These Clinical Study Results are provided for informational purposes only.

The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2. STUDY SYNOPSIS

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Name of Finished Product:	**Name of Active Ingredient:**	**Study Indication:**
Natalizumab (Tysabri®)	Natalizumab	Multiple sclerosis

Title of Study:

A prospective, open-label, non-randomized, clinical trial to evaluate the safety and efficacy in Russian RRMS patients on one year treatment with natalizumab (Tysabri®)

Principal Investigator/Coordinating Investigator:

[redacted] Russia

Study Period:	**Phase of Development:**
Date of first treatment: 08 June 2012 End of Study Date: 27 December 2013	4

Study Objectives:

Primary Objective:

The primary objective of this study was to evaluate the safety and tolerability of natalizumab in the study population.

Secondary Objectives:

Secondary objectives of this study were as follows:

- Clinical evidence of disease activity:
  - Relapses
    - Annualized relapse rate (ARR)
    - Time to first relapse
    - Evolution of severity of the relapse:
      - Number of relapses requiring hospitalization
      - Number of relapses requiring steroid treatment
    - Proportion of patients free of relapses at 12 months
  - EDSS
    - Progression on EDSS is defined by at least 1.0 point, sustained for 12 weeks (or 1.5 for patients with an EDSS score of 0 at Baseline)
    - Time to EDSS progression

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- Proportion of patients without progression on EDSS
- Proportion of patients with improvement on EDSS by at least 1.0 point sustained for 12 weeks for patients with an EDSS score ≥2 at Baseline
- EDSS score and change from Baseline to year 1

• Functional tests
- Evolution of Nine-Hole Peg Test (9HPT) score
- Evolution of Timed 25-Foot Walk (T25FW)
- Evolution in cognitive changes as assessed by the Symbol Digit Modalities Test (SDMT)
- Evolution in visual function test (VFT)

• Quality of life (QoL) self-assessment questionnaires (SF-36 and Multiple Sclerosis Impact Scale, 29 items [MSIS-29])
- Evolution of the SF-36 Mental Component Scale (MCS) and Physical Component Scale (PCS) from baseline over the Treatment Period with natalizumab

• Evidence of MRI disease activity
- Number of gadolinium (Gd)-enhancing lesions at Week 48
- Number of new or enlarging T2 hyperintense lesions at Week 48 compared with baseline
- Number of new T1 hypointense lesions (black holes) compared with baseline
- Proportion of conversion of Gd-enhancing lesions into black holes at 12 months
- Free of disease activity (clinical activity and/or MRI activity):
  - Proportion of patients with no relapses and no progression in EDSS score at 12 months
  - Proportion of patients free of MRI activity (no new Gd-enhancing and no new or newly enlarging T2 hyperintense lesions)
  - Proportion of patients free of disease activity (no clinical or MRI activity)

• Anti-JCV antibody evaluation
- At Baseline: evaluation of prevalence of positive anti-JCV antibody test results in this Russian MS patient cohort.
- For patients with negative anti-JCV antibody test results at Baseline: rate of seroconversion after 1 year

Study Design:

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Natalizumab (Tysabri®)	Natalizumab	Multiple sclerosis

Study RUS-TYS-11-10158 was a prospective, open-label, non-randomized, multicenter**,** clinical study to evaluate the safety and efficacy in Russian patients with relapsing-remitting multiple sclerosis (RRMS) on 1 year of treatment with natalizumab.

Eligible patients received infusions of natalizumab 300 mg intravenously (IV) once every 4 weeks for 48 weeks**.**

Number of Subjects (Planned and Analyzed):

Planned:

Approximately 100 Russian patients with RRMS were planned for the study.

Analyzed:

A total of 100 patients were included in the analysis population.

Study Population:

Main Inclusion Criteria:

- Must have given written informed consent and provided all authorizations required by local law (e.g., Protected Health Information).
- Men or women between 18 and 60 years of age, inclusive.
- Must have been natalizumab naïve.
- Must have had a documented diagnosis of a relapsing remitting form of MS as defined by the revised McDonald Committee criteria.
- Must have had at least 1 relapse in the previous year; patients must have fulfilled the following criteria:
- Patients with high disease activity despite treatment with interferon-beta (IFN-β) or glatiramer acetate (GA) defined as patients who had failed to respond to a full and adequate course of IFN-β or GA. Patients must have had at least 1 relapse in the previous year while on therapy, and have had at least 9 T2 hyperintense lesions on brain magnetic resonance imaging (MRI) or at least 1 Gd-enhancing Gd-enhancing lesion

  OR

- Patients with rapidly evolving severe RRMS defined as patients who have had 2 or more disabling relapses in 1 year and either 1 or more Gd-enhancing lesions on brain MRI or a significant increase in T2 lesions as compared with a previous MRI.
- Must have been stable in disability for at least 30 days prior to enrollment to the study.
- Must have been stable in symptomatic management of the disease, specifically spasticity, depression and fatigue for at least 30 days prior to enrollment into the study.
- Must have been considered by the Investigator to be free of signs and symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on medical history, physical examination, or laboratory testing.

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- Must have been willing to discontinue and remain free from concomitant immunosuppressive or immunomodulatory treatment (including IFN-β and GA) while being treated with natalizumab during the study.

Main Exclusion Criteria:

- Onset of a relapse within 50 days prior to first infusion.
- Considered by the Investigator to be immunocompromised, based on medical history, physical examination, or laboratory testing or due to prior immunosuppressive treatment.
- History of, or available abnormal laboratory results indicative of, any significant viral, cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric (including major depression), renal, and/or other major disease that would have precluded the administration of a recombinant humanized antibody immunomodulating agent. The Investigator must have re-reviewed the patient's medical fitness for participation and consider any diseases that would preclude treatment.
- History of malignancy (patients with basal cell carcinoma that has been completely excised prior to study entry remained eligible).
- Known history of human immunodeficiency virus infection or hematological malignancy.
- History of organ transplantation (including antirejection therapy).
- A clinically significant infectious illness (e.g., abscess, pneumonia, septicemia) within 30 days prior to the Screening Visit.

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

Commercially available natalizumab (Tysabri) was administered once every 4 weeks according to the Summary of Product Characteristics (SmPC).

Duration of Treatment and Follow-Up:

Treatment Period:

The study included a Screening Visit, a Baseline Visit, and a 48-week Treatment Period. All screening tests and assessments were to be performed prior to the first infusion at the Baseline Visit. Patients reported to the study site to receive natalizumab once every 4 weeks (28 days ± 7 days) for 48 weeks.

Follow-up:

A telephone follow-up was performed at Week 52 to assess adverse events (AEs) and serious adverse events (SAEs). This was considered the end of study.

Criteria for Evaluation:

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

Efficacy:

- Evaluation of relapse activity:

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MS relapses were defined as new or recurrent neurological symptoms, confirmed by the Investigator, not associated with fever, lasting for at least 24 hours, and following a period of improvement or stabilization of symptoms of at least 30 days.

- ARR
- Time time to first relapse
- Evaluation of severity of the relapse:
  - Number of relapses requiring hospitalization
  - Number of relapses requiring steroid treatment
- Proportion of patients free of relapses at 12 months

- Evaluation of disability:
  - Progression on Expanded Disability Status Scale (EDSS) score by at least 1.0 point sustained for 3 months (or 1.5 points for patients with an EDSS score of 0 at Baseline)
  - Time to EDSS progression
  - Proportion of patients with no EDSS progression
  - Percentage of patients with improvement on EDSS score by at least 1.0 point sustained for 3 months patients with EDSS ≥2 at Baseline
  - Evolution in 9HPT score from baseline
  - Evolution of T25W from baseline
  - Evolution of cognitive changes as assessed by the SDMT from baseline
  - Evolution of VFT changes from baseline
  - Free of clinical disease activity

Evaluation of natalizumab impact on patient's health problems based on SF-36 and MSIS-29 self-assessment questionnaires about aspects of daily life MRIs were read locally and stored in case of need for comparison with future MRIs and/or for future access by Biogen Idec or its designee(s).

- Evaluation of MRI activity:
  - Number of T1 Gd-enhancing lesions at Week 48
  - Number of new or newly enlarging T2 hyperintense lesions at Week 48 compared with baseline
  - Number of new T1 hypointense lesions (black holes) at Week 48
  - Proportion of conversion of Gd-enhancing lesions into black holes at Month 12
  - Proportion of patients free of MRI activity (no new Gd-enhancing lesions and no new or newly enlarging T2 lesions)

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- Free of disease activity (no clinical and no MRI activity since Baseline)

Safety:
The long-term safety (incidence and pattern of AEs and SAEs, including infections and discontinuations; high and low exacerbations of hematology and clinical chemistry findings) of natalizumab.

In addition:

- Anti-natalizumab antibodies if the patient had disease activity or persistent infusion reactions after 6 months.
- Anti-JCV antibody at Week 48 for patients who had anti-JCV antibody negative results to evaluate seroconversion.

Statistical Methods:

Demographics and Baseline Disease Characteristics:

All data were summarized by presenting the frequency distributions for discrete endpoints and summary statistics (i.e., mean, standard deviation [SD], median, and range) for continuous endpoints.

The demographic data collected in this study were age, gender, height, weight, and body mass index (BMI). MS history (time since onset of symptoms and time since diagnosis) and relapse history (number of relapses during the previous 1 and 2 years) were summarized.

Medical history data, including concomitant medications, previous treatments for MS, history of treatment with immunosuppressants and steroids, baseline EDSS and functional test results, brain and spinal cord MRI, anti-JCV antibody status, and SF-36 and MSIS-29 scores, were summarized.

Efficacy:

All efficacy data were summarized by presenting frequency distributions and/or basic summary statistics (mean, SD, median, and range). All analyses were conducted using a 2-sided test and a significance level of 0.05.

For efficacy data based on proportion (e.g., patients who experienced infusion reactions during the study), these data were summarized using proportion estimate and a 95% confidence interval (CI) based on a binomial distribution. For efficacy data based on time to event occurrence (e.g., time to first relapse, time to confirmed EDSS progression), these variables were summarized using Kaplan-Meier estimates. For other efficacy data (e.g., EDSS score, MSFC score, Gd-enhancing lesion counts, SF-36, and MSIS-29), these variables were summarized by presenting frequency distributions and/or basic summary statistics (mean, SD, median, and range). For changes from baseline in continuous variables (e.g., EDSS, MSFC), these variables were analyzed using a 1-sample test. If these data were not normally distributed, a nonparametric Wilcoxon signed rank test was used to evaluate the null hypothesis that the median difference was equal to 0. If these data were approximately normally distributed, then a paired t-test was used. Stratified, correlation, and graphical analyses were performed to explore the association between baseline characteristics and change scores. Discrete categorical data were analyzed using McNemar's test. If required, a repeated measures analysis was performed to assess changes in EDSS and in MSFC and its subscores.

All secondary analyses were based on the Efficacy Population.

For the secondary endpoints of time to first relapse and time to confirmed EDSS progression, Kaplan-Meier

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estimates was used to estimate the median time for the event to occur. A Cox proportional hazard model was also used to evaluate the effect of important baseline characteristics (e.g., age, baseline EDSS, disease duration, relapses in the previous year) on these secondary endpoints.

For secondary endpoints, including ARR, number of relapses requiring hospitalization, and number of relapses requiring steroid treatment, summary statistics, including mean, median, SD, and range, were provided as well as the 95% CI; if needed, an analysis of covariance (ANCOVA) model adjusting for important baseline characteristics was used to assess the effect of baseline characteristics for these secondary endpoints.

For the ARR, a negative binomial regression model was used for analysis. If the data were under-dispersed, or if the negative binomial regression did not converge, a Poisson regression model with the same covariates was used instead of the negative binomial regression model. Comparison of ARR before and after natalizumab infusion was performed using a negative binomial regression or Poisson regression.

For EDSS score and change in EDSS scores, 9HPT score, T25FW, SDMT, and SF-36 and MSIS-29 self-assessment questionnaires, the scores and changes were summarized at Baseline, Week 24, and Week 48; a paired t-test or signed rank test was used to evaluate the changes in these secondary endpoints under the assumption of no change over time; McNemar's test was also used to test the categorized change of these endpoints. Furthermore, a repeated measures analysis was performed to assess the raw changes in these secondary endpoints over the whole study time. Besides the time covariate, additional covariates including most of the baseline characteristics will also be evaluated in the longitudinal data analysis for their effect on the changes and their interactions with the time covariate. The average change from baseline over all post-baseline timepoints was also assessed.

For secondary endpoints involving proportion (relapse free at 12 months, progression on EDSS, improvement on EDSS, freedom from clinical disease activity, prevalence of anti-JCV antibody positivity, percentage of seroconversion rate for patients who had negative anti-JCV antibody results at Baseline), these endpoints were summarized using the estimated proportion, along with the 95% CI following a binomial distribution. Any further exploration of these secondary endpoints (e.g., comparison between certain subgroups by baseline age group, by prior treatment) was performed using the Chi square or Fisher's exact test. The SF-36 was summarized based on PCS, MCS, and normalized component score. The mean and mean change from baseline of these scores was summarized descriptively at each visit. The MSIS-29 was summarized based on the physical impact and psychological impact composite scores. Mean and mean change from baseline in MSIS-29 composite scores was summarized descriptively at each visit. A paired t-test or signed rank test was used to evaluate the changes.

For the secondary endpoints involving MRI, the number of lesions was summarized at Baseline and Week 48, and percentage reduction in lesion counts was summarized at Week 48. In addition, the percentage of patients with unchanged or decreased (vs. increased) lesion counts from baseline to Week 48 was summarized.

Safety:

The incidence of clinical AEs was summarized overall, by severity and by relationship to natalizumab. The summary tables included incidence estimates for overall system organ classes (SOCs) as well as for individual events within each SOC. The incidence of AEs that resulted in study drug discontinuation was summarized. Hypersensitivity reactions were summarized. An overall incidence of SAEs, which is the percentage of patients experiencing at least 1 SAE, was summarized. Incidences of SAEs were also presented by SOC and preferred term.

Laboratory data (hematology and biochemistry) were analyzed using shift tables. Each patient's hematology and

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biochemistry values were flagged as "low," "normal," or "high" relative to the normal ranges of the central laboratory. Shifts from baseline to high/low status for hematology and biochemistry parameters were presented.

Vital signs were summarized by visit. Mean and mean changes from baseline were summarized descriptively.

Sample Size Calculations:

Up to 125 patients with RRMS were to be included in Study RUS-TYS-11-10158. With a sample size of 100 patients and an expected 20% occurrence of infusion reactions among patients receiving natalizumab, the upper and lower 95% confidence bounds would extend ± 0.08 (or 8%) from the estimated proportion of occurrence of infusion reactions during the first year of therapy. Assuming approximately a 20% dropout rate, the target sample size was 125. A total of 100 patients with RRMS were enrolled in this study.

Results:

Subject Accountability:

All 100 patients (100%) were included in the Safety and Efficacy Populations. Ninety-two (92.0%) of the patients who were dosed completed the study. Eight patients (8.0%) discontinued study treatment and withdrew from the study; of these, 2 patients were noncompliant and 6 patients discontinued voluntarily for reasons other than an AE.

Demographics and Baseline Disease Characteristics:

The median age of the study population was 37.0 years, with a range of 19 to 61 years. The majority of patients were between 20 and 60 years old, with 1 patient ≤20 years old and 1 patient older than 60 years. Mean time since the onset of MS symptoms was 7.9 years (± 5.56 years), and the mean time since the diagnosis of MS was 4.4 years (± 3.85 years). The mean weight and height were 67.3 kg (± 14.27 kg) and 170.0 cm (± 8.74 cm), respectively. The mean (± SD) body mass index was 23.16 (± 4.030). The majority (60.0%) of the patients were female. The mean number of relapses within the prior 1 year and 2 years was 1.8 (± 0.73) and 2.8 (± 1.14), respectively. Prior to starting treatment with natalizumab, the majority of patients had experienced 1 or 2 relapses (36.0% and 57.0%, respectively). Overall, 82.0% of patients had received at least 1 prior approved treatment for MS, and 34% had received more than 1 prior treatment. Concomitant medications or nondrug therapies were taken by 41% of patients. The most commonly used medication (12% of patients) was methylprednisolone; methylprednisolone was given to 12 of the 13 patients who experienced a relapse during the study. All patients received natalizumab 300 mg IV once every 4 weeks as per label for 12 doses; 1 patient missed the Week 12, Week 16, and Week 20 infusions of natalizumab.

Efficacy:

Clinical evidence of disease activity was assessed by relapse data, EDSS scores, functional test scores, MRI activity, and QoL assessments.

Only 13 patients experienced a relapse during the course of the study; this represented a decrease in ARR from a prestudy value of 1.75 (95% CI of 1.61, 1.90) to 0.16 (95% CI of 0.09, 0.27). This decrease in ARR was very statistically significant ($p < 0.0001$). A Kaplan-Meier analysis of the time to first relapse was determined to be 13.33% at Week 48. Of the 13 patients who experienced a relapse during the study, 5 patients were hospitalized and 12 received treatment with a steroid.

Overall, there was a small but statistically significant improvement from baseline in mean EDSS scores at Week 24 (-0.1 ± 0.45, $p = 0.0131$) and Week 48 (-0.1 ± 0.52, $p = 0.0116$), although these improvements may not have been

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clinically meaningful. When stratified by baseline EDSS score, the mean improvements at Week 24 and Week 48 for patients with a baseline score ≥3 were still statistically significant (p = 0.0212 and p = 0.0142, respectively). However, the mean improvements at Week 24 and Week 48 for patients with a baseline score <3 were not statistically significant (p = 0.3590 and p = 0.3559, respectively). The loss of significance for the improvement over baseline for patients with a baseline score <3 may reflect the small number of patients in this group (n = 20).

Five patients (5.1%) exhibited an improvement in EDSS score (defined as an improvement of at least 1.0 point sustained for 12 weeks in patients with an EDSS score of ≥2 at Baseline) at Week 48. Sixty-two patients showed no improvement from baseline in EDSS score at Week 48. The numbers of patients who showed an improvement in EDSS score of -0.5, -1.0, -1.5, and -2.0 over baseline at Week 48 were 14, 7, 2, and 1, respectively, although not all of these improvements met the criteria for a sustained improvement (i.e., improvements below -0.5, baseline EDSS score <2, and improvements occurring after the Week 36 dose).

Four patients (4.0%) exhibited a progression on EDSS score (defined as a progression of at least 1.0 point sustained for 12 weeks in patients with an EDSS score of ≥2 at Baseline) at Week 48. The cumulative probability of a sustained progression at Week 48 was 4.22%. Only 1 patient who experienced a relapse had a baseline EDSS score < 3.0; the other 12 patients had baseline scores of ≥3.0.

Functional tests included the 9HPT, the T25FW, SDMT, and VFT.

An improvement over baseline scores in mean response times for the 9HPT was observed at Week 24 (1.6 ± 4.97 seconds) and Week 48 (-1.3 ± 4.9 seconds); these improvements were statistically significant (p = 0.0021 and p = 0.0118, respectively) but were not considered clinically meaningful. An additional analysis revealed that 13.0% of patients had at least a 15% improvement in 9HPT scores at Week 48, and 7.0% of patients had at least a 20% improvement at Week 48. For patients with the greatest improvement in 9HPT scores, there did not appear to be any relationship to their baseline EDSS score or to the change in EDSS score at Week 48.

There was no change over baseline in either the mean or median time to perform the T25FW at Week 24 and Week 48 or the mean or median speed on the T25FW at Week 24 and Week 48. However, an additional analysis of the percentage improvement revealed that 17.0% of patients had at least a 15% improvement in their T25FW mean times at Week 48, and 12.0% of patients had at least a 20% improvement at Week 48. For patients with the greatest improvement in T25FW scores, there did not appear to be any relationship to their baseline EDSS score or change in EDSS score at Week 48.

Overall, there was an improvement over baseline scores in the mean SDMT scores at Week 24 (1.0 ± 8.35) and Week 48 (3.1 ± 8.74). Although the improvement in mean score at Week 48 was statistically significant (p = 0.0009), the mean change was small and not considered clinically meaningful.

For the VFT, at Week 24 there were small improvements in the mean scores for the 100%, 2.5%, and 1.25% charts, all of which showed some statistically significant difference from the baseline values (p = 0.0151, p = 0.0257, and p = 0.0264, respectively). However, there was no change in the median values at Week 24 for all 3 charts, and by Week 48 the median changes from baseline were smaller. The only mean change to reach statistical significance at Week 48 was for the 1.25% chart result (p = 0.0366).

An additional analysis of the VFT data to determine the number of patients who exhibited a ≥ 7-letter improvement or a ≥ 5-letter improvement over baseline at Week 48 showed that, for the 100%, 2.5%, and 1.25% charts, 9.0%, 10.0%, and 13.0% of patients, respectively, showed a 7-letter improvement; and 13.0%, 19.0%, and 21.0% of patients, respectively, showed a 5-letter improvement.

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Evidence of disease activity was evaluated by changes in MRI. There no change from baseline in the median number of T1 Gd-enhancing lesions at Week 48, but there was a reduction in the mean number (37.6% ± 50.89%). Overall, 36 (38.7%) patients had a decrease in the number of Gd-enhancing lesions at Week 48 compared with baseline, and 56 (60.2%) had no change in the number of Gd-enhancing lesions at Week 48 compared with baseline. Only 1 patient experienced 1 or more new Gd-enhancing lesions at Week 48. The proportion of Gd-enhancing lesions that converted to black holes at Week 48 was not determined.

There was no change from baseline in the median number of T2 lesions at Week 48. Overall, 5 patients (5.4%) had a decrease in the number of T2 lesions at Week 48 compared with baseline, and 66 (70.1%) had no change in the number of T2 lesions at Week 48 compared with baseline. Twenty-two patients (23.7%) had an increase in the number of T2 lesions at Week 48 compared with baseline.

There was no change from baseline in the median number of T1 lesions (black holes) at Week 48, and no meaningful change in the mean number of T1 lesions at Week 48 (-1.2% ± 36.86%). Overall, 9 patients (9.7%) had a decrease in the number of T1 lesions at Week 48 compared with baseline, and 74 (79.6%) had no change in the number of T1 lesions at Week 48 compared with baseline. Ten patients (10.8%) had an increase in the number of T1 lesions at Week 48 compared with baseline.

Overall, 98.9% of patients had no change or a decrease in the number of T1 Gd-enhancing lesions at Week 48 compared to baseline; 76.3% of patients had no change or a decrease in the number of T2 lesions at Week 48 compared to baseline; and 89.2% of patients had no change or a decrease in the number of T1 lesions at Week 48 compared to baseline.

Overall, after 12 months of treatment with natalizumab, 86 (86.0%) patients were free of clinical disease activity at Week 48; 87 (87.0%) patients had not experienced any relapses by Week 48; and 96 (96.0%) had not experienced any progression in their EDSS score by Week 48.

Changes in QoL were assessed by the SF-36 and the MSIS-29 questionnaires. For the SF-36 PCS scores, there was no statistically significant change from baseline at any assessment visit; SF-36 MCS scores showed small but statistically significant ($p \leq 0.05$) improvements at Week 4 ($p = 0.0019$), Week 8 ($p = 0.0158$), and Week 24 ($p = 0.0409$) but not at Weeks 12 and 48. For the SF-36 component score, improvements were statistically significant at all 5 timepoints for the role physical score, at 3 timepoints for the mental health and social functioning scores, at 2 timepoints for the physical functioning and vitality score, and at 1 timepoint for the role emotional score. The physical functioning, role physical, and vitality were the only SF-36 components to show statistically significant improvement at Week 48 ($p = 0.0366$, $p = 0.0228$, and $p = 0.0236$, respectively). However, the improvements from baseline for scores that did reach statistical significance were not considered clinically meaningful.

Improvement over mean baseline score was observed at Weeks 4, 8, 12, 24, and 48 for both the physical and psychological scores of the MSIS-29 assessment. For the Week 24 and Week 48 physical scores, the mean change from baseline was noticeably significantly different from baseline ($p = 0.0002$ and $p = 0.0067$, respectively). The mean changes from baseline in the psychological score of -5.0 ± 14.91 and -3.8 ± 16.8 for the Week 24 and Week 48 Visits, respectively, were also statistically significant ($p = 0.0019$ and $p = 0.0356$, respectively). Mean improvements over baseline of both physical and psychological scores that were statistically significant at Week 24 were also considered to indicate a clinically meaningful improvement.

Safety:

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The extensive safety data from clinical studies and postmarketing use of natalizumab patients have resulted in a well-characterized safety profile. The use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by JCV, which may be fatal or result in severe disability. Factors that increase the risk of developing PML are the presence of anti-JCV antibodies, duration of natalizumab treatment (especially with more than 2 years of therapy), and prior use of an immunosuppressant therapy. These 3 risk factors can be used to stratify subpopulations of patients into varying risk levels and thereby provide an important tool for physicians and patients when making individual decisions regarding initiation or continuation of natalizumab therapy. There were no events of PML in Study RUS-TYS-11-10158. Approximately 72% of Russian patients had positive anti-JCV antibody test results in this study. However, because the number of patients evaluated was low, it was not possible to determine whether this was representative of Russian MS population, although it is comparable with the incidence of 68.2% reported for a Turkish MS population.

Infusion and hypersensitivity reactions are also known risks associated with natalizumab use, with the latter considered an important risk; however, they are manageable in routine clinical practice. In Study RUS-TYS-11-10158, only 1 patient had an infusion-related AE, and no hypersensitivity reactions were reported. Central nervous system (CNS) herpes infections (meningitis and encephalitis) and hepatotoxicity events are additional safety concerns; however, no such events were observed in Study RUS-TYS-11-10158.

In summary, natalizumab appears to be well tolerated in Russian MS patients; there were no deaths, only 3 patients experienced an SAE, and only 1 patient discontinued therapy with natalizumab and withdrew from the study due to an AE (the patient experienced 2 SAEs one of which was assessed as related to natalizumab treatment). The majority of AEs were assessed as mild; only 1 AE was assessed as severe in intensity. Only 2 AEs were assessed as related to natalizumab treatment. Overall, Study RUS-TYS-11-10158 demonstrates that natalizumab, at a dose of 300 mg administered every 4 weeks by IV infusion, is well tolerated and has a safety profile in Russian patients that was generally consistent with the safety profile established in natalizumab studies outside Russia.

Conclusions:

Overall, with the exception of a slightly greater proportion of males and a higher mean baseline EDSS score, the demographics and disease history of patients treated in this study were similar to those of patients described in other postmarketing studies, but when compared with the pivotal study (C-1801), they had a longer duration of MS disease. They also had a higher disease activity in the previous year and a higher disability score than in Study C-1801. The higher mean EDSS score at Baseline when compared with other studies may be a reflection of the greater proportion of men in the study. The proportion of patients who received prior immunosuppressant therapy was also comparable to that seen in other postmarketing studies.

Based upon the results of this study, natalizumab appeared to be well tolerated in this cohort of Russian MS patients, with a rate of study completion greater than 90% and a safety profile that compared favorably with other postmarketing studies, with few SAE, no deaths, and no cases of PML during the 12 months of treatment with natalizumab. Seventy-one patients (71.7%) had positive anti-JCV antibody test results at Baseline, higher than the prevalence of 55% in the general MS population but comparable to that reported for a Turkish MS population (68.2%).

The ARR at Week 48 was 0.16, a statistically significant ($p < 0.0001$) decrease from baseline, and the proportion of patients free of relapses at 12 months was 87%; both results are comparable to or slightly better than that reported for other postmarketing studies. The time to first relapse that required hospitalization or treatment with steroids was determined to be 13.33% at Week 48.

Name of Sponsor/Company: Biogen Idec International GmbH Landis & Gyr-Strasse 3 CH 6300 Zug Switzerland	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Natalizumab (Tysabri®)	**Name of Active Ingredient:** Natalizumab	**Study Indication:** Multiple sclerosis

In this study there was no apparent relationship between the number of infusions received and the occurrence of a relapse. Nor was there any apparent relationship between a patient's relapse history in the 2 years prior to enrollment and the occurrence of a relapse during the study. Thirteen patients experienced at least 1 relapse during the study; 12 patients were hospitalized and received therapy with steroids, and 1 patient was neither hospitalized nor received steroids.

There was a small but statistically significant improvement from baseline in the mean EDSS scores at Week 48 ($p = 0.0116$), similar to the improvement reported in some postmarketing studies over 12 months of treatment with natalizumab.

At Week 48, 86.0% of patients were free of clinical disease activity, 87.0% had not experienced any relapses by Week 48, and 96.0% had not experienced any progression in EDSS score by Week 48. These results are comparable to those reported for other postmarketing studies.

Three components of the MSFC (9HPT for arm/hand function, T25FW for leg function and ambulation, SDMT for cognitive function, and VFT for visual function) were employed in this study to determine clinical outcome. Minor improvements were observed in the mean values for these evaluations, some of which reached statistical significance. At Week 48, 12.0% of patients had at least a 20% improvement in walking speed in the T25FW that was considered to be clinically meaningful.

Overall, the patients in this study experienced a stabilization of their MRI profile. At Week 48, 98.9% of patients had no change or a decrease in the number of Gd-enhancing lesions compared with baseline, 76.3% had no change or a decrease in the number of T2 lesions, and 89.2% had no change or a decrease in the number of T1 lesions. At Week 48, 38.7% of patients experienced a decrease in the number of Gd-enhancing lesions and 5.4% experienced a decrease in the number of T2 lesions. New Gd-enhancing lesions at Week 48 were reported for only 1 patient.

The 2 QoL assessments used (SF-36 and MSIS-29) both demonstrated improvements in QoL. For the MSIS-29, the mean improvements from baseline at Week 48 in both the physical score and the psychological score were statistically significant at $p = 0.0067$ and $p = 0.0356$, respectively. For the SF-36, there were small but statistically significant ($p \leq 0.05$) improvements at Week 4 ($p = 0.0019$), Week 8 ($p = 0.0158$), and Week 24 ($p = 0.0409$) for the MCS, but there were no statistically significant improvements for the PCS at any timepoint. Additionally, 6 of the 8 component scores (role physical score, mental health, social functioning, physical functioning, vitality, and role emotional) had improvements from baseline that reached statistical significance at 1 or more timepoints. These results appear to be in accord with QoL reports from other postmarketing studies.

Overall, the Study RUS-TYS-11-10158 patient population was comparable to those in other natalizumab studies for RRMS, exception that the percentage of male patients and anti-JCV antibody positivity were slightly higher. There was no safety information inconsistent with the Periodic Safety Update Report, and the reduction in clinical disease and MRI activity as well as improvements in EDSS, MSFC components, and QoL assessments were comparable to those seen in other postmarketing studies.

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Version: 1