These Clinical Study Results are provided for informational purposes only.

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

2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen 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: Tysabri® (natalizumab)	**Name of Active Ingredient:** Natalizumab (BG00002)	**Study Indication:** Multiple Sclerosis

Title of Study:

JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri®: STRATIFY-2

Principal Investigator/Coordinating Investigator:

[redacted], MD ([redacted]) was selected as the Coordinating Investigator for Study 101JC402.

Study Period:	**Phase of Development:**
Date of first sample collection: 31 March 2010 End of study date: 12 February 2016	4

Study Objectives:

Primary Objective:

The primary objective of this study was to demonstrate that the incidence of progressive multifocal leukoencephalopathy (PML) in Tysabri-treated patients who did not have detectable antibodies to John Cunningham virus (JCV) [antibody negative] was lower than in patients who had detectable antibodies to JCV (antibody positive).

Secondary Objectives:

The secondary objectives of this study were as follows:

- To estimate the incidences of PML in Tysabri-treated patients who were anti-JCV antibody negative and anti-JCV antibody positive, based on a meta-analysis of data obtained from this study and other data sources
- To define the prevalence of anti-JCV antibody in relapsing MS patients receiving Tysabri within the TYSABRI Outreach United Commitment to Health (TOUCH) Prescribing Program
- To determine changes in anti-JCV antibody status over time

[redacted]

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[redacted]

Study Design:

This was an observational, longitudinal cohort study. No treatment was provided in this study, and there were no study-mandated visits. No routine clinical laboratory measurements were performed, and no vital sign measurements or physical examinations were performed for this observational study.

After the subjects provided written informed consent, a serum sample was collected to test for the presence of anti-JCV antibodies. Serum samples were initially collected annually and then changed to every 6 months. Samples were collected during routine subject care or follow-up visits for up to 4 years after the initial sample collection at enrollment. Samples were sent to a central laboratory. Results of the serum anti-JCV antibody tests (detectable [positive]/not detectable [negative]) were provided to the Investigator and the Prescribing Physician. All serum samples collected after a subject was determined positive for anti-JCV antibody, and the remaining serum aliquots of samples from all the other subjects, were stored for future JCV research.

Number of Subjects (Planned and Analyzed):

Planned: At least 8000 subjects

Analyzed: 35,895 subjects

Study Population:

Subjects with relapsing multiple sclerosis (MS) who were treated with Tysabri were eligible to participate. Subjects who were receiving Tysabri at the time of enrollment into this study and their prescribers had to be already enrolled in the TOUCH Prescribing Program before enrollment into this study. Subjects could have participated in other clinical studies sponsored by Biogen or Elan; however, if the anti-JCV antibody test was included in the other clinical study and that study was performing a longitudinal analysis of those samples, the subject was required to withdraw from this study (the STRATIFY-2 study). All subjects who were enrolled and had provided at least one serum sample were included in the analysis. This included MS subjects who were treated with Tysabri in studies such as STRATA (Studies 101MS321 and 101MS322), TOP (Tysabri Observational Program), and TYGRIS (Studies 101MS402 and 101MS403).

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

This was an observational study; therefore, no study treatment was administered. No additional information was collected about prior and concomitant therapy.

Comparator Therapy/Therapies, Dose, Mode of Administration, Batch Numbers:

Not applicable

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Duration of Treatment and Follow-Up:

After the subjects provided written informed consent, a serum sample was collected to test for the presence of anti-JCV antibodies. Serum samples were initially collected annually and then changed to every 6 months for up to 4 years.

There were no study-mandated visits.

Criteria for Evaluation:

Anti-JCV Antibody Data Analysis:

Serum samples were tested for the presence of anti-JCV antibodies. Over the course of the study, samples were analyzed using 2 slightly different versions of the anti-JCV assay – GEN1 and GEN2 assays.

Safety:

Only serious adverse events (SAEs) related to the venipuncture and /or blood draws were collected.

Statistical Methods:

Planned Analyses:

Analyses were presented for all subjects enrolled, Tysabri-treated subjects (subjects who received Tysabri prior to and/or during the study), and untreated subjects. All analyses were descriptive, and no formal statistical testing was performed.

Demographics and Baseline Disease Characteristics:

Demographics were presented using summary statistics (number, mean, standard deviation, median, minimum, and maximum) and frequency distributions.

Anti-JCV Antibody Analyses:

Primary Analysis

Confirmed cases of PML during the study and up to the date of database lock were identified and provided by the Safety and Benefit-Risk Management group at Biogen from the global safety database. For the purpose of calculating PML incidence for risk stratification, a 6-month cut-off was used to ensure that these samples reflected the subject's anti-JCV antibody status prior to PML. The incidence (per 1000 subjects) of PML was presented by anti-JCV antibody status in subjects with known anti-JCV antibody status available ≥6 months before diagnosis and was compared using a 1-sided Fisher's exact test.

Secondary Analyses

The percentages of subjects who tested anti-JCV antibody positive or negative were presented at each timepoint. The overall anti-JCV antibody serostatus (positive at least once or negative at all available timepoints) was also presented for all subjects enrolled.

A longitudinal analysis was conducted on those subjects who had serum anti-JCV antibody results from at least 5 timepoints.

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The number and percentage of subjects who were consistently negative and ever positive were presented along with the 95% confidence interval (CI).

Time to event was analyzed using Kaplan-Meier curves for those subjects who were negative for serum anti-JCV antibodies at baseline. In addition, the longitudinal stability of anti-JCV antibody index was evaluated using Kaplan-Meier analyses. Subjects who had index values from at least 2 timepoints were included in this analysis. Two thresholds were used to define a high-index value, 0.9 and 1.5. Baseline was defined as the first available anti-JCV antibody result.

Meta-analysis

Data from this study were pooled with data from other Biogen studies STRATA (Studies 101MS321 and 101MS322), TOP (Tysabri Observational Program), and TYGRIS (Studies 101MS402 and 101MS403). The incidence (per 1000 subjects) of PML in anti-JCV antibody positive subjects was stratified by the known risk factors of prior immunosuppressant therapy and treatment exposure. A Kaplan-Meier curve of the time to PML in anti-JCV positive subjects was plotted over time by prior immunosuppressant use.

[redacted]

Sample Size Calculations:

Assuming that the prevalence of anti-JCV antibodies in Tysabri-treated subjects is 54% and that the anti-JCV antibody assay has a false negative rate of 2%, an overall PML incidence in subjects treated for at least 2 years of approximately 1.3 cases per 1000 subjects implies that the incidence for subjects who tested positive for anti-JCV antibody is 2.4 (=1.3/[0.54+0.46x0.02]) per 1000 subjects and 0.05 (=2.37x0.02) per 1000 subjects for subjects who tested negative for anti-JCV antibody. These calculations assume that PML would not occur in subjects who were truly anti-JCV antibody negative and that subjects who tested anti-JCV antibody positive are truly anti-JCV antibody positive (i.e., no false positives). With the PML incidence of 1.3 cases per 1000 subjects among subjects with at least 2 years of Tysabri treatment, a sample size of approximately 6000 subjects was required to detect a difference in the incidence of PML between anti-JCV antibody positive and antibody negative subjects with 83% power, based on a 1-sided Fisher's exact test at a 0.05 level of significance. Assuming that the annual drop-out rate from this study was approximately 10%, at least 8000 subjects were planned to be enrolled into this study. [redacted], a sample size of at least 5000 subjects was needed.

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Results:

Subject Accountability:

A total of 35,895 subjects were enrolled in this study; of whom, 24,482 subjects were treated with Tysabri (including 18,289 treated with at least one infusion prior to enrollment) and 11,413 subjects were never treated with Tysabri.

Demographics and Baseline Disease Characteristics:

Out of 24,482 subjects treated with Tysabri, the majority of subjects were female (74%), and the majority of subjects were 40 to 49 years of age (32%). Ages ranged from 8 to 86 years (median 44 years, mean 44.1 years). Of the 23,945 subjects with data available for prior immunosuppressant use, 12% (2802) reported use of immunosuppressant therapy as most recent therapy prior to enrollment in the TOUCH program. Of the 23,330 subjects with data available for prior immunomodulatory therapy use, 85% (19,905) reported use of immunomodulatory therapy as the most recent therapy prior to enrollment in the TOUCH program.

Out of 13,191 subjects with data available for the number of years since the start of MS symptoms until enrollment in the TOUCH program, 28% reported <5 years since the start of MS symptoms, 37% reported 5 to 10 years, 17% reported 11 to 15 years, and 18% reported >15 years.

At the time of enrollment in this study, 68% of treated subjects (16,648 out of 24,482) had received at least one infusion of Tysabri within 3 months of the baseline sample collection and 32% (7834 of 24,482) had not received any doses within 3 months of the baseline sample collection date. Out of all subjects treated with Tysabri, <1% of the subjects temporarily discontinued Tysabri (missed 3 to 6 doses) and 6% permanently discontinued participation from the TOUCH program or missed >6 Tysabri infusions. Out of the 24,482 treated subjects, 6193 subjects (25%) were Tysabri naïve (had never received treatment) prior to enrollment in STRATIFY-2. For the 18,289 subjects who had received Tysabri before enrollment, the number of doses of Tysabri ranged from 1 to 66 (median 13.0, mean 17.5).

Tysabri Exposure:

The number of infusions of Tysabri received ranged from 0 to >96. Out of the 13,781 subjects who ever tested positive for the anti-JCV antibody and were treated with Tysabri, 2049 subjects had not received a Tysabri infusion at the time of first positive anti-JCV antibody result and 5 subjects (<1%) had received 97 to 108 Tysabri infusions at the time of first anti-JCV antibody positive result. Out of 13,781 subjects, 2591 subjects discontinued therapy due to anti-JCV positive antibody result. Of these subjects, 8 (<1%) were identified as having PML. Of the 11,190 subjects who continued to receive Tysabri after testing positive for anti-JCV antibody, 62 (<1%) were identified as having PML.

Safety:

No SAEs related to venipuncture or blood draws were reported during the study.

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Anti-JCV Antibody Data:

Baseline Anti-JCV Antibody Results

Of the 24,310 subjects who were treated with Tysabri and had anti-JCV antibody assessment data available at baseline, 49% (11,949 [95% CI: 48.5 to 49.8]) tested anti-JCV antibody positive and 5% (12,361 [95% CI: 50.2 to 51.5] tested anti-JCV antibody negative.

At baseline, 49% (1378 [95% CI: 47.6 to 51.3]) of the 2786 subjects who were identified as anti-JCV antibody positive had prior immunosuppressant use and 49% (10,255 of 20,993 subjects [95% CI: 48.2 to 49.5]) had no prior immunosuppressant use. Similarly 51% of the 2786 subjects who were identified as anti-JCV antibody negative (1408 [95% CI: 48.7 to 52.4]) had prior immunosuppressant use and 51% had no prior immunosuppressant use (10,738 of 20,993 subjects [95% CI: 50.5 to 51.8]).

Number of PML Cases

There were a total of 73 confirmed PML cases, of which 70 subjects tested anti-JCV antibody positive prior to diagnosis of PML, 2 subjects tested anti-JCV antibody negative, and the anti-JCV antibody status was unknown for 1 subject. Of the 72 cases with a known anti-JCV antibody status, 62 subjects had samples collected and tested for anti-JCV antibody status at least 6 months prior to PML diagnosis. Of these 62 subjects with PML, 60 subjects tested anti-JCV antibody positive and the remaining 2 subjects tested anti-JCV antibody negative at least 6 months prior to diagnosis of PML.

The remaining 10 confirmed PML cases had samples that were collected and tested for anti-JCV antibody status <6 months prior to PML diagnosis. Nine of these 10 PML cases tested positive for anti-JCV antibodies and one PML case tested negative for anti-JCV antibodies. One subject who tested negative at least 6 months prior to diagnosis had turned positive 2 months before diagnosis of PML. In addition, the 1 subject whose anti-JCV antibody status was unknown based on data in the clinical database, and consequently not included in the estimated PML incidence, was subsequently determined to have been anti-JCV antibody positive 2 years prior to the diagnosis of PML based on data in Biogen's global safety database.

Estimated PML Incidence

Of the total number of subjects (24,451) who had anti-JCV antibody status available, 12,848 subjects had tested anti-JCV antibody positive and 11,603 subjects tested anti-JCV antibody negative. The incidence of developing PML in anti-JCV antibody negative subjects was low (0.17 per 1000 subjects) [95% CI: 0.02 to 0.62] compared with the incidence in subjects who tested anti-JCV antibody positive (4.67 per 1000 subjects) [95% CI: 3.57 to 6.01].

Meta-Analysis: Incidence of PML in Anti-JCV Antibody Positive Subjects Stratified by Prior immunosuppressant and Tysabri Exposure:

Data from STRATIFY-2 were pooled along with data from STRATA (Studies 101MS321 and 101MS322), TOP (Tysabri Observational Program), and TYGRIS (Studies 101MS402 and 101MS403)

In subjects receiving 1 to 24 Tysabri infusions, the incidence of developing PML per 1000 subjects was 0.761 (95% CI: 0.092, 2.745) with prior immunosuppressant use and 0.592 (95% CI: 0.284 to 1.089) with no prior immunosuppressant use. In subjects who received 25 to 48 Tysabri infusions, with or

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without prior immunosuppressant use, the incidence of developing PML per 1000 subjects was 9.704 (95% CI: 5.937 to 14.947) and 4.350 (95% CI: 3.269 to 5.671), respectively. In subjects who received 49 to 72 Tysabri infusions, the incidence of developing PML was similar (9.330 with prior immunosuppressant use and 7.406 without prior immunosuppressant use). The incidence of developing PML among subjects who had 73 to 96 Tysabri infusions and prior immunosuppressant use was 9.615 (95% CI: 2.626 to 24.435). The incidence of developing PML in subjects who had 73 to 96 Tysabri infusions and no prior immunosuppressant use was 4.996 (95% CI: 2.663 to 8.528). Only 20 subjects received >72 infusions.

The risk of developing PML in subjects who tested anti-JCV antibody positive and had prior immunosuppressant use and up to72 Tysabri infusions was 0.0272 (27.2 per 1000 subjects). The risk of developing PML in subjects without prior immunosuppressant use and up to72 Tysabri infusions was 0.0175 (17.5 per 1000 subjects).

Anti-JCV Antibody Index and Risk of PML

Among subjects with anti-JCV antibody index values and receiving Tysabri and with no prior immunosuppressant use, 7 subjects had PML, but no PML cases were reported in subjects with anti-JCV antibody index values ≤0.9. Five of the 7 subjects (71%) had anti-JCV antibody index values >1.5.

Based on data from the clinical database only, the risk of developing PML in subjects with an anti-JCV antibody index value >0.9 who received up to 72 infusions was 6.3 per 1000 subjects; no PML case was reported in subjects with anti-JCV antibody index values ≤0.9. The risk of developing PML was also higher in subjects with anti-JCV antibody index value >1.5 (6.1 per 1000 subjects) than in subjects with anti-JCV antibody index value ≤1.5 (1.9 per 1000 subjects).

Combining index data from study samples with additional safety data from Biogen's global safety database resulted in more PML cases with index values available for analysis. Therefore, the estimates of the risk of PML were higher compared with using only data from the clinical database (1.22 and 36.75 PML cases per 1000 subjects for subjects receiving up to 72 infusions with anti-JCV antibody index values ≤0.9 and >0.9, respectively, and 5.89 and 42.94 PML cases per 1000 subjects for subjects receiving up to 72 infusions with anti-JCV antibody index values ≤1.5 and >1.5, respectively. However, including additional index data only from subjects with PML introduces a bias, since the number of subjects with no PML occurrences with an index greater or less than a threshold is underestimated; thus, these risk estimates are not a true reflection of the actual PML risk.

Anti-JCV Antibody Status Over Time

At baseline, 49% of subjects (12,015 out of 24,435) tested anti-JCV antibody positive and 51% (12,420 out of 24,435) tested anti-JCV antibody negative. Over time, the trend of the percentage of subjects who tested anti-JCV antibody positive decreased, and at all the timepoints after 30 months, the percentage of subjects who tested positive was approximately 32%.

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Longitudinal Analysis of Anti-JCV Antibody Status

Thirteen percent (3070 subjects) of the 24,482 subjects treated with Tysabri in the study had samples available for at least 5 timepoints. Of these, 34% (1055 subjects) tested positive for anti-JCV antibodies at any of the 5 timepoints, or more, during the study, and 66% (2015 subjects) consistently tested negative for anti-JCV antibodies. Of the 3070 subjects, 12% of subjects (378 subjects) converted from negative status at one or more timepoints to positive status at any timepoint and remained positive, known as seroconversion. Seroreversion (i.e., when a subject reverts from an initially positive status at one or more timepoints to a negative status at any timepoint and remains negative) was observed in <1% of subjects (25 subjects). This also includes subjects who stayed positive and then reverted to negative at the last timepoint. Approximately 6.8% of subjects (211 of 3070) had an antibody status that changed at 2 timepoints at least during the study, that is they may have changed from positive to negative and then back to positive, or changed from negative to positive and then back to negative. Of those 210 subjects who were intermittently positive, 172 were anti-JCV antibody negative at baseline and 38 subjects were anti-JCV antibody positive at baseline.

Conclusions:

- In subjects with relapsing MS receiving Tysabri, the risk of PML in anti-JCV antibody negative subjects was statistically significantly lower than that in anti-JCV antibody positive subjects ($p<0.0001$).
- The meta-analysis confirmed the 3 risk factors associated with PML in Tysabri-treated subjects including positive anti-JCV antibody status, increased duration of exposure especially >2 years, and prior IS use.
- A higher anti-JCV antibody index value was associated with a higher risk of developing PML in subjects treated with Tysabri and who had no prior immunosuppressant exposure.

Date of Report: 01 December 2016

Version: 1