1. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen Idec Inc./Biogen Idec Ltd.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Tysabri™	**Name of Active Ingredient:** Natalizumab	**Study Indication:** Multiple sclerosis

Title of Study:

A Multicenter, Randomized, Rater-Blinded Study to Compare the Efficacy and Safety of Natalizumab (300mg IV every four weeks) with Interferon beta-1a (44 mcg SC three times a week) in subjects with Relapsing Multiple Sclerosis previously treated with Interferon beta-1a (22 or 44 mcg SC three times a week).

Approval of the Sponsor's responsible signatory is provided in Appendix 16.1.5.

Principal Investigator/Coordinating Investigator:

The Sponsor's Study Medical Director signature indicating approval of this report is provided in Appendix 16.1.5.

The approval of the Sponsor's Responsible Signatory in place of the Principal Investigator is also provided in Appendix 16.1.5.

Study Period:	**Phase of Development:**
Date of first treatment: 10 January 2005 Date of early study termination: February 2005	3b

Study Objectives:

The primary objective of this study was to compare the effect of natalizumab with interferon beta-1a (IFN β-1a) on the annualized rate of clinical relapses.

Secondary objectives included evaluation of the relative efficacy of natalizumab with IFN β-1a on other relapse and magnetic resonance imaging (MRI) outcomes.

The safety, tolerability, and relative effects of natalizumab and IFN β-1a on quality of life were also to be assessed.

Study Design:

The study was a multicenter, randomized, rater-blinded, parallel-group study of subjects with relapsing-remitting multiple sclerosis (MS).

Subjects were to be randomized to 1 of 2 treatment groups:

- Group 1: Approximately 700 subjects were to receive 300 mg of natalizumab by intravenous (IV) infusion every 4 weeks for 48 weeks.
- Group 2: Approximately 350 subjects were to receive 44 mcg IFN β-1a by subcutaneous (SC) injection 3 times a week (TIW) for 48 weeks.

Subjects were to undergo clinical and neurological evaluation (Expanded Disability Status Scale [EDSS], Karnofsky Performance Status Scale [KFS], and MS Functional Composite [MSFC] measurement) at baseline and every

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12 weeks. Blood and urine samples were to be collected at Weeks 4 and 12 and every 12 weeks thereafter for routine safety and natalizumab antibody screening. MRIs were to be performed at baseline evaluation, and at Week 48 following initiation of study drug treatment. All subjects were to attend the clinic for relapse and adverse event (AE) determination every 4 weeks.

Number of Subjects (Planned and Analyzed):

1050 subjects were planned; 6 subjects were screened but only 3 subjects enrolled in the study (i.e., received study drug). No analyses were performed on the enrolled subjects.

Study Population:

Main inclusion criteria:

- Male and female subjects between 18 and 55 years of age
- A diagnosis of relapsing-remitting MS (RRMS) as defined by McDonald et al., criteria #1-4 (McDonald WJ, et al. Recommended diagnostic criteria for MS. Ann Neurol. 2001;50:121-127)
- A baseline EDSS score between 0.0 and 5.5, inclusive
- Treatment with IFN β-1a at either 22 or 44 µg SC TIW for at least 9 months prior to randomization
- At least 1 medically documented clinical relapse experienced during IFN β-1a therapy within the 24 months prior to randomization

Main exclusion criteria:

- Diagnosis of any other form of MS
- MS relapse had occurred, in the opinion of the investigator, within 30 days prior to randomization AND/OR the subject had not stabilized from a previous relapse, in the opinion of the investigator, prior to randomization
- A clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within 30 days prior to randomization
- History of malignancy (basal cell carcinoma with successful surgical resection was permitted)
- History of, or abnormal laboratory results indicative of, any significant cardiac, endocrinologic, hematological, hepatic, immunological, metabolic, agrological, pulmonary, gastrointestinal, dermatological, psychiatric, renal, and/or other major disease, that, in the opinion of the investigator, would preclude the administration of a recombinant humanized antibody immunomodulating agent
- History of severe allergic or anaphylactic reactions or known drug hypersensitivity
- Abnormal results from blood tests, performed at the screening visit
- Any prior treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, or natalizumab or any other therapeutic monoclonal antibody
- Treatment with mitoxantrone or cyclophosphamide within 1 year prior to randomization
- Treatment with cyclosporine, azathioprine, methotrexate, SC glatiramer acetate, IV immunoglobulin,

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Tysabri™	Natalizumab	Multiple sclerosis

plasmapheresis or cytapheresis, or mycophenoylate mofetil within 6 months prior to randomization

- Treatment with IV or oral corticosteroids, or 4-aminopyridine or related products within 30 days prior to randomization
- Female subjects who were pregnant or breastfeeding or were considering becoming pregnant
- Participation in any other investigational study within 6 months prior to randomization.

A complete list of exclusion criteria is provided in Section 8.3 of the protocol (see Appendix 16.1.1).

Study Treatment, Dose, Mode of Administration, Batch Number(s):

In Group 1, natalizumab was to be administered by IV infusion every 4 weeks. All infusions were to be performed in a clinic setting to allow monitoring for safety. Infusions were to take approximately 1 hour. Subjects were to remain in the clinic for 1 hour after the infusion for observation. Subjects were to be treated with study drug for up to 48 weeks. The scheduling of all visits was to be calculated based on the baseline visit date.

No dose modifications were foreseen with natalizumab.

Natalizumab was packaged as a liquid in 15 mL vials containing 300 mg natalizumab per vial. Each vial contained excipient materials (sodium chloride, sodium dibasic phosphate heptahydrate, sodium monobasic phosphate monohydrate, Polysorbate 80). The natalizumab label included any pertinent information in accordance with the revised Good Manufacturing Practices (GMP) annex 13, in the local language. The lot number for natalizumab distributed to the study site prior to termination of the study was [redacted]

In Group 2, IFN β-1a was to be administered by SC injection TIW. Administration could be self-administered or given by a caregiver at home.

If deemed necessary for individual subject's safety, the treating physician could modify the schedule of dosage of IFN β-1a according to the approved package insert; however, every attempt was to be made to maintain the 44 μg SC TIW dosing.

For subjects who entered the study on 22 mcg SC TIW, the dose was to be escalated to 44 mcg SC TIW. The increase in dose was to be performed at the study start after randomization. If dose-limiting AEs occurred, the IFN β-1a dose could be reduced or study drug treatment could be interrupted. In such a case, a re-escalation to full dose was to be attempted. The following schedule of dose escalation during the study was recommended: after interruption and recovery of the AE to mild or normal status, 50% of full dose was to be reintroduced and escalation to full dose attempted within a period of 4 weeks. For subjects on IFN β-1a, leucopenia or elevated liver function tests may have necessitated dose reductions of 20% to 50% until toxicity was resolved.

IFN β-1a was to be provided by the sponsor. The IFN beta-1a was to be packaged as liquid in a pre-filled syringe.

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The IFN β-1a label on the outer box was to include any pertinent information in accordance with the revised GMP annex 13, in the local language.

Duration of Treatment and Follow-Up:

Treatment period: The treatment period for both Group1 (natalizumab) and Group 2 (IFN β-1a) was 48 weeks. Following the Baseline Visit, subjects were to report to the clinic for visit-specific assessments and samples every 4 weeks.

Follow-up period: An End of Study Visit was required at Week 52 (±7 days) for final assessments and sampling.

Follow-up after premature discontinuation of study treatment: If a subject prematurely discontinued study treatment, they were required to complete the tests and evaluations for the Week 48 Visit.

Extension Study: Subjects who completed all protocol-required evaluations would have the option of enrolling into the extension study. All subjects were to be offered monthly IV infusions of 300 mg natalizumab until regulatory approval and reimbursement in the country of conduct. The Week 48 visit was to be the first open-label extension study visit at which subjects received an IV infusion of 300 mg natalizumab if deemed safe by the investigator.

Criteria for Evaluation:

Efficacy:

- The assessment of clinical relapses
- EDSS [Kurtzke 1983]
- The MSFC, consisting of the Timed 25-Foot Walk, 9-Hole Peg Test, 3-Second Paced Auditory Serial Addition Test [Fischer 1999]
- Brain MRI sequences:
  - Pre- and postgadolinium-T1 weighted scan
  - Progression of disease and T2 weighted scan
- Multiple Sclerosis Quality of Life Inventory [The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee 1997]
- EQ-5D
- Visual Analogue Scale - global impression of change from baseline

Safety:

- Physical examinations (including vital signs)
- AEs and serious AEs
- Blood chemistry
- Hematology
- Urinalysis

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Product/ Study-Specific Safety Assessments

- Anti-natalizumab antibodies
- Binding and neutralizing antibodies to IFN β-1a

Statistical Methods:

This study screened 6 subjects, only 3 of whom received 1 dose of study treatment before the study was stopped by the Sponsor. No data on these 3 subjects are available. No formal statistical testing was conducted.

Results:

Subject disposition:

Prior to the study being stopped in February 2005:

- 2 subjects were randomized to Group 1 (natalizumab) and received 2 infusions of natalizumab 300 mg IV.
- 1 subject was randomized to Group 2 (IFN β-1a) and received 11 doses of IFN β-1a 44 µg SC TIW.
- 3 subjects signed informed consents but were not treated.

Demographics:

- No data

Efficacy:

- No data

Safety:

- No data

Conclusion(s):

Study IMA-04001 was terminated early by the Sponsor in February 2005, when dosing of natalizumab was voluntarily suspended in the United States market and in clinical studies, when 3 cases of progressive multifocal leukoencephalopathy (PML) were identified in natalizumab-treated MS (n=2) and Crohn's disease (n=1) clinical trial subjects. An extensive safety evaluation of 3116 of 3417 subjects who had received natalizumab while participating in clinical studies found no new cases of PML and suggested a risk of PML of approximately 1 in 1000 subjects treated with natalizumab for a mean of 17.9 months [Yousry 2006].

Based on efficacy data from other studies and the results of the above mentioned safety evaluation, the Food and Drug Administration re-approved natalizumab for use in the United States for relapsing forms of MS in July 2006. All the subjects in this study subsequently enrolled into Study 101MS321 in 2007.

No data from Study IMA-04001 are available; therefore, no conclusions can be drawn.

Date of Report: 15 July 2014