1. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen MA Inc./Biogen Idec Research Limited	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Natalizumab (BG00002; Tysabri®)	**Name of Active Ingredient:** Natalizumab (BG00002; Tysabri®)	**Study Indication:** Focal Epilepsy

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects With Drug-Resistant Focal Epilepsy

Coordinating Investigator:

Dr [redacted] US was the Coordinating Investigator for this study.

Study Period:	**Phase of Development:** 2
Date of first treatment: 20 March 2018 End of Study Date: 18 November 2020	

Study Objectives:

Primary Efficacy Objective:

- To determine if adjunctive therapy of natalizumab 300 mg IV infusion every 4 weeks reduced the frequency of seizures in adult participants with drug-resistant focal epilepsy.

Secondary Efficacy Objective:

- To assess the effects of natalizumab versus placebo in drug-resistant focal epilepsy on additional measures of seizure frequency.

Exploratory Efficacy Objective:

- [redacted]

PK Objective:

- To evaluate the PK of natalizumab in participants with focal epilepsy.

Safety Objective

- To assess the safety and tolerability of natalizumab in participants with drug-resistant focal epilepsy. Safety and tolerability assessments included AE/SAE data, clinical laboratory data, and suicide ideation and behavior evaluation (eC-SSRS/C-SSRS).

Study Design:

This was a Phase 2, multicenter, double-blind, placebo-controlled, randomized study and consisted of the following phases:

- 6-week prospective baseline period
- 24-week, double-blind, placebo-controlled treatment period

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– 8-week, double-blind, placebo-controlled active run-in period (in order for natalizumab to achieve approximately 75% of steady state in participants without anti-natalizumab antibodies)

– 16-week, double-blind, placebo-controlled efficacy period

- 24-week, open-label active treatment period (open-label phase)
- 12-week, post-treatment follow-up period (equates to 16 weeks after the last dose of study treatment)
- Follow-Up Safety Phone Call (24 weeks after the last dose of study treatment)

After all participants completed the 6-week prospective baseline period, they were randomized in a 1:1 ratio and received 1 dose of study treatment at Week 0 with dosing every 4 weeks for 24 weeks according to 1 of the following 2 regimens: 300 mg IV natalizumab infused over 1 hour or placebo IV. The randomization was stratified, as much as possible, based on the presence or absence of structural etiology for focal epilepsy and on the presence or absence of a high seizure frequency (≥ 24 seizures) during the 6-week prospective baseline period.

The primary database lock and readout of data occurred at the end of the placebo-controlled phase after all the participants had the opportunity to complete the Week 24 visit.

At the end of the placebo-controlled phase, participants continued into a 24-week open-label safety and efficacy phase in which all participants received natalizumab 300 mg IV infusion every 4 weeks for 24 weeks.

Approximately 70 participants were expected to be enrolled, randomized, and dosed (~35 participants in each treatment group) at approximately 44 sites in the US. The study aimed to include approximately 28 participants with a structural etiology for focal epilepsy and approximately 28 participants with a high seizure frequency, and those were not mutually exclusive.

Number of Participants (Planned and Analyzed):

Planned:

Approximately 70 participants were expected to be enrolled, randomized, and dosed (~35 participants in each treatment group) at approximately 44 sites in the US.

Analyzed:

A total of 67 participants (33 participants in the natalizumab group and 34 participants in the placebo group) were randomized at 31 sites in the US.

A total of 66 participants received study treatment during the placebo-controlled phase and comprised the ITT population and Safety Population for placebo-controlled phase. A total of 61 participants completed the placebo-controlled phase and comprised the PP Population

A total of 61 participants entered the open-label phase of the study and received natalizumab and comprised the ITT population and Safety population for open-label phase.

Study Population:

Main Inclusion Criteria:

1. Ability of the participant or his/her legally authorized representative (e.g., parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

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2. Aged 18 to 75 years, inclusive, at the time of informed consent or participant met the minimum age of consent in accordance with national regulations (whichever was higher).
3. Had focal epilepsy diagnosed on clinical grounds and as applicable supported by electroencephalogram findings [Scheffer 2017] and brain imaging. Participants with multifocal epilepsy were included if all other entry criteria were met.
4. Had a drug-resistant epilepsy defined as failure of adequate trials of 2 (or more) tolerated and appropriately chosen and used AEDs (whether as monotherapies or in combination) [Kwan 2010].
5. Had an MRI scan of the brain within 48 months of the Screening Visit (Week -6) to assist in the electroclinical assessment of a structural etiology for focal epilepsy. For participants not meeting this criterion, an MRI could have been obtained within the prospective baseline period. Participants without an MRI of the brain within 48 months prior to screening and with an absolute contraindication to MRI were considered on a case-by-case basis.
6. Had confirmation of diagnosis of drug-resistant focal epilepsy by a member of the IERC. The independent reviewer also adjudicated the presence or absence of a structural etiology for focal epilepsy. Appropriate diagnostic information had to be sent to the reviewer as soon as possible after the Screening Visit (Week -6) but preferably no less than 2 weeks prior to randomization.

   The study aimed to include approximately 28 participants with a structural etiology for focal epilepsy and approximately 28 participants with a high seizure frequency (≥ 24 seizures during the 6-week prospective baseline period), and these were not to be mutually exclusive.
7. Experienced 6 or more seizures during the 6-week prospective baseline period and was not seizure-free for > 21 consecutive days during the prospective baseline period. Seizures included in counts were focal aware seizures (previously termed “simple partial seizures”) with motor signs, focal impaired awareness seizures (previously termed “complex partial seizures”), and focal to bilateral tonic-clonic seizures (previously termed “partial onset with secondary generalization”). Focal aware seizures without motor signs were not included.
8. Stable regimen of 1 to 5 AEDs. Stable was defined as no modification of AED dosing within 4 weeks prior to the Screening Visit (Week -6). Dosing regimen also had to be stable throughout the 6-week prospective baseline period.

Main Exclusion Criteria:

1. Focal aware seizures without motor signs were the only seizure type.
2. Diagnosis of generalized, combined generalized and focal, or unknown epilepsy.
3. Known progressive structural CNS lesion.
4. History of seizures occurring in predominantly clustered patterns, as determined by the Investigator, over the 12 months prior to the Screening Visit (Week -6) or during the 6-week prospective baseline period, where individual seizures could not be counted.
5. History of status epilepticus within the previous 6 months.
6. Known history or presence of nonepileptic seizures.

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7. Current major depressive episode, a positive report on the "baseline/screening" eC-SSRS at the Screening Visit (Week -6) or on the "since last visit" eC-SSRS at Week 0, or considered at risk of suicide or self-harm based on the clinical judgement of the Investigator.
8. Known planned epilepsy surgery or admission to the epilepsy monitoring unit with intended drug change within 12 months of Week 0.
9. Any clinically significant medical condition that could contraindicate the use of natalizumab, impair reliable participation in the study, or necessitate the use of medication not allowed per protocol.
10. Evidence of significant active hepatic disease including elevations of AST or ALT > 3 × ULN or bilirubin > 2 × ULN.
11. Evidence of significant active renal disease including creatinine > 2 × ULN.
12. Evidence of significant active hematologic disease including ANC < 1000 µL; platelet count < 80,000; absolute lymphocyte count < 800 cells/µL.
13. Immunocompromised participants as determined by the Investigator, based on medical history, physical examination, laboratory testing, or immunosuppressive or immunomodulating treatment. Immunosuppressive or immunomodulating treatment, including chronic oral or IV steroids, should have been discontinued at least 4 weeks prior to screening.
14. Exposure to monoclonal antibodies, cytokines, growth factors, soluble receptors, other recombinant products, or fusion proteins within 6 months prior to the Screening Visit (Week -6).
15. Prior exposure to natalizumab.
16. Inability to comply with study requirements including completing or updating seizure diary. Participants who missed > 6 days of seizure diary data during the 6-week prospective baseline period could not be randomized and were considered as screen failures. Participants with limitations who were unable to complete the QOLIE-31, HADS-D, and/or SDMT were not excluded from the study; however, other study requirements had to be completed. At the discretion of the Investigator, the C-SSRS could have been completed in place of the eC-SSRS in these participants.
17. Participants with modification of AEDs during the 6-week prospective baseline period were not to be randomized and were considered as screen failures.

Study Treatment, Dose, Mode of Administration:

In the placebo-controlled phase, participants received the first dose of 300 mg natalizumab or matching placebo by IV infusion at Week 0, and then dosing continued every 4 weeks for 24 weeks. Study treatment was infused over 1 hour, and participants were observed for 1 hour after completion of infusion.

In the open-label phase of the study, all participants received 300 mg IV natalizumab infused over 1 hour. Natalizumab was administered every 4 weeks over a period of 24 weeks. Participants were observed for 1 hour after completion of infusion.

A total of 7 lot numbers of study treatment were used.

Duration of Treatment and Follow-Up:

The total duration of study participation for each participant was up to approximately 74 weeks for participants

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completing the placebo-controlled, open-label, and follow-up phases.

Criteria for Evaluation:

Efficacy:

Daily records of seizures were used to evaluate the primary, secondary, and some of the exploratory efficacy endpoints. Participants (or their caregivers) recorded their seizure type and frequency. Participants brought their seizure diary with them to each study visit.

Efficacy assessments (including seizures) were made using data from eCOA, on a device developed and supported by the eCOA vendor. Study site staff monitored data via a secure Web portal developed and supported by the eCOA vendor. Paper versions of the clinical outcome assessments were available to sites in case of problems or difficulty with connectivity of the e-devices. The SDMT was completed on a paper form and recorded in the eCRF.

In addition, QOLIE-31, HADS-D, and SDMT scores were used to evaluate some of the exploratory efficacy endpoints.

Pharmacokinetics:

The PK of natalizumab were assessed by serum concentrations of natalizumab, for which samples were collected prior to study treatment administration at Week 0 through Week 48 and after infusion at 3 visits at Weeks 0, 20, and 44.

Pharmacodynamics:

[redacted]

- [redacted]
- [redacted]

Safety:

The following clinical assessments were performed to evaluate the safety of the study treatment:

- Medical history, which included an assessment of prior substance abuse.
- Physical examinations and neurological assessments, including height and weight measurements.
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate.
- eC-SSRS/C-SSRS: The participant completed the "baseline/screening" version of the scale at the Screening Visit (Week -6) and the "since last visit" version at all subsequent visits. Participants with a positive report on the eC-SSRS/C-SSRS at the Screening Visit (Week -6) or Week 0 were to be excluded from the study. A positive report was defined as a "yes" response on ideation items 4 and/or 5 or a "yes" response to any behavior item (except nonsuicidal self-injury). All responses at each assessment were reviewed for both positive and negative reports; the Investigator had to determine

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the appropriate level of care for the participant for any "yes" response even if it did not constitute a positive report.

- Concomitant therapy and procedure recording.
- AE and SAE recording: seizures (with the exception of status epilepticus or a clinically significant increase in seizure frequency or intensity or emergence of a new seizure type resulting in discontinuation of study treatment, which should be reported as an SAE) were not to be collected as AEs, as they were considered part of the primary efficacy endpoint; however, they were to be recorded in the seizure diary. New seizure types resulting in discontinuation of study treatment or previous seizures demonstrating a clinically significant increase in frequency or intensity were to be captured as AEs.

Statistical Methods:

Planned Analyses:

Analyses were performed for the predefined populations that included the ITT, PP, safety, PK, and PD populations.

Demographics and Baseline Disease Characteristics:

Demographic and study baseline data (demography, medical history, epilepsy history, seizure history, number of prior and concomitant epilepsy drug and nondrug therapies) were summarized for the ITT population only. Formal statistical analyses were not done to test for homogeneity between treatment groups. If there were apparent heterogeneities between the groups in any of the participant characteristics that were of clinical importance or could affect the treatment outcome, the impact of the imbalances was to be investigated, and adjustments were to be made in the efficacy and safety analyses, if appropriate.

Efficacy Analyses During Placebo-Controlled Phase:

Primary Efficacy Analysis

The efficacy endpoints were analyzed for the ITT population. The primary efficacy endpoint of change from study baseline of log-transformed seizure frequency (number of seizures per 28 days) was summarized using descriptive statistics by treatment group and visit (including 28-day standardized seizure frequency during Weeks 8 to 24). The MMRM model was the primary method for analyzing the change from study baseline of log-transformed seizure frequency. The average effect over Weeks 8 to 24 of each treatment group, as well as the treatment difference, was displayed with a 95% CI and p-value. The effect of each treatment group, as well as the treatment difference, was summarized by visit.

In addition, sensitivity analyses were performed for:

- The same analysis as the primary analysis in the ITT population including observed seizure frequency at all visits regardless of whether compliance was ≥ 85% or not.
- The same analysis as the primary analysis was repeated for the PP population.
- The same analysis as the primary analysis in the ITT population using stratification factors based on observed or adjudicated data instead of the ones used in IXRS for randomization stratification.
- Multiple imputation of missing daily seizure occurrence was also performed. The ANCOVA model was used in analyzing the change from study baseline of log-transformed seizure frequency (number of seizures per 28 days) over Weeks 8 to 24 of treatment, and the imputations were performed on the

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daily seizure data. Seizure frequency over Weeks 8 to 24 was calculated based on the imputed daily seizure data.

Subgroup analysis was performed for the primary endpoint using the MMRM for these variables: structural etiology category for focal epilepsy (presence, absence), seizure frequency category (high: ≥ 24; low: < 24 seizures), and duration of epilepsy (in years) from diagnosis to randomization date (< 10 and ≥ 10 years).

Secondary Efficacy Analysis

Proportion of Responders: The proportion of responders (defined as a participant with a ≥ 50% reduction from study baseline in seizure frequency [number of seizures per 28 days] during Weeks 8 to 24 of treatment) was analyzed using a logistic regression model. The odds ratio from the logistic regression model was displayed with 95% CI and p-value, and the responder rate was summarized by treatment group.

Sensitivity analyses were performed to evaluate the proportion of responders with ≥ 25% reduction and ≥ 75% reduction from study baseline.

These analyses were repeated for the PP population.

Proportion of Participants Free From Seizures: The proportion of participants free from seizures during Weeks 8 to 24 of treatment was summarized descriptively with proportion and 95% exact binomial CI by treatment group for the ITT population who had at least 1 postbaseline seizure assessment after Week 8. The difference of the proportion between the natalizumab and placebo group and the 95% Miettinen-Nurminen CI of the difference were presented.

A sensitivity analysis was performed based on the reported seizure data assuming that no seizure occurred when the diary was missing. If the participants had no seizure reported between the Week 8 visit and the Week 24 visit and did not discontinue the study due to lack of efficacy, the participant was considered seizure-free.

These analyses were repeated for the PP population.

Percentage of Seizure-Free Days Gained, Standardized Over 28 Days, During Weeks 8 to 24 of Treatment Compared With Study Baseline: An MMRM was used to analyze the change from study baseline of log-transformed seizure-free days per 28 days. The average effect over Weeks 8 to 24 of each treatment group and the effect by visit, as well as the treatment difference, were displayed with a 95% CI and p-value.

These analyses were repeated for the PP population.

Proportion of Participants With Inadequate Treatment Response During Weeks 8 to 24: The proportion of participants with protocol-defined inadequate treatment response after the Week 8 visit and prior to the Week 24 visit were analyzed using a logistic regression model.

If there were fewer than 5 events, the IXRS randomization stratification factors were to be dropped out of the logistic model. Protocol-defined inadequate treatment response was to include participants who withdrew from treatment because of lack of efficacy after the 8-week active run-in period, required modifications to AEDs prior to Week 24 (completion of the placebo-controlled phase), or died in a manner related to epilepsy. The odds ratio from the logistic regression was displayed with 95% CI and p-value. The proportion of participants with protocol-defined inadequate treatment response was to be tabulated by treatment group and visit.

Time to inadequate treatment response was analyzed using the Cox proportional hazards model. Independent variables to be included in the model were treatment and IXRS randomization stratification factors. Kaplan-Meier curve by treatment group was also presented. Time to inadequate treatment response was defined as the time from the first infusion of study treatment to the first reported date of protocol-defined inadequate treatment response.

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Participants who did not have a protocol-defined inadequate treatment response during the placebo-controlled phase were censored. The censor date was the time of the last study contact (last scheduled/unscheduled visit) during the placebo-controlled phase.

These analyses were repeated for the PP population.

Exploratory Efficacy Analysis

[redacted]

Efficacy Analyses During Open-Label Phase:

Summary statistics were presented for seizure frequency data by visit (including 28-day standardized seizure frequency during Weeks 32 to 48) and treatment group during the open-label phase.

The durability of treatment response to natalizumab in the open-label phase was assessed by the proportion of participants who continued to respond to natalizumab in the open-label phase among the responders in the placebo-controlled phase. A responder in the open-label phase was defined as a participant with a $\geq$ 50% reduction from study baseline in seizure frequency (number of seizures per 28 days) during Weeks 32 to 48 of treatment. Sensitivity analyses were performed to evaluate the durability of treatment response by defining responders as 1) participants with $\geq$ 25% reduction and 2) participants with $\geq$ 75% reduction from study baseline for both the placebo-controlled phase and open-label phase.

Summary statistics for change from study baseline and change from open-label phase baseline in QOLIE-31 total and subscale scores were presented by visit and treatment group during the open-label phase. In addition, summary statistics for the actual values of QOLIE-31 scores over time were presented. QOLIE-31 scores during the open-label phase were listed for each participant by visit. No imputation was performed for the open-label phase.

Summary statistics for change from study baseline and change from open-label phase baseline in HADS-D total score were presented by visit and treatment group during the open-label phase. In addition, summary statistics for the actual values of HADS-D scores over time were presented. HADS-D scores during the open-label phase were listed for each participant by visit. No imputation was performed for the open-label phase.

Summary statistics for change from study baseline and change from open-label phase baseline in SDMT (using imputed data as defined below) were presented by visit and treatment group during the open-label phase. In addition, summary statistics for the actual values of SDMT scores over time were presented. SDMT results during the open-label phase were listed for each participant by visit. No imputation was performed for the open-label

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phase.

Pharmacokinetics:

The serum concentration of natalizumab was summarized by visit using standard descriptive statistics (e.g., median, mean, standard deviation, range, CV%).

Pharmacodynamics:

[redacted]

Safety:

No formal statistical testing was performed on the safety data. Safety assessments were presented separately for the placebo-controlled phase and the open-label phase based on the date of sample collection. The baseline used in safety assessments for the placebo-controlled phase and open-label phase was primarily the study baseline and open-label phase baseline, respectively, unless otherwise specified.

AEs were presented separately for the placebo-controlled phase and the open-label phase based on the start date of the event. AEs were coded using MedDRA (version 22.1). TEAEs were defined as events having onset on/after the date of the first infusion in each phase or a sign, symptom, or diagnosis that worsened since the event was previously reported. If a participant was not enrolled into the open-label phase of the study or never received open-label infusion of natalizumab during the open-label phase, all TEAEs were considered as occurring during the placebo-controlled phase of the study. A summary of the incidence of TEAEs was provided by treatment group overall, by severity, by relationship to study treatment, by seriousness, by treatment discontinuation, by study withdrawal, and by AESI.

Sample Size Calculations:

For the analysis of primary endpoint, 29 participants per treatment arm would provide 80% power to detect a treatment difference of -0.375 between natalizumab and placebo in the natural log-transformed seizure frequency, standardized over 28 days, at a 2-sided significance level of 0.050, assuming a common standard deviation of the log-transformed frequency of 0.5.

Based on an estimated dropout rate of approximately 15%, a total of approximately 70 participants were randomized

Results:

Participant Accountability:

A total of 66 participants (32 participants in the natalizumab group and 34 participants in the placebo group) received study treatment during the placebo-controlled phase. Overall, 61 participants (91%) completed the placebo-controlled phase of the study, and 5 participants (7%) discontinued study treatment during the placebo-controlled phase.

A total of 61 participants entered the open-label phase of the study and received natalizumab (ITT population and Safety population). Of these 61 participants, 56 participants (84%) completed the open-label phase of the study, and 5 participants (7%) discontinued study treatment during the open-label phase.

Overall, a total of 51 participants (76%) completed the study including the follow-up period.

No participant discontinued the study treatment or discontinued study due to COVID-19 during the placebo-controlled phase of the study, and 5 participants (8.2%) discontinued the study due to the COVID-19

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pandemic during the open-label phase. The reasons for study discontinuation due to COVID-19 pandemic were fear related to the COVID-19 pandemic, site closed due to the COVID-19 pandemic, and other reasons due to the COVID-19 pandemic.

Demographics and Baseline Disease Characteristics:

Overall, the mean (SD) age of participants was 40.9 (13.41) years; 20 participants (30%) were aged ≤ 30 years, 23 participants (35%) were aged 31 to 45 years, 17 participants (26%) were aged 46 to 60 years, and 6 participants (9%) were aged > 60 years. The mean (SD) age was higher for participants in the natalizumab group compared with the placebo group (42.8 [14.56] years and 39.1 [12.17] years, respectively). The majority of participants in the overall population were male (36 participants, 55%) and were of White (42 participants, 64%) or Black or African American (15 participants, 23%) races. The mean (SD) height, weight, and BMI of the overall study population were 167.6 (8.92) cm, 85.1 (21.15) kg, and 30.4 (7.52) kg/m^2, respectively.

Baseline disease characteristics were balanced between the treatment groups. The mean (SD) age of first epilepsy diagnosis for the overall study population was 19.6 (13.93) years and ranged from 0 to 63 years. The majority (80%) of participants had an epilepsy duration of ≥ 10 years, and the mean (SD) duration of epilepsy diagnosis was higher in the natalizumab group than it was in the placebo group (23.8 [14.48] years, range from 4 to 55 years and 20.2 [12.18] years, range from 2 to 45 years, respectively).

The majority of participants in the natalizumab and placebo groups received 2 AEDs (13 participants [41%] and 8 participants [24%], respectively) or 3 AEDs (15 participants [47%] and 15 participants [44%], respectively).

Overall, 34 participants (52%) were registered in the IXRS as having the presence of structural etiology for focal epilepsy, and 46 participants (70%) were registered in IXRS as having high seizure frequency (≥ 24 seizures) during the 6-week prospective baseline period. The IERC assessments for the presence or absence of structural etiology for the study population were generally in alignment with their assessment as registered in the IXRS; however, the standard seizure frequency during baseline period categorization based on diary data was different from that registered in the IXRS and noted 22 participants (33%) with high seizure frequency (≥ 24 seizures) during the 6-week prospective baseline period.

Exposure:

During the placebo-controlled phase, the mean (SD) number of total study treatment infusions administered was similar between the placebo group and the natalizumab group (5.6 [1.24] and 5.8 [1.02], respectively). The mean (SD) compliance rate for the placebo and natalizumab groups was 95.6% (14.40%) and 100.0%, respectively.

During the open-label phase, participants either switched from placebo to natalizumab (placebo to natalizumab group) or continued to receive natalizumab (natalizumab to natalizumab group). Overall, the mean (SD) number of total study treatment infusions administered was similar between the placebo to natalizumab group and natalizumab to natalizumab group (5.7 [0.83] and 5.9 [0.35], respectively). The mean (SD) compliance rate for the placebo to natalizumab and natalizumab to natalizumab groups was 98.9% (4.16%) and 99.4% (3.04%), respectively.

Efficacy:

Efficacy Results During Placebo-Controlled Phase

The efficacy assessments performed in this study support the following conclusions:

- The results for primary efficacy endpoints demonstrated a greater LS mean (SE) log-transformed change for seizure frequency from baseline during Weeks 8 to 24 of the treatment period in the

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natalizumab group (-0.58 [0.17]) than in the placebo group (-0.43 [0.16]). However, the LS mean logarithmic difference for natalizumab to placebo of -0.16 (95% CI: -0.62, 0.32) did not demonstrate a statistically significant difference between the 2 treatment groups (p = 0.51).

- The subgroup analyses performed for the primary endpoint using variables of structural etiology for focal epilepsy (presence, absence), seizure frequency category (high: ≥ 24; low: < 24 seizures), and duration of epilepsy from diagnosis to randomization date (≥ 10 years) were consistent with the overall primary analysis results seen in the ITT population. Subgroup analyses results showed higher reduction in seizure frequency over Weeks 8 to 24 in the natalizumab group compared with the placebo group for all different subgroups studied, except for the subgroup with a duration of epilepsy diagnosis < 10 years. These results for different subgroup analyses did not reach statistically significant level.
- Natalizumab demonstrated an approximately 100% increase in the odds of a ≥ 50% reduction in seizure frequency from study baseline during Weeks 8 to 24 of the treatment period; however, the difference was not statistically significant (OR = 2.09 [95% CI: 0.64, 6.85; p = 0.22]).
- The number of seizure-free days gained from study baseline during Weeks 8 to 24 of treatment was higher in the natalizumab group than in the placebo group, with the LS mean (SE) log transformed change of 0.15 (0.18) in the natalizumab group and -0.24 (0.17) in the placebo group. However, the difference for seizure-free days gained between the natalizumab and placebo groups did not reach statistically significant levels (LS mean logarithmic difference: 0.39 [95% CI: -0.10, 0.88; p = 0.11]).
- One participant in the placebo group (3%) and no participants in the natalizumab group were free from seizure during Weeks 8 to 24 of the treatment period. This small number of seizure-free participants preclude any relevant comparison between the 2 treatment groups for seizure-free analysis.
- Two participants (6%) in the placebo group and 1 participant (3%) in the natalizumab group met criteria of inadequate treatment response during Weeks 8 to 24 of the treatment period. The low number of participants meeting these criteria preclude any relevant comparison of inadequate treatment response between the 2 treatment groups.
- There was no statistically significant difference between the 2 treatment groups for exploratory efficacy endpoints of change from study baseline in frequency of focal (not including focal to bilateral tonic-clonic seizures) and focal to bilateral tonic-clonic seizures during Weeks 8 to 24 of the treatment period.
- There was no difference in the placebo and natalizumab treatment groups for exploratory efficacy endpoints of change from baseline in scores for QOLIE-31, HADS-D, and SDMT scales during Weeks 8 to 24 of the treatment period.

Efficacy Results During Open-Label Phase

- Generally, the efficacy analysis results from the open-label phase are consistent with those from the placebo-controlled phase.
- The mean (SD) change (decrease) of natural log-transformed seizure frequency was not different in the natalizumab to natalizumab and placebo to natalizumab groups (-0.79 [1.41] and -0.73 [1.00],

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respectively).

- The number of seizure-free days gained during the open-label phase treatment period was higher in the natalizumab to natalizumab group than in the placebo to natalizumab group. At Week 48, the mean (SD) change (increase) from study baseline in natural log-transformed seizure-free days was higher in the natalizumab to natalizumab group (0.14 [1.15]) than in the placebo to natalizumab group (-0.02 [0.85]).
- Natalizumab demonstrated durability of treatment response, and the majority of participants (80%) continued to demonstrate a ≥ 50% reduction in the seizure frequency from study baseline throughout the study treatment period.
- QOLIE-31, HADS-D, and SDMT total scores at open-label phase baseline continued to demonstrate more severe disease condition for participants in the natalizumab to natalizumab group than in the placebo to natalizumab group. However, the mean change in scores during the treatment period demonstrated greater improvement or disease stability in the natalizumab to natalizumab group than in the placebo to natalizumab group.

Pharmacokinetics and Pharmacodynamics:

- During both placebo-controlled phase and open-label phase, results of the PK assessments following multiple infusions were consistent with the known PK profile of natalizumab in MS.
- [redacted].
- In the open-label phase, as expected, for participants who switched from placebo to natalizumab in the open-label phase, the α4 integrin saturation increased, with a median (range) value of 84.45% (1.5%, 93.2%) at Week 48.

Safety:

Key safety results from this study are summarized below:

Placebo-Controlled Phase

- The incidence of AEs was similar between the groups (natalizumab, 75%; placebo, 65%).
- Most AEs were mild or moderate in severity. The incidence of severe AEs was low in both groups (natalizumab, 3%; placebo, 6%).
- The incidence of treatment-related AEs was similar between groups (natalizumab, 16%; placebo, 21%).
- An SAE of seizure was reported by 1 participant (3%) in each group. The SAE of seizure reported in the placebo group was considered to be related to study treatment by the Investigator.
- One participant (3%) in each group had an AE that led to discontinuation of study drug and study withdrawal.
- No participants died during the study.

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- Three participants in the natalizumab group and 1 participant in the placebo group reported suicidal ideation during the placebo-controlled phase. No participants had positive reports of suicidal ideation and suicidal behavior during treatment based on the responses provided on the eC-SSRS/C-SSRS.
- Six participants in the placebo group had AESIs (flushing, cough, ALT increased, AST increased, hepatic enzyme increased, and infusion site discomfort), and 2 participants in the natalizumab group had AESIs (rash and urticaria). No participants had AESIs of PML or opportunistic infections.
- Results of laboratory and vital sign assessments did not reveal any new safety concerns.
- Two participants in the natalizumab group were persistently positive for anti-natalizumab antibodies.

Open-Label Phase

- The incidence of AEs was similar between groups (natalizumab to natalizumab group, 57%; placebo to natalizumab group, 65%).
- Most AEs were mild or moderate in severity. The incidence of severe AEs was low in both groups (natalizumab to natalizumab group, 13%; placebo to natalizumab group, 10%).
- The incidence of treatment-related AEs was similar between groups (natalizumab to natalizumab group, 13%; placebo to natalizumab group, 19%).
- Three participants in the placebo to natalizumab group reported 1 SAE each (seizure, seizure cluster, COVID-19) and 2 participants in the natalizumab to natalizumab group reported a total of 3 SAEs (seizure, large intestine perforation, pneumonia aspiration). The SAEs were not considered to be treatment related.
- Two participants (6%) in the placebo to natalizumab group had an AE that led to discontinuation of study drug and study withdrawal, respectively.
- No participants died during the study.
- One participant (5%) in the natalizumab to natalizumab group had at least 1 positive report of suicidal ideation and suicidal behavior (aborted attempt, interrupted attempt, and nonfatal suicide attempt) during treatment based on the responses provided on the eC-SSRS/C-SSRS in the open-label phase.
- Five participants in the placebo to natalizumab group had AESIs (chest discomfort, choking, cough, dyspnea, and flushing) and 2 participants in the natalizumab to natalizumab group had AESIs (rash and ALT increased). No participants had AESIs of PML, infusion site reactions, or opportunistic infections.
- Results of laboratory and vital signs assessments did not reveal any new safety concerns.
- A total of 5 participants (7.7%), including 3 participants (8.8%) in the placebo to natalizumab group and 2 participants (6.5%) who continued to receive natalizumab, were persistently positive for anti-natalizumab antibodies during the overall study.

Conclusions: The reduction in seizure frequency from baseline, as assessed by log-transformed seizure frequency using the MMRM during Weeks 8 to 24 efficacy analyses treatment period, while high for the natalizumab group

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compared with placebo group, did not reach statistical significances.

- A greater proportion of subjects in the natalizumab group demonstrated a reduction in seizure frequency and a gain in seizure-free days during Weeks 8 to 24 efficacy analyses treatment period.
- Better outcomes were generally observed in participants who had a confirmed presence of structural etiology of focal epilepsy than in participants in whom structural etiology for focal epilepsy was absent and in participants with an epilepsy diagnosis duration of ≥ 10 years.
- The overall safety evaluation of natalizumab in this study is consistent with its known safety profile.
- Results of the PK assessments following every 4-week infusion interval in this study were consistent with the known PK profile of natalizumab in MS.
- [redacted]

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