

Analyzed: A total of 499 participants were randomized at 89 study sites in 11 countries. Of the 499 participants randomized, 497 participants received at least 1 dose of study treatment in Part 1 and were included in the safety population (N = 250 in the Q6W group and N = 247 in the Q4W group) and 489 participants received at least 1 dose of study treatment and had at least 1 postbaseline clinical efficacy assessment and were included in the modified intent to treat (mITT) population (N = 247 in the Q6W group and N= 242 in the Q4W group).

Study Population:

Main Inclusion Criteria:

1. Participants aged 18 to 60 years old, inclusive, at the time of informed consent.
2. Diagnosis of RRMS according to the McDonald criteria.
3. Treatment with natalizumab as disease-modifying monotherapy for RRMS that was consistent with the approved dosing for a minimum of 12 months prior to randomization. The participant should have

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received at least 11 doses of natalizumab in the 12 months prior to randomization with no missed doses in the 3 months prior to randomization.

4. Expanded Disability Status Scale (EDSS) score ≤ 5.5 at Screening.
5. No relapses in the last 12 months prior to randomization, as determined by the enrolling Investigator.

Main Exclusion Criteria:

1. Primary- and secondary-progressive MS.
2. MRI positive for gadolinium (Gd)-enhancing lesions at Screening.
3. Participants for whom MRI was contraindicated (e.g., had a contraindicated pacemaker or other contraindicated implanted metal device, had suffered, or were at risk for, side effects from Gd, or have claustrophobia that cannot be medically managed).
4. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic (including diabetes), urologic, pulmonary, neurologic (except for RRMS), dermatologic, psychiatric, renal, or other major disease that would preclude participation in a clinical study, in the opinion of the Investigator.
5. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that had been completely excised and were considered cured).
6. History of transplantation or any antirejection therapy.
7. History of severe allergic or anaphylactic reactions or known hypersensitivity to any antibody drug therapy.
8. A clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within 30 days prior to Screening, or progressive multifocal leukoencephalopathy (PML) or other opportunistic infections at any time.
9. Presence of anti-natalizumab antibodies at Screening.

Treatment History

10. Prior treatment with cladribine, mitoxantrone, T-cell or T-cell receptor vaccination, cyclophosphamide, cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil.
11. Prior treatment with any therapeutic monoclonal antibody (mAb) other than natalizumab within 24 months prior to randomization.
12. Prior treatment with total lymphoid irradiation.

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13. Prior treatment with IV immunoglobulin, plasmapheresis, or cytapheresis within 12 months prior to randomization.
14. Treatment with IV or oral corticosteroids (topical or inhaled corticosteroids were acceptable) or related products (e.g., Acthar®) within 3 months prior to randomization.

Study Treatment, Dose, Mode of Administration: Q6W group (EID): natalizumab as a 300 mg IV infusion Q6W (42 [-2/+5] days)

Comparator Therapy/Therapies, Dose, Mode of Administration: Q4W Group (SID): natalizumab as a 300 mg IV infusion Q4W (28 [-2/+5] days)

Duration of Treatment and Follow-Up: The planned study duration for each participant enrolled only in Part 1 was approximately 102 weeks, comprising the following:

- 6-week Screening period
- 72-week Treatment period
- 12-week Follow-up period
- Follow-up safety phone call 12 weeks after the follow-up period (24 weeks after the last dose of study treatment)

Criteria for Evaluation:

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

Efficacy:

The following clinical assessments were performed to evaluate the efficacy of natalizumab in Part 1:

MRI Efficacy Assessments

- T2 hyperintense lesion number and volume
- Gd-enhancing lesion number and volume
- T1 hypointense lesion number and volume
- Percentage of brain volume change (PBVC)
- Cortical and thalamic brain region volume

Clinical Efficacy Assessments

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- Relapses (clinical relapses are assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours)
- Neurological examination and EDSS score
- [redacted]
- [redacted]
- [redacted]

[redacted]

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

Safety:

Clinical Safety Assessments

The following clinical assessments were performed in Part 1 to evaluate the safety profile of natalizumab:

- C-SSRS
- Medical history
- Physical examination

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- Body weight
- Vital sign measurements: temperature, systolic and diastolic blood pressures, pulse rate, and respiratory rate
- Concomitant therapy and procedure recording
- Adverse event (AE) and serious AE (SAE) recording

Laboratory Safety Assessments

The following laboratory assessments were performed to evaluate the safety profile of natalizumab by determining clinical laboratory abnormalities:

- Hematology: complete blood count with differential and platelet counts and absolute neutrophil count
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium

[redacted]

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- [redacted]

Statistical Methods:

Planned Analyses:

Analyses were performed for the predefined populations that included the mITT, per-protocol (PP), safety, immunogenicity, [redacted] populations.

Demographics and Baseline Disease Characteristics:

Demographic data were summarized by treatment groups using descriptive statistics. These included age (years), age category (< 40 and ≥ 40), sex, ethnicity, race, country/region, height, weight, and body mass index.

Baseline disease characteristics were summarized by treatment groups, using descriptive statistics. These included years since disease (MS) onset, years since diagnosis, number of relapses during the one year prior to first dose of natalizumab, score of last EDSS assessment prior to first dose of natalizumab and baseline EDSS scores. In addition, summary statistics of these baseline MRI assessments were also presented: T2 hyperintense lesion volume, Gd-enhancing lesion number and volume, T1 hypointense volume, and normalized brain volume.

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Number and percentage of participants with previous MS treatments other than natalizumab were summarized by medications and treatment groups. Prior MS treatments other than natalizumab was also listed.

In addition, natalizumab treatment history was also summarized.

Efficacy

Primary endpoint

The primary endpoint, the number of new or newly enlarging T2 hyperintense lesions at Week 72, was analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region (North America [includes USA and Canada], United Kingdom, Europe [includes Belgium, France, Germany, Italy, Netherlands, and Spain], Israel, and Australia) as covariates. The ratio of mean lesion numbers of Q6W versus Q4W (Q6W/Q4W) was derived from the model with a 95% CI and associated p-value. The treatment was considered different if the lower limit of the 95% CI was above 1. As a secondary inference, the possibility of a 2-fold increase in the mean lesion number in the Q6W group compared with the Q4W group was considered ruled out if the upper limit of 95% CI was no greater than 2. The proportion of participants with no new or newly enlarging T2 hyperintense lesions was analyzed using logistic regression models with the same covariates as those described above.

Handling of intercurrent events using primary estimand method: The primary estimand analysis was based on the treatment policy approach and utilized all measurements regardless of intercurrent events (e.g., treatment discontinuation). Intercurrent events were captured by electronic case report form, but the reasons for the missing data caused by them were classified into 'possibly efficacy related', 'possibly safety related', 'no information' or 'no information/not related' by an independent medical staff.

Handling of intercurrent events using secondary estimand method: The secondary estimand analysis was based on a hypothetical strategy, with assumption no intercurrent events occurred.

Handling of intercurrent events using multiple imputation method: All missing data due to the reasons of 'no information' or 'no information/not related' under primary estimand, and all those due to the reasons of 'possibly safety related', 'no information' or 'no information/not related' under secondary estimand, then they were handled using multiple imputation with fully conditional specification (FCS) logistic regression method.

Sensitivity analysis: Performed for mITT population for both estimands using tipping point analysis and adjusting for baseline volume of T2 hyperintense lesions

Secondary endpoints

Time to First Relapse

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Relapses that occurred after participants had received rescue Q4W natalizumab prior to Week 72 were excluded from the analyses of time to first relapse, and the participant's time in the study was censored at the time the participant started rescue Q4W natalizumab treatment. If a participant withdrew from the study prior to Week 72 and the participant did not experience relapse as adjudicated by the independent neurology evaluation committee (INEC) prior to withdrawal, the participant was censored on the last day the participant was in the study if the reason for withdrawal was not related to lack of efficacy. For withdrawals due to lack of efficacy, the withdrawal time was considered the event time. The start date for time to first relapse or censoring was defined as the baseline/first dose date.

The proportion of relapsed participants was estimated using the Kaplan-Meier (KM) product-limit method and presented as KM curves over time. The comparison of treatment groups was based on Cox regression models with the same covariates as those described for the primary endpoint analysis. The hazard ratio of relapse (Q6W/Q4W) was derived from the model with a 95% CI and associated p-value.

Annualized Relapse Rate

The annualized relapse rate at Week 72 was analyzed using Poisson regression models with treatment as the classification variable and the same covariates as those described for the primary endpoint analysis. The ratio of annualized relapse rate (Q6W/Q4W) was derived from the model with a 95% CI and associated p-value.

EDSS Worsening

Confirmed EDSS worsening was defined as an increase of at least 1.0 point from a baseline EDSS score $\geq$ 1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 that was confirmed after at least 24 weeks. If participants had a tentative EDSS worsening at Week 72, the EDSS evaluation at Week 84 was used to confirm the tentative worsening. Time to EDSS worsening was analyzed using KM estimates and Cox regression models similar to the method described for time to first relapse.

Secondary MRI Endpoints

The number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48 and the number of new Gd-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72 were analyzed using the same approach as that for the primary endpoint.

[redacted]

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[redacted]

Safety:

For Part 1, the safety population was defined as all randomized participants who received at least 1 dose of study treatment in Part 1.

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All AEs including SAEs were collected throughout the study. These AEs including SAEs were coded using the Medical Dictionary for Regulatory Activities 23.1. The incidence of treatment-emergent AEs including SAEs was summarized for Part 1 by the following:

- preferred term (PT)
- primary system organ class
- primary system organ class and preferred term
- severity and relationship to study treatment, primary system organ class (SOC) and PT

Adverse events were analyzed based on the principle of treatment emergence, with treatment-emergent AEs defined as AEs having an onset date on or after the first randomized infusion date and up to 84 days after the last randomized infusion date for all AEs except PML cases, which were captured up to 168 days after the last randomized infusion date.

Summary statistics for actual values and changes from baseline for laboratory data (hematology and blood chemistry) were also summarized by treatment group and timepoint

The analysis of vital signs focused on clinically relevant abnormalities.

C-SSRS data were summarized using descriptive statistics and included descriptive summary of participants who answered "Yes" to any question (1-12) as well as participants who had suicidal ideation or suicidal behavior at screening visit and at any postscreening visits, descriptive summary of participants who had treatment-emergent suicidal ideation (new and worsening), and descriptive summary of participants who had treatment-emergent suicidal behavior.

Immunogenicity Data and [redacted] Analysis

In Part 1, the immunogenicity analysis population included all randomized participants who received at least 1 dose of study treatment and had at least 1 postbaseline assessment for anti-drug antibody (ADA).

The percentage of participants who developed antibodies to natalizumab was determined and summarized by treatment group and timepoint.

[redacted]

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[redacted]

[redacted]

Sample Size Calculations

Historical data on MS treatments, including a meta-analysis on the relationship between new or newly enlarging T2 lesions and relapses, suggest little or no clinical relevance of a difference of 0.2 to 0.3 in mean lesion numbers over 72 weeks. With the planned sample size of N = 200/group, the precision of the estimated mean lesion numbers was sufficient to allow > 80% probability to observe the lower limit of the 95% CI for the ratio of Q6W to Q4W in the estimated mean lesion number above 1 if the true mean is 0.5 and 0.3 in the Q6W and Q4W group, respectively. If the true mean is 0.6 and 0.3 in the Q6W and Q4W group, respectively, the probability was approximately 90%. In the other direction, the sample size provided a precision that allows approximately 90% probability to observe the upper limit of the 95% CI to be ≤ 2 if the true mean lesion numbers in both groups were 0.3. Approximately 480 participants were determined that need to be enrolled to account for a drop-out rate of approximately 17%.

Results:

Participant Accountability

The first participant was enrolled on 26 December 2018, and the last participant for Part 1 of the study was enrolled on 30 August 2019. The last participant completed Week 84 visit (end of study of Part 1) on 12 April 2021. A total of 499 participants were randomized at 89 study sites in 11 countries.

Of the 499 participants randomized, 497 participants received at least 1 dose of study treatment in Part 1 and were included in the safety population (N = 250 in the Q6W group and N = 247 in the Q4W group), and 489 participants received at least 1 dose of study treatment and had at least 1 postbaseline clinical efficacy assessment and were included in the mITT population (N = 247 in the Q6W group and N = 242 in the Q4W group). Of the 250 participants in the safety population for the Q6W group, 202 participants completed study treatment and 207 participants completed the study. Of the 247 participants in the safety population for the Q4W group, 194 participants completed study treatment and 195 participants completed the study.

Demographics and Baseline Disease Characteristics

Demographic characteristics were balanced between the 2 treatment groups. The majority of participants were White (84.5%) and female (71.6%). The mean (SD) age was 40.6 (9.80) years, with 54.4% of participants ≥ 40 years of age. The mean (SD) weight was 79.16 (19.916) kg, and 58.1% of participants weighed ≤ 80 kg. The mean (SD) duration of natalizumab exposure at Baseline was 4.649 (2.9856) years; the majority of participants (63.2%) had natalizumab exposure > 3 years.

As expected, the number of participants randomized in both groups based on stratification factors (covariates) was well balanced.

Participants enrolled in this study were stable on natalizumab and received natalizumab Q4W for at least 12 months without relapses in the last 12 months prior to being randomized in this study. Baseline disease characteristics were representative of the population stable on natalizumab Q4W regimen. The overall MRI evaluation of MS disease characteristics was balanced between participants in the 2 treatment groups.

No participant had Gd-enhancing lesions, and there were no major differences in the 2 treatment groups for the mean values of T1 hypointense lesion volume, T2 hyperintense lesion volume, and normalized brain volume.

Overall, the mean (SD) number of years since the onset of MS symptoms was 11.1 (7.09) years, and the mean (SD) number of years since the diagnosis of MS was 9.2 (6.14) years. Overall, the mean EDSS score at Baseline was 2.31 (1.301). The mean (SD) number of relapses during 1 year prior to the first dose of natalizumab was 1.0 (1.01) and ranged from 0 to 8. MS disease history characteristics were balanced between the 2 treatment groups

Exposure to Study Treatment

The mean (SD) number of infusions received during the randomized treatment window was 11.8 (2.90) in the Q6W group and 16.7 (4.97) in the Q4W group. The mean (SD) number of infusions missed during the randomized dosing window was 1.2 (2.90) for the Q6W group and 2.3 (4.97) for the Q4W group. The overall mean (SD) compliance rate, calculated as (drug infusion actually received under randomized treatment dosing window / total planned infusions for 72 weeks) × 100, was 90.5% (22.34%) for the Q6W group and 88.0% (26.14%) for the Q4W group.

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Of the total 247 participants in the Q6W group, 6 participants (2.4%) switched to the Q4W treatment that was used as a rescue treatment, all of which met the protocol-defined criteria for this modification of treatment schedule based on relapse. No other rescue treatment was used for any participants in both treatment groups. Of note, an additional 5 participants in the Q4W group also met the criteria of the use of rescue treatment (any non-natalizumab approved DMT) based on relapse; however, they did not change their treatment.

Efficacy

Primary Endpoint

Using the primary estimand analysis criteria, the adjusted mean (SD) numbers of new or newly enlarging T2 hyperintense lesions detected a small numerical difference between the Q6W and Q4W groups (0.20 [95% CI: 0.07, 0.63] and 0.05 [95% CI: 0.01, 0.22], respectively). The mean lesion numbers ratio for Q6W/Q4W was 4.24 (95% CI: 0.86, 20.85; p = 0.0755). For primary estimand analysis, there was no difference in Q6W and Q4W groups for new or newly enlarging T2 hyperintense lesions at Week 72 because the lower limit of 95% CI was < 1 (0.86). In addition, a 2-fold increase in new or newly enlarging T2 hyperintense lesions cannot be ruled out because the upper limit for 95% CI is > 2 (20.85).

Using the secondary estimand analysis criteria, the adjusted mean (SD) numbers of new or newly enlarging T2 hyperintense lesions detected a small numerical difference between the Q6W and Q4W groups (0.31 [95% CI: 0.12, 0.82] and 0.06 [95% CI: 0.01, 0.31], respectively). The mean lesion numbers ratio for Q6W/Q4W was 4.93 (95% CI: 1.05, 23.20; p = 0.0437). For secondary estimand analysis, there was a difference between the Q6W and Q4W groups for new or newly enlarging T2 hyperintense lesions at Week 72 because the lower limit of 95% CI is > 1 (1.05). In addition, a 2-fold increase in new or newly enlarging T2 hyperintense lesions cannot be ruled out because the upper limit for 95% CI is > 2 (23.20).

Of note, a higher value for ratio of mean numbers for N/NE T2 lesions (Q6W/Q4W) can be attributed to 2 participants in the Q6W group who had higher (outlier) N/NE T2 lesion values (30 and 25). No other participants with available N/NE T2 lesions data at Week 72 (211 in the Q6W group and 197 in the Q4W group) had > 2 N/NE T2 lesions, and distributions for 0 (81.8% vs. 78.1%), 1 (2.0% vs. 2.9%), and 2 (0.8% vs. 0.4%) N/NE T2 lesions were comparable between the Q6W and Q4W groups, respectively.

Secondary Endpoints

Time to first relapse (relapses were adjudicated by an INEC)

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Based on the KM estimate of the time to first protocol-defined relapses (confirmed by INEC), the proportion of participants with protocol-defined relapse at Week 72 was small and comparable between the Q6W and Q4W groups: 2.8% and 2.1%, respectively.

Annualized relapse rate at Week 72

The adjusted annualized relapse rate (ARR) at Week 72 was comparable for the Q6W and Q4W groups (0.00013 [95% CI: 0.00006, 0.00027] and 0.00010 [95% CI: 0.00004, 0.00024], respectively; p = 0.6312).

Time to first EDSS worsening (confirmed after at least 24 weeks)

Based on the KM estimate of time to the first confirmed EDSS worsening in the overall mITT population, the proportion of participants with confirmed EDSS worsening at Week 72 was comparable between the Q6W and Q4W groups: 10.1% and 7.9%, respectively.

Number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48

Results for change from baseline in N/NE T2 hyperintense lesions at Week 24 and Week 48 were in alignment with results of the primary endpoint (Week 72). One of the 2 participants with a high number of N/NE T2 lesions had their lesions by Week 24.

Number of new Gd-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72

By Week 24 and Week 48, no participants in the Q6W group and 1 participant in the Q4W group had 1 new Gd-enhancing lesion. By Week 72, 1 participant each in the Q6W group and Q4W group had new Gd-enhancing lesions. The participant with new Gd-enhancing lesions in the Q6W group was 1 of the 2 primary endpoint outlier participants.

The number of participants who had new T1 hypointense lesions was small and comparable in the Q6W and Q4W groups at all timepoints analyzed: Week 24, 1 lesion (0.4% and 0, respectively) and 2 lesions (0 and 0.4%, respectively); Week 48, 1 lesion (0.4% and 0.4%, respectively) and 2 lesions (0 and 0.4%, respectively); Week 72, 1 lesion (0.4% and 0.4%, respectively), 2 lesions (0.4% and 0.4%, respectively), and 4 lesions (0.4% and 0, respectively).

[redacted]

[redacted]

Subgroup Analyses:

Overall, disease activity in the study, as noted by reported events for the key secondary efficacy endpoints was very low collectively; therefore, no inferences can be drawn from subgroup analyses for comparing Q6W and Q4W dosing regimens.

Subgroup analyses by body weight were of particular interest, as previously done modeling simulation suggested that patients with body weight > 80 kg receiving Q6W dosing may be at an increased risk of disease activity. For primary endpoint analysis by subgroup analyses by weight, of the 9 participants in the Q6W group with N/NE T2 lesions, 8 participants (89%) had body weight < 80 kg (1 participant with baseline body weight of 40 kg to < 60 kg, 5 participants with ≥ 60 kg to < 80 kg) and 1 participant (11%) weighed > 80 kg (baseline body weight of ≥ 90 kg). Of the 8 participants in the Q4W group with N/NE T2 lesions, 5 participants (62.5%) had baseline body weight < 80 kg (3 participants with 40 kg to < 60 kg, 2 participants with ≥ 60 kg to < 80 kg) and 3 participants (37.5%) had baseline body weight > 80 kg (1 participant with ≥ 80 kg to < 90 kg and 2 participants with > 90 kg). These results showed that there is no difference between the 2 groups for subgroup analyses by body weight. Also, these results demonstrated that there is no correlation between higher body weight (> 80 kg) and increase risk of disease activity in participants receiving Q6W dosing.

As for the primary endpoint, subgroup analyses by body weight for key secondary efficacy endpoints also support outcomes from the primary endpoint and demonstrate that there is no correlation in higher body weight (> 80 kg) and an increase risk of disease activity in participants receiving Q6W dosing.

[redacted]

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The least square (LS) mean change from baseline in the lymphocyte, T-cell counts, CD4, and CD8 counts over 72 weeks was similar for both Q6W and Q4W groups ($p > 0.05$).

B-cell counts remained higher in the Q4W group than in the Q6W group at each timepoint, and the LS mean difference between the Q6W and Q4W groups was statistically significant over 72 weeks ($p < 0.01$).

No apparent differences were observed in the natural killer cell counts between the Q6W and Q4W groups ($p > 0.05$).

Safety:

Overall Summary of AEs

A similar proportion of participants in both treatment groups experienced a TEAE (194 participants [77.6%] in the Q6W group and 190 participants [76.9%] in the Q4W group). TEAEs reported in ≥ 5% of participants in either group included nasopharyngitis (27 participants [10.8%] in the Q6W group and 32 participants [13.0%] in the Q4W group), urinary tract infection (24 participants [9.6%] in the Q6W group and 19 participants [7.7%] in the Q4W group), upper respiratory tract infection (12 participants [4.8%] in the Q6W group and 17 participants [6.9%] in the Q4W group), arthralgia (18 participants [7.2%] in the Q6W group and 9 participants [3.6%] in the Q4W group), pain in extremity (14 participants [5.6%] in the Q6W group and 7 participants [2.8%] in the Q4W group), headache (26 participants [10.4%] in the Q6W group and 23 participants [9.3%] in the Q4W group), fatigue (25 participants [10.0%] in the Q6W group and 8 participants [3.2%] in the Q4W group), fall (14 participants [5.6%] in the Q6W group and 14 participants [5.7%] in the Q4W group), and cough (14 participants [5.6%] in the Q6W group and 4 participants [1.6%] in the Q4W group).

The majority of TEAEs reported in the study were mild or moderate in severity (Q6W group: mild [29.6%], moderate [40.4%]; Q4W group: mild [39.7%], moderate [33.6%]). A greater proportion of participants experienced a severe TEAE in the Q6W group (7.6%) than in the Q4W group (3.6%).

A greater proportion of TEAEs were reported as related to study treatment by the Investigator in the Q6W group (11.6%) than in the Q4W group (7.7%).

Study treatment was discontinued due to TEAEs in 1 participant with pain in extremity (Q6W group), 1 participant with peripheral neuropathy (Q6W group), and 1 participant with claustrophobia (Q4W group). The event of peripheral neuropathy was an SAE. In addition, for 2 participants in the Q6W group, positive JC polyomavirus test was reported as a TEAE leading

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to study treatment discontinuation; however, JC polyomavirus-positive was captured incorrectly as TEAEs in the clinical study report tables, which came from incorrect entry of JC polyomavirus as an AE in the electronic data capture database. Three participants withdrew from the study due to TEAEs: 1 participant in the Q4W group (claustrophobia) and 2 participants in the Q6W group (pain in extremity and peripheral neuropathy); none of these events were reported by the Investigator as related to study treatment.

SAEs

Overall, 34 participants reported an SAE: 17 participants (6.9%) in the Q4W group and 17 participants (6.8%) in the Q6W group. The only SAE reported by > 1 participant was cholelithiasis, which was reported in 2 participants in the Q6W group. None of the SAEs in the Q4W group and 3 SAEs (PML [mild], respiratory tract infection [severe], and COVID-19 pneumonia [severe]) in the Q6W group were reported by the Investigator as related to study treatment.

A total of 4 SAEs in 3 participants were reported as life-threatening events (1 participant in the Q4W group had events of pulmonary embolism and limb venous thrombosis, 1 participant in the Q6W group had an event of suicide attempt, and 1 participant in the Q6W group had an event of progressive multifocal leukoencephalopathy [PML]). Other than the event of progressive multifocal leukoencephalopathy, none of the other life-threatening events were considered by the Investigator as related to study treatment.

AESIs

- One participant (0.4%) in the Q6W group reported mild asymptomatic PML, and no participants in the Q4W group reported PML.
- 13 participants reported TEAEs of infusion reaction (6 participants [2.4%] in Q6W and 7 participants [2.8%] in Q4W group).
- 12 participants reported TEAEs of opportunistic infections (other than PML) (9 participants [3.6%] in Q6W group and 3 participants [1.2%] in Q4W group).
- There was no drug-induced liver injury (DILI) event reported in either group.
- 52 participants reported TEAEs of hypersensitivity reactions (30 participants [12.0%] in Q6W group and 22 participants [8.9%] in Q4W group).

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Other Safety Parameters

- One participant in the Q6W group experienced a TEAE of malignant melanoma that was reported by the Investigator as not related to study treatment.
- 4 participants reported TEAEs of hepatic injury (1 participant [0.4%] in Q6W group and 3 participants [1.2%] in Q4W group)
- A similar proportion of participants in the Q6W and Q4W groups had COVID-19 TEAEs (10 participants [4.0%] and 9 participants [3.6%], respectively).
- During the study period, 4 participants (1.6%) in the Q4W group and 8 participants (3.2%) in the Q6W group reported treatment-emergent suicidal ideation. Of these, 3 participants in the Q4W group and 7 participants in the Q6W group reported new suicidal ideation. One participant in each group reported worsening of suicidal ideation during the study. Two participants in the Q6W group and 1 participant in the Q4W group had treatment-emergent suicidal behavior.
- No participant was ADA positive in the Q4W group. Two participants were ADA positive in the Q6W group.
- A similar proportion of participants had anti-JCV antibodies in the Q6W group (33.2%) and the Q4W group (28.3%).

Conclusions:

Taking all of the study data into consideration, including 1) an in-depth understanding of the primary endpoint difference (via observed distributions, outlier case narratives, and contributions of rescue treatment decisions), 2) the absence of differences in the secondary [redacted] endpoints, and 3) the overall high degree of MS disease control observed for both groups in the study, the collective results show that both treatment regimens are effective at managing MS disease in participants who were clinically stable on at least 1 year of prior Q4W dosing. Overall, data from this study are informative for clinicians in supporting treatment management decisions for patients treated with natalizumab.

Overall, the safety profile of natalizumab 300 mg IV Q6W group is similar to that of natalizumab 300 mg IV Q4W group. No new safety signals/new aspect of known risk for Q6W dosing regimen compared with the Q4W dosing regimen were identified during this study, recognizing that this study was too small to be informative on rare events such as PML.

Date of Report: 02 November 2021

Version: 1

2. STUDY SYNOPSIS

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Title of Study:

A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration

Principal Investigator/Coordinating Investigator:

Dr [redacted], MD ([redacted] Netherlands) was the Coordinating Investigator for this study

Study Period: Date of first treatment: 25 November 2020 End of Study date: 24 July 2023	**Phase of Development:** 3b

Study Objectives:

Primary Objectives:

- To evaluate participant preference for subcutaneous (SC) versus intravenous (IV) route of natalizumab administration

Secondary Objectives:

- To evaluate treatment satisfaction with SC versus IV route of administration.
- To evaluate drug preparation and administration time between SC and IV routes of natalizumab administration.
- To evaluate the safety and immunogenicity of SC versus IV routes of natalizumab administration.
- To evaluate the efficacy of SC versus IV routes of natalizumab administration.
- To characterize pharmacokinetics (PK) and pharmacodynamics (PD) of SC versus IV routes of natalizumab administration.

[redacted]

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Study Design: Part 2 of Study 101MS329 was a randomized, open-label, 2-treatment (SC Q6W versus IV Q6W), crossover, multicenter study designed to assess preference for SC natalizumab Q6W treatment and explore the long-term efficacy, safety, and tolerability of Q6W administration.

The study was a 108-week open-label extension for participants who completed their randomized treatment in Part 1 and participants who did not participate in Part 1 but satisfied the inclusion and exclusion criteria and eligibility requirements of Part 1, including treatment with natalizumab every 4 weeks (Q4W) for at least 12 months without relapses in the last 12 months. Participants were stratified by their treatment assignment in Part 1 (Q4W, Q6W, or new participants).

Number of Participants (Planned and Analyzed):

Planned: Approximately 160 participants.

Analyzed: A total of 158 participants enrolled in Part 2 of the study, all of whom received treatment with natalizumab IV Q6W during the run-in period. Of the 158 participants enrolled, 153 were randomized to receive treatment during the crossover phase. A total of 141 participants received at least 1 dose of study treatment during the crossover phase and were included in the safety population; all of these participants were also included in the full analysis set (FAS). A total of 131 participants received at least 1 dose of natalizumab SC during the randomized crossover phase and completed at least the first question in the Participant Preference Questionnaire on 1 occasion and were included in the modified intent to treat (mITT) population.

Study Population:

Main Inclusion Criteria:

To be eligible to participate in this study, candidates who previously enrolled in Part 1 met the following eligibility criteria:

1. Ability of the participant to understand the purpose and risks of the study and provide signed and dated informed consent for Part 2 and authorization to use confidential health information in accordance with national and local participant privacy regulations.

2. Completed Part 1 Week 72 visit while remaining on their randomized treatment assignment of Q4W or Q6W.

The inclusion criteria for participants who did not participate in Part 1 were the same as those for participants who did participate in Part 1:

1. Ability of the participant to understand the purpose and risks of the study and provided signed and dated informed consent and authorization to use confidential health information in accordance with national and local participant privacy regulations.

2. Aged 18 to 60 years old, inclusive, at the time of informed consent.

3. Diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to the McDonald criteria.

4. Treatment with natalizumab as disease-modifying monotherapy for RRMS that was consistent with the approved dosing for a minimum of 12 months prior to randomization. The participant must have

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received at least 11 doses of natalizumab in the 12 months prior to randomization with no missed doses in the 3 months prior to randomization.

5. Expanded Disability Status Scale (EDSS) score ≤ 5.5 at Screening.

6. No relapses in the last 12 months prior to randomization, as determined by the enrolling Investigator.

7. All women of childbearing potential practiced highly effective contraception during the study and for 3 months after their last dose of study treatment.

Main Exclusion Criteria:

Candidates who completed Part 1 were excluded from Part 2 entry if any of the following exclusion criteria existed at the timepoint specified in the individual criterion listed:

1. Participant treated with natalizumab EID was reverted to natalizumab SID by choice or as rescue treatment in Part 1.

2. Participant received treatment with any multiple sclerosis (MS) disease-modifying therapy other than natalizumab in Part 1 or in the period between Part 1 and Part 2.

3. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic (including diabetes), urologic, pulmonary, neurologic (except for RRMS), dermatologic, psychiatric, renal, or other major disease that would preclude participation in a clinical study, in the opinion of the Investigator.

4. History of human immunodeficiency virus or history of other immunodeficient conditions.

5. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that had been completely excised and were considered cured).

6. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use was to be administered within 30 days (or 5 half-lives of the agent, whichever was longer) prior to the Baseline Visit or at any time during this study.

7. Inability to comply with study requirements.

8. Other unspecified reasons that, in the opinion of the Investigator or Biogen, made the subject unsuitable for enrollment.

9. Women who were pregnant or breastfeeding, and women intending to become pregnant during the study.

The main exclusion criteria for new participants who did not participate in Part 1 of the study were the same as those for subjects who did participate in Part 1:

1. Primary- and secondary-progressive MS.

2. Magnetic resonance imaging (MRI) positive for gadolinium (Gd)-enhancing lesions at Screening.

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3. Participants for whom MRI was contraindicated (e.g., had a contraindicated pacemaker or other contraindicated implanted metal device, had suffered, or were at risk for, side effects from Gd, or had claustrophobia that could not be medically managed).

4. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic (including diabetes), urologic, pulmonary, neurologic (except for RRMS), dermatologic, psychiatric, renal, or other major disease that would have precluded participation in a clinical study, in the opinion of the Investigator.

5. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that had been completely excised and were considered cured).

6. History of transplantation or any antirejection therapy.

7. History of severe allergic or anaphylactic reactions or known hypersensitivity to any antibody drug therapy.

8. A clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within 30 days prior to Screening, or progressive multifocal leukoencephalopathy (PML) or other opportunistic infections at any time.

9. Presence of anti-natalizumab antibodies at Screening.

Treatment History

10. Prior treatment with cladribine, mitoxantrone, T cell or T cell receptor vaccination, cyclophosphamide, cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil.

11. Prior treatment with any therapeutic monoclonal antibody (mAb) other than natalizumab within 24 months prior to randomization.

12. Prior treatment with total lymphoid irradiation.

13. Prior treatment with IV immunoglobulin, plasmapheresis, or cytapheresis within 12 months prior to randomization.

14. Treatment with IV or oral corticosteroids (topical or inhaled corticosteroids were acceptable) or related products (e.g., Acthar®) within 3 months prior to randomization.

Study Treatment, Dose, Mode of Administration: Participants received natalizumab 300 mg IV Q6W for 36 weeks. During the crossover treatment period, participants received natalizumab 300 mg Q6W for 24 weeks by SC injection and for 24 weeks by IV infusion (SC followed by IV or IV followed by SC). For the final natalizumab dose (at Week 156), participants chose the route of administration (IV or SC).

Duration of Treatment and Follow-Up:

For participants enrolled in both Part 1 and Part 2 of the study, the total duration of study participation in Part 1 was up to 78 weeks, comprising the following:

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- Screening period of up to 6 weeks
- Randomized Q4W or Q6W treatment period of 72 weeks

The total duration of the study for these participants in Part 2 was approximately 108 weeks, comprising the following:

- IV Q6W treatment for 36 weeks
- Randomized SC Q6W versus IV Q6W crossover treatment period of 48 weeks
- Follow-up period of 12 weeks
- Follow-up safety phone call 12 weeks after the follow-up period

The total duration of study participation for participants who participated in both Part 1 and Part 2 was approximately 186 weeks.

For participants who enrolled in Part 2 of the study only, the total duration of study participation comprised the following:

- 6-week screening period
- IV Q6W treatment for 36 weeks
- randomized SC Q6W versus IV Q6W crossover treatment period of 48 weeks
- follow-up period of 12 weeks
- follow-up safety phone call 12 weeks after the follow-up period

The total duration of study participation for participants who participated in Part 2 only was approximately 114 weeks.

Criteria for Evaluation:

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

Participant Preference, Time for Treatment, Efficacy, PK, and PD Results

The following clinical assessments were performed to evaluate participant preference, time for treatment, efficacy, PK, and PD of natalizumab in Part 2:

MRI Efficacy Assessments

- T2 hyperintense lesion number and volume
- Gd-enhancing lesion number and volume
- T1 hypointense lesion number and volume
- Percentage of brain volume change (PBVC)

Clinical Efficacy Assessments

- Relapses (clinical relapses were assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours)

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- Neurological examination and EDSS score
- Treatment Satisfaction Questionnaire for Medication (TSQM), [redacted]

Participant Preference

- Patient preference questionnaire (PPQ) for route of administration

Pharmacokinetics

- C_{trough} (trough serum natalizumab concentration) to assess the PK of natalizumab

[redacted]

Safety

Clinical Safety Assessments

The following clinical assessments were performed in Part 2 to evaluate the safety profile of natalizumab:

- Medical history
- Physical examination
- Body weight
- Vital sign measurements: temperature, systolic and diastolic blood pressures, pulse rate, and respiratory rate
- Concomitant therapy and procedure recording
- Adverse event (AE) and serious AE (SAE) recording

Laboratory Safety Assessments

The following laboratory assessments were performed to evaluate the safety profile of natalizumab by determining clinical laboratory abnormalities:

- Hematology: complete blood count with differential and platelet counts and absolute neutrophil count
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium

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[redacted]

Statistical Methods:

Planned Analyses

Analyses were performed for the predefined populations that included the mITT, per-protocol (PP), safety, immunogenicity, [redacted], PK, [redacted] populations.

Demographics and Baseline Disease Characteristics

Demographic data were summarized by treatment groups using descriptive statistics. These included age (years), age category (< 40 and ≥ 40), sex, ethnicity, race, country/region, height, weight (≤ 80 kg and > 80 kg), and body mass index.

Baseline disease characteristics were summarized by treatment groups, using descriptive statistics. These included years since disease (MS) onset, years since diagnosis, number of relapses during the 1 year prior to first dose of natalizumab, score of last EDSS assessment prior to first dose of natalizumab, and baseline EDSS scores. In addition, summary statistics of these baseline MRI assessments were presented: T2 hyperintense lesion volume, Gd-enhancing lesion number and volume, T1 hypointense volume, and normalized brain volume.

The number and percentage of participants with previous MS treatments other than natalizumab were summarized by medications and treatment groups. Prior MS treatments other than natalizumab was also listed.

In addition, natalizumab treatment history was summarized.

Primary endpoint: proportion of participants indicating a preference for natalizumab SC administration

The proportion of participants preferring natalizumab SC at the end of the randomized crossover phase was estimated, and the 95% confidence interval (CI) was calculated using the exact binomial method. Summary statistics (presented by treatment sequence and overall) were provided for the preferred route of administration, strength of preference, and 2 main reasons for preference at each visit (Week 30, Week 42 relative to the randomization visit). Participants' choice of last dose on the study (IV or SC) was summarized by treatment sequence and overall. Analysis was performed in the mITT population.

Secondary endpoints:

Total score on TSQM

Summary statistics for total TSQM score, each subscore, and the change in each from baseline to Week 24 and Week 48 were presented by treatment sequence and visit. Change from baseline in total TSQM score for each route of administration after 24 weeks was analyzed using a linear mixed effect model. Estimates for each route

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of administration, as well as the difference between IV and SC routes after 24 weeks of treatment, were presented, along with the 95% CI and p-value. Analysis was performed in the FAS population.

Mean time for drug preparation and administration

Data were collected for the preparation and administration of each route of administration at each visit and were pooled before summarizing. Preparation time, administration time, and total administration time (preparation time + administration time) were calculated and presented by route of administration. Analysis was performed in the FAS population.

Number of new or newly enlarging (N/NE) T2 hyperintense lesions, new Gd-enhancing lesions, and new T1 hypointense lesions

The number of N/NE T2 hyperintense lesions was summarized over time by treatment sequence and visit. The number from Baseline to Week 96, Week 24 to Week 48, and Baseline to Week 48 (calculated cumulatively over time) was presented.

The number of N/NE T2 hyperintense lesions after 24 weeks of treatment relative to the beginning of the period was also summarized and analyzed using a negative binomial generalized linear model. The model included route of administration (IV or SC), treatment period, and treatment sequence as fixed effects and participant as random effect, adjusting for baseline body weight (continuous variable), baseline duration of natalizumab exposure (≤ 3 years versus > 3 years), stratification factor (Q4W, Q6W, new participants), and baseline number of lesions.

The same model was used for the following parameters:

- number of new Gd-enhancing lesions
- number of new T1 hypointense lesions

The ratio of mean lesion numbers of SC versus IV was derived from the model with a 95% CI and associated p-value. If the total number of lesions across the 2 groups was less than 15 for each visit, then the negative binomial model was not conducted. Analysis was performed in the FAS population.

Time to first relapse

The proportion of relapsed participants was estimated using the Kaplan-Meier (KM) product limit method and presented as KM curves over time by treatment sequence. The hazard ratio of SC/IV versus IV/SC was estimated from the Cox model with terms for treatment sequence, baseline body weight (continuous), baseline duration of natalizumab exposure (≤ 3 years versus > 3 years), and stratification factor (Q4W, Q6W, or new participants). Analysis was performed in the FAS population.

PBVC and change in cortical and thalamic brain region volume

Summary statistics, change from baseline, and percentage change from baseline were presented for PBVC by treatment sequence and visit. Percentage change from baseline was also calculated for PBVC after 24 weeks of treatment relative to the beginning of the treatment period and analyzed using the linear mixed effect model. Summary statistics and change from baseline by treatment sequence and visit were presented for cortical and thalamic brain region volume. Estimates for each route of administration, as well as the mean difference between

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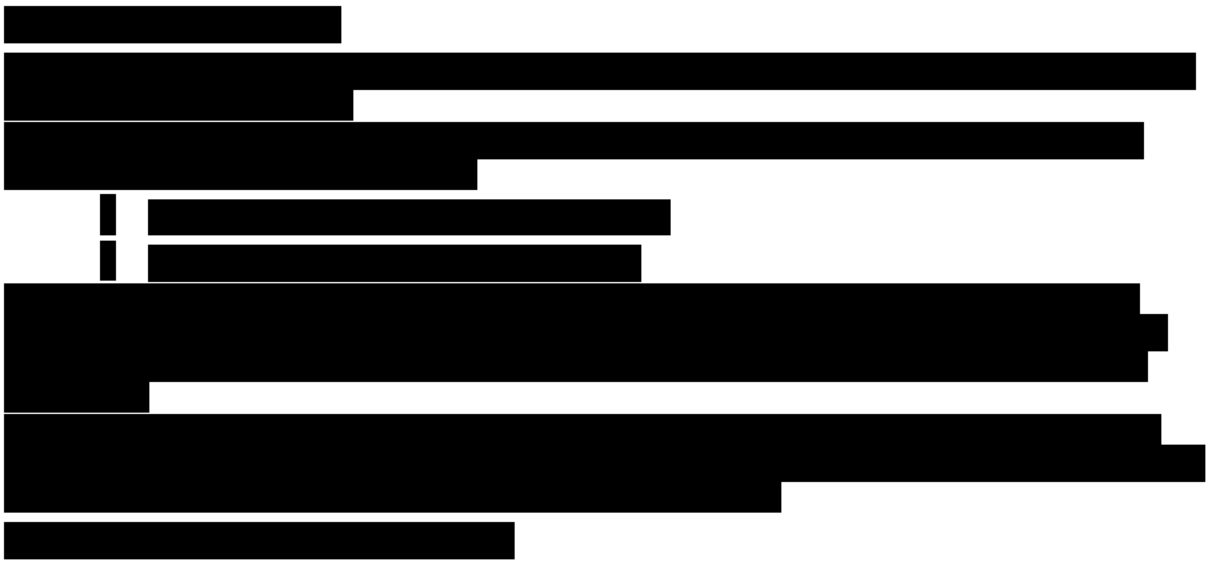
the IV and SC groups after 24 weeks of treatment, were presented, along with the 95% CI and p-value for PBVC and change in cortical and thalamic brain region volume. Analysis was performed in the FAS population.

Annualized relapse rate

The relapse rate for each route was calculated as the total number of relapses experienced for the administration route divided by the total number of participant-years on study at the end of each period for the route of administration (unadjusted relapse rate). Similarly, the relapse rate for an individual participant was also calculated. Based on these individual relapse rates, the mean and median for each route were presented (participant relapse rate). The annualized relapse rate at the end of each period was analyzed using a negative binomial regression model. The logarithmic transformation of the number of years in the study at the time end of each period was included in the model as the "offset" parameter. The ratio of mean annualized relapse rate of SC versus IV was derived from the model with a 95% CI and associated p-value. Analysis was performed in the FAS population.

Change in EDSS score

EDSS score and change from baseline were summarized over time by treatment sequence and visit. Change from baseline was also calculated after 24 weeks relative to the beginning of the period and analyzed by route of administration in the same manner as described for the TSQM total score. The number of participants with confirmed EDSS worsening or improvement will be presented by treatment sequence. The proportion of participants free of confirmed EDSS worsening at Week 48 will be estimated based on the KM product limit method. Worsening or improvement observed at Week 48 only could not be confirmed without follow-up data. Analysis was performed in the FAS population.



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Pharmacokinetics:

C_{trough} was summarized using descriptive statistics. Summary statistics were presented by treatment sequence and by route of administration. Plots of arithmetic mean concentration by visit were provided for all timepoints. Analysis was performed in the PK population. Subgroup analyses were performed for participants with baseline weight ≤ 80 kg versus > 80 kg.

[redacted]

Safety:

The overall summary table of AEs presents the number of participants with AEs for each treatment sequence and route of administration. The incidence of AEs was also presented for each treatment sequence and route of administration and summarized by preferred term (PT), by primary system organ class (SOC), by primary SOC and PT, and by severity and relationship to study treatment.

The incidences of SAEs, AEs that led to withdrawal from study, AEs that led to discontinuation of study drug, and adverse events of special interest (AESIs) were also summarized by treatment group and route of administration.

[redacted]

Laboratory data (hematology and blood chemistry) were presented over time by treatment sequence and indicated the most recent route of administration received before the assessment where appropriate.

A summary table for participants with any clinically relevant postbaseline abnormalities was provided. For each vital sign parameter, actual values and changes from baseline were summarized using descriptive statistics by treatment sequence and visit.

Participants with any postbaseline clinically relevant abnormalities in vital signs were tabulated by treatment sequence and route of administration and listed. Clinically relevant abnormalities in vital signs were assigned to the most recent route of administration received before the date of assessment.

Body weight, collected at the screening visit, Baseline of the crossover phase, Week 24, and Week 48, was summarized by treatment sequence over time.

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All safety analyses were performed in the safety population, [redacted]

Immunogenicity

The proportion of participants who developed ADAs was determined and summarized over time by treatment sequence and route of administration. Analysis was performed in the immunogenicity population.

Sample Size Calculations

For Part 2, in the absence of EID SC natalizumab data, it was assumed that the proportion of participants who would prefer SC natalizumab would be 75%, with a 7.5% margin of error; therefore, a sample size of 130 subjects was required for the 95% CIs to be within 67.5% and 82.5%. Approximately 160 participants were needed to allow for the 20% of participants who did not provide an evaluable preference assessment (calculated by nQuery Advisor Version 7).

Results:

Participant Accountability

The first participant for Part 2 of the study was enrolled on 25 November 2020, and the last participant was enrolled on 20 June 2021. The last participant completed the end of study (EOS) visit on 24 July 2023.

All of the 158 participants enrolled in Part 2 received treatment with natalizumab IV Q6W during the run-in period, and 153 of these participants were randomized to receive treatment during the crossover phase. Of the 153 participants randomized during the crossover phase, 29 (19.0%) had received treatment with natalizumab IV Q4W during Part 1 of the study, 38 (24.8%) had received natalizumab IV Q6W during Part 1, and 86 (56.2%) were new participants in Part 2.

A total of 141 of the 153 randomized participants (92.2%) received at least 1 dose of study treatment during the crossover phase, and 127 participants (83.0%) received study treatment during both Period 1 and Period 2. Overall, 136 participants received at least 1 dose of natalizumab IV during the crossover phase, and 132 participants received at least 1 dose of natalizumab SC during the crossover phase. The number of participants who discontinued the study treatment and prematurely withdrew from the study was similar between the randomization groups and was similar for both routes of administration.

Demographics and Baseline Disease Characteristics

The majority of participants were White (85.1%) and female (67.4%). The mean (standard deviation [SD]) age was 38.8 (10.13) years, with 51.8% of participants < 40 years of age. The mean (SD) weight was 76.44 (18.896) kg, and 64.5% of participants weighed ≤ 80 kg. Demographic characteristics were balanced between the randomized treatment groups. As expected, the number of participants randomized in both treatment groups based on stratification factors was well balanced.

Participants enrolled in the study were stable on natalizumab and had received natalizumab Q4W for at least 12 months and without relapses in the last 12 months prior to the relevant Screening visit. Baseline disease characteristics were representative of the population stable on natalizumab Q4W regimen.

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The overall MRI evaluation of MS disease characteristics was balanced between participants in both randomized treatment groups. At baseline of the randomized crossover period, 1 participant in the IV/SC group had 1 Gd-enhancing lesion. There were no major differences between the treatment groups for the mean values of T1 hypointense lesion volume, T2 hyperintense lesion volume, and normalized brain volume.

Overall, the mean (SD) number of years since the onset of MS symptoms was 11.3 (6.91) years, and the mean (SD) number of years since the diagnosis of MS was 9.9 (6.50) years. The mean (SD) score of last EDSS assessment prior to first dose of natalizumab was 2.15 (1.181), and the mean EDSS score at Baseline was 2.01 (1.322). The mean (SD) number of relapses during the 1 year prior to the first dose of natalizumab was 1.1 (0.88) and ranged from 0 to 3. MS disease history characteristics were balanced between the treatment groups.

Exposure to Study Treatment

Overall, the mean (SD) time on study after randomization in Part 2 was 67.2 (14.76) weeks, with mean (SD) time participants were exposed to study treatment of 50.2 (10.91) weeks and mean (SD) time on randomized treatment of 44.2 (10.91) weeks.

The majority of participants completed dosing in Period 1 (95.0%) and Period 2 (87.2%) of the randomized treatment phase. A similar proportion of participants in the IV/SC and SC/IV treatment groups completed dosing in Part 1 (96.0% and 93.9%, respectively). However, although 72 of the 75 participants (96.0%) in the IV/SC treatment group completed IV dosing in Period 1, only 66 of these participants (88.0%) received any SC treatment in Period 2. The other 6 participants in the IV/SC treatment group completed dosing in Period 1 but discontinued prior to starting Period 2, all with the reason of consent withdrawn. Overall, a lower proportion of participants in the IV/SC treatment group than in the SC/IV treatment group received any Period 2 treatment (88.0% and 92.4%, respectively) or completed Period 2 treatment (84.0% and 90.9%, respectively).

Patient Preference, Treatment Satisfaction, and Time for Treatment

Primary efficacy endpoint: 87.8% of participants preferred the SC method of administration at Week 42, and 81.3% of participants chose SC administration for the last dose on the study. The main reasons for preference of SC at Week 42 were “requires less time in the clinic” (selected by 77.9% of participants) and “feels more comfortable during administration” (selected by 40.5% of participants).

There were no significant differences between IV and SC administration in treatment satisfaction based on the TSQM global satisfaction score during the randomized crossover phase.

The mean (SD) total administration time was considerably shorter for the SC route of administration (4.3 [5.11] minutes) than for the IV route of administration (65.8 [5.94] minutes).

Efficacy

For a total of 10 participants, the investigators reported a clinical relapse during Part 2 of the study. For 7 of the participants, clinical relapses were reported during the run-in period (when all participants were treated with IV Q6W). For 1 participant, the clinical relapse was reported while the participant was receiving SC Q6W during Period 2 of the crossover phase. This participant missed the Week 36 SC dose and reported a relapse at Week 41 (Day 292). The participant received the Week 42 dose, [redacted] At Week 48, a N/NE T2 lesion was detected on the MRI scan. The participant completed the study. For 2 participants, clinical relapses were reported during the follow up period after

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completion of study treatment (1 participant was in the IV/SC treatment group, and 1 participant was in the SC/IV treatment group; both participants received SC administration for their last dose in the study).

There were no significant differences between IV and SC administration in EDSS score during the randomized crossover phase, and the majority of participants were free of confirmed EDSS worsening.

The majority of participants had no N/NE T2 lesions during Part 2 of the study. Four participants had N/NE T2 lesions detected during the randomized crossover phase: from Baseline to Week 24 in 1 participant receiving SC treatment and from 24 to 48 weeks in 2 participants receiving SC treatment and 1 participant receiving IV treatment. No new Gd-enhancing lesions were observed during Part 2 of the study, and only 1 participant had a new T1 hypointense lesion.

There were no significant differences between IV and SC administration in percentage change from baseline in normalized brain volume or in change in cortical brain region grey matter and thalamic brain region volume during the randomized crossover phase.

[redacted]

There were no significant differences between IV and SC administration in change in volume of T2 hyperintense lesions and change in volume of nonenhancing T1 hypointense lesions after 24 weeks in the randomized crossover phase.

[redacted]

Pharmacokinetics

Over the 24-week treatment period for each route of administration (not including Baseline of each treatment period), there was a trend of lower mean serum trough concentrations in participants on SC Q6W dosing (9.2 to 10.4 µg/mL) compared with participants on IV Q6W dosing (10.7 to 12.9 µg/mL).

Mean trough serum concentrations over time were higher in participants with lower baseline body weight (≤ 80 kg) compared with those who had higher baseline body weight (> 80 kg) in both treatment groups (IV/SC and SC/IV).

[redacted]

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[redacted]

Safety

Safety assessment was a secondary endpoint in this study. No deaths were reported during the study. During the randomized crossover period of the study, treatment-emergent SAEs were reported in 6 participants: 2 participants (1.5%) during IV treatment and 4 participants (3.0%) during SC treatment. The incidence of TEAEs that were assessed by the Investigator as related to study treatment was 19.9% overall (8.8% of participants during IV treatment, 14.4% of participants during SC treatment). The higher incidence of treatment-related TEAEs during SC treatment than during IV treatment was primarily due to Injection site pain, which was reported in 6 participants (4.3%) during SC treatment. Most treatment-emergent AEs were mild in severity (40.4% of participants during IV treatment, 40.2% of participants during SC treatment). No ADAs were reported during the study.

Conclusions:

In the extension phase of the Phase 3b study (Part 2), the majority of participants (87.8%) on Q6W dosing preferred SC administration versus IV administration. Disease activity was low overall during the crossover period of the study when participants on Q6W dosing received both SC and IV administration. [redacted] Conclusions regarding efficacy, safety, and clinical pharmacology of SC versus IV administration are limited by the crossover design and short follow-up duration of the study. The safety of natalizumab (IV and SC) administered with extended interval dosing (Q6W) as observed in Part 2 of the NOVA study is consistent with the known safety profile of natalizumab.

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