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**PROTOCOL TITLE:** TOP: TYSABRI Observational Program

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# 1. CONTACT LIST

## 1.1. Biogen Personnel

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## 1.2. CRO

Organization: [redacted]
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## 1.3. Coordinator of MSBase Control Group Study

Organization: MSBase Foundation

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# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| CNS | central nervous system |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| DCC | Data Compilation Center |
| DMT | disease modifying therapy |
| DNA | deoxyribonucleic acid |
| eCRF | electronic case report form |
| EDSS | Expanded Disability Status Score |
| EU | European Union |
| HIV | human immunodeficiency virus |
| IMA | International Medical Affairs |
| IV | intravenous |
| [redacted] | [redacted] |
| MAdCAM-1 | mucosal addressin cell adhesion molecule-1 |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| MSBase | international Neuro-Immunology Registry |
| PML | progressive multifocal leukoencephalopathy |
| Q4W | every 4 weeks |
| RRMS | relapsing remitting multiple sclerosis |
| SAE | serious adverse event |
| SC | subcutaneous |
| SmPC | Summary of Product Characteristics in the EU |
| TOP | TYSABRI Observational Program |
| VLA-4 | very late antigen-4 |
| VCAM-1 | vascular cell adhesion molecule-1 |

# 3. SYNOPSIS

| | |
|---|---|
| Protocol number: | IMA-06-02 |
| Protocol title: | TOP: **T**YSABRI **O**bservational **P**rogram |
| Study design: | Open-label, multinational, multicenter, prospective, observational study |
| Study duration: | 10 to 15 years for an enrolled patient |
| Study objectives: | To assess the long-term safety and impact on disease activity and progression of Tysabri in patients with relapsing remitting multiple sclerosis (RRMS) in a clinical practice setting |
| Primary endpoint: | • Long-term safety (incidence and pattern of serious adverse events [SAEs]) in patients receiving Tysabri |
| Secondary endpoints: | • Multiple sclerosis (MS) disease activity as determined by the occurrence of clinical relapses (annualized relapse rate, distribution of the total number of relapses over a period of up to 15 years, time to first relapse, proportions of patients with and without relapse)<br>• Disability progression as determined by Expanded Disability Status Score (EDSS) [based on neurological examination, "physical EDSS"]<br>• Evaluation of baseline disease characteristics as prognostic indicators for disease activity and disability progression over time. Such baseline disease characteristics will be:<br>– EDSS<br>– Disease duration at baseline<br>– Number of relapses during 1 and 2 years before baseline<br>– Previous use of disease modifying therapy<br>– Age, gender, and any other characteristics available for the total population or sufficiently large subgroups to be defined by the Study Steering Committee as putative prognostic indicators to be studied<br>• Evaluation of short-term (1 year) disease outcomes as prognostic indicators for disease activity and disability progression over time. Such short-term outcomes will be:<br>– EDSS progression during first 12 months<br>– Occurrence of relapses during first 12 months |

– Others to be defined by the Study Steering Committee as putative prognostic indicators to be studied

[redacted]

Study population: Patients with RRMS who are therapy-naïve to Tysabri and who meet the criteria defined in the indication statement for prescription in the respective country. Patients will be enrolled after the decision to treat with Tysabri had been made, or as soon as possible after the start of Tysabri treatment but before their fourth dose at the latest.

Number of patients: At least 4500 MS patients

Visit schedule: Data collection starts with previous medical history. Further data collection will take place at regular clinical practice visits. Additional data may be collected at visits that take place in order to evaluate new or worsening neurological symptoms, SAE(s), or discontinuation from the TOP study.

Assessments: The following information will be collected to assess safety and efficacy in TOP:

- Demographic data
- Medical history (in reference to the time prior to enrollment), including:
  - History of serious opportunistic infection, malignancy, organ transplant, and human immunodeficiency virus (HIV) infection
  - Date of first MS symptoms
  - Number of Tysabri doses prior to enrollment, date of first dose given
  - Last EDSS score prior to treatment with Tysabri
  - Most recent magnetic resonance imaging (MRI) data prior to enrollment in TOP
  - Number and description of relapses (use of steroids, hospitalizations) during 1 and 2 years prior to treatment with Tysabri
  - Prior use and duration of disease-modifying, anti-neoplastic, or other immunosuppressive medication
- Status of treatment with Tysabri (including reason for possible discontinuation)

- Use of concomitant disease-modifying, anti-neoplastic, or immunosuppressive medications, and systemic steroids
- Employment status (where permitted by local authorities)
- SAEs, including serious infections and malignancies
- EDSS score
  - Based on neurological exam
- Occurrence and description of relapses (severity)
- [redacted]

Applicable personnel at Biogen will review all SAEs on a regular basis.

Statistical analysis: Sample size of at least 4500 patients with up to 15 years of follow-up within TOP whether continuing on drug or not.

- Safety will be analyzed using the incidence of SAEs, which will be estimated with percentage of patients experiencing at least one SAE. Patterns of the SAEs will also be investigated
- Disability progression will be assessed by evaluating EDSS evolution over time. These analyses include:
  - Proportion of patients that progress at least 1 point on EDSS sustained after 6 months
  - Proportions of patients that reach EDSS milestones such as 4.0, 6.0, and 7.0 sustained after 6 months
  - Proportion of patients who improve at least 1 point on EDSS sustained after 6 months
  - Proportions of patients whose disability status worsened, stabilized, or improved will also be estimated (values sustained after 6 months)
- MS disease activity will be assessed by evaluating the frequency of relapses over time:
  - Annualized relapse rate

  - Distribution of total number of relapses over a period of up to 15 years
  - Time to first relapse
  - Proportions of patients with relapse
- Prognostic factors for disability progression and MS disease activity will be assessed in different patient cohorts stratified according to their baseline characteristics:
  - EDSS
  - Disease duration
  - Number of relapses in previous 1 and 2 years
  - Previous use of disease modifying therapies
  - Age, gender, and any other factors that the Steering Committee will deem to be appropriate
- [redacted]

Interim analysis: Interim analyses will be performed when the following milestones are achieved:

- The first 500 patients have completed 1 year of observation
- The first 1000 patients have completed 1 year of observation

Data analyses will be performed on an annual basis thereafter.

External control group: A prospective, external control cohort that is matched with TOP patient baseline characteristics will be identified from the independent MSBase project, which contains long-term data of MS patients on treatment with disease-modifying therapies other than Tysabri and will be used for the efficacy assessments. The selection of the control cohort patients will be based on the propensity score technique, which allows matching of individual TOP patients with individual MSBase patients that have a similar propensity score.

# 4. SCHEDULE OF ASSESSMENTS

| Data Assessment/Information | Enrollment visit (baseline) | Data collected at regular clinical practice visits[1, 2] on a biannual basis | TOP study drop out visit[3] | Visits for the evaluation of new or worsening neurological symptoms |
|---|---|---|---|---|
| Consent | X | | | |
| Patient characteristics | X | | | |
| Demographic data | X | | | |
| Medical history[4] | X | | | |
| Status of Tysabri treatment (including reason for possible discontinuation) | | X | X | X |
| Concomitant disease-modifying, anti-neoplastic, immunosuppressive medications and systemic steroids | | X | X | X |
| SAEs including serious infections and malignancy[5] | | X | X | X |
| EDSS score - based on neurological examination | X | X | X | |
| Data on relapses | | X | X | X |
| Reason for study discontinuation incl. vital status | | | X | |
| [redacted] | | | | |
| Employment status[7] | (X) | X | X | |

1. It is anticipated that regular clinical practice visits will occur every 6 months ± 1 month.
2. If the patient discontinues Tysabri treatment but agrees to remain in TOP the Prescribing Physician will continue to collect data including potential new MS therapy during the entire study observation period.
3. Drop out from TOP is defined as a patient discontinuing TOP, but not necessarily discontinuing Tysabri treatment.
4. In reference to the time prior to enrollment. Medical history will include:
   - history of serious opportunistic infection, malignancy, organ transplant, and human immunodeficiency virus (HIV) infection;
   - date of first MS symptoms;
   - number of Tysabri doses prior to enrollment, date of first dose given;
   - last Expanded Disability Status Score (EDSS) prior to treatment with Tysabri;
   - most recent magnetic resonance imaging (MRI) data prior to enrolment in TOP;
   - number and description of relapses (use of steroids, hospitalizations) during 1 and 2 years prior to treatment with Tysabri;
   - prior use and duration of disease-modifying, anti-neoplastic, or other immunosuppressive medication.

5. Uncomplicated pregnancy is not an SAE. However, an unfortunate outcome of a pregnancy (e.g., spontaneous abortion) must be regarded as an SAE and reported. MS relapse fulfilling the criteria of an SAE will not be considered a SAE for the purposes of this study.
6. [redacted]
7. Questions regarding employment status may be asked where permitted by local regulatory authorities; retrospective collection of data regarding employment status prior to treatment with Tysabri may be done for patients who were not asked at the time of their original enrollment.

# 5. INTRODUCTION

Tysabri is a recombinant humanized monoclonal antibody, which selectively binds to and interferes with the interaction of α4β1 integrin (also known as very late antigen-4, VLA-4) on leukocytes with its counter receptor, vascular cell adhesion molecule-1 (VCAM-1), on endothelial, and possibly on glial cells near the site of an inflammation. Similarly, Tysabri interferes with the interaction of α4β7 integrin expressed on leukocytes interacting with mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Disruption of these cell adhesion molecule interactions reduces transmigration of mononuclear leukocytes across the endothelium into the inflamed parenchymal tissue. Another mode of action of Tysabri is the modulation of ongoing inflammatory reactions by inhibiting the binding of α4-positive leukocytes with fibronectin and osteopontin in the central nervous system (CNS).

Through the blockage of the molecular interactions of α4β1 with its targets, Tysabri may suppress inflammatory activity at the disease site and inhibit further recruitment of immune cells into inflamed tissues, leading to positive effects on patients' outcomes.

Based on data from pivotal studies in relapsing remitting multiple sclerosis (RRMS), Tysabri demonstrates a substantial benefit compared to placebo. However, severe safety concerns ensued after 2 clinical trial cases of progressive multifocal leukoencephalopathy (PML) were detected in multiple sclerosis (MS) patients exposed to combined treatment with Tysabri and interferon-β-1a (AVONEX®). Biogen and Elan Pharmaceuticals voluntarily suspended marketing and dosing of Tysabri in clinical trials on 28 February 2005. A full safety analysis was performed, and documentation submitted to regulatory agencies for marketing approval. Following a positive vote from the Advisory Committee on drugs for Peripheral and Central Nervous System in March of 2006, the FDA approved resumed marketing of Tysabri in the US on 05 June 2006 with an FDA-mandated risk management program. In addition, Tysabri was approved for relapsing-remitting forms of MS in the EU on 27 June 2006, in Canada on 28 September 2006, and in Australia on 30 October 2006, with country-specified risk management plans.

Progressive multifocal leukoencephalopathy (PML) and serious herpes infections are important identified risks for Tysabri. Malignancies are an important potential risk for Tysabri. The safety of the drug in patients with renal or hepatic impairment has not been studied, and the safety of the drug in children or adolescents has not been established. For further details, refer to the Tysabri prescribing information.

[redacted]

Efficacy of Tysabri as monotherapy in RRMS patients has been evaluated in a randomized, double-blind, placebo controlled study lasting 2 years [Polman 2006]. In this study, treatment with Tysabri reduced the risk of sustained EDSS progression by 42% over 2 years. Tysabri reduced the rate of clinical relapse over 2 years by 68% and led to a dramatic reduction in the

accumulation of new or enlarging hyperintense lesions, as detected by T2-weighted MRI, over 2 years. A 10-year interim analysis of TOP data showed a decrease in mean annualized relapse rate from 1.99 in the 12 months prior to baseline to 0.15 ($p < 0.0001$); significantly lower annualized relapse rates were particularly observed in patients who used Tysabri as their first MS therapy, in patients with lower baseline EDSS scores, and in patients with lower pre-Tysabri relapse rates. Mean EDSS scores remained unchanged for up to 10 years [Butzkueven 2020].

Efficacy of the Tysabri SC formulation was evaluated in Studies 101MS102 (DELIVER) and 101MS206 (REFINE) [Plavina 2016; Trojano 2021]. Specifically, Study 101MS206 demonstrated that 300 mg every 4 weeks (Q4W) dosing of Tysabri SC formulation provided comparable efficacy, pharmacokinetic/pharmacodynamics, and safety outcomes as 300 mg Q4W dosing of Tysabri IV(intravenous) formulation in patients who had received at least 11 doses of IV formulation prior to randomization [Trojano 2021].

Therefore, continued assessments of long-term treatment with Tysabri are needed to better define the long-term effect of this treatment on disease activity and progression.

## 5.1. Rationale for TOP

Randomized clinical trials are extremely useful to examine the short-term benefit/risk profile of new therapies, but are intrinsically limited when determining long-term treatment outcomes in a chronic disease, such as MS. In addition, clinical trials may include a slightly different population to that prescribed the drug in normal clinical practice. The exact relationship between short-term benefit-risk balance in the course of a 2- to 3-year clinical trial and long-term use remains unclear. As a result, a longer-term follow-up study based on a large observational cohort of new drug users, such as TOP, has the ability to provide a better understanding of the long-term effects of a drug in an actual chronic disease. Using this methodology, the safety profile and the impact on disease activity and progression at large of a drug used in normal clinical practice can be determined over the long term. Indeed, the utility of observational cohorts to study the effectiveness of a drug in clinical practice has been the subject of an editorial [D'Agostino 2007]. An analysis of prognostic factors based on cross-sectional and longitudinal data can be obtained, providing a basis for patient selection for treatment. Prerequisites of a valid estimate of the effect of a therapeutic intervention in such a setting without internal controls are high retention rates over a long period of time, and the choice of an appropriate external control group.

TOP is an epidemiological observational study of patients receiving Tysabri, with each patient to be followed for up to 15 years. This study is designed to address the long-term safety profile and the long-term impact on disease activity and progression of Tysabri with marketed use, and the impact of treatment on disability in particular by comparing the results with prospectively determined controls from established databases.

The specifications for the use of Tysabri contained in the marketing authorizations include a clear directive for regular clinical visits. The Tysabri Summary of Product Characteristics (SmPC) states: "Use of TYSABRI has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers

on early signs and symptoms of PML." It is a widely accepted consensus amongst MS experts that "regular intervals" implies biannual visits as a minimum for assessing patients. Collection of efficacy and safety data at 6-monthly intervals to coincide with regular clinic visits and routine clinical practice will therefore be undertaken during the TOP observational period.

# 6. OBJECTIVES

The objectives of TOP are to evaluate the long-term safety and impact on disease activity and progression of Tysabri as a single disease modifying agent in patients with RRMS in a clinical practice setting. The safety of Tysabri will be assessed by collecting data on the incidence of non-MS-related serious adverse events (SAEs), including all serious infections irrespective of causality. The impact on disability progression and disease activity will be evaluated by assessing the effect of Tysabri on the disability status (EDSS), and on clinical relapses, and by comparing with external controls. The analysis will take into account the patients' EDSS status, disease duration, number of past relapses, and history of previous disease modifying therapies at enrollment into TOP. This will allow studying the impact of these baseline factors on the long-term disease activity and disability progression.

Change in EDSS versus baseline will be evaluated by assessing the proportion of patients reaching predefined EDSS milestones (4.0, 6.0, and 7.0). Progression in disability will also be assessed by estimating the proportion of patients whose EDSS increased by at least 1.0 EDSS point and sustained for 6 months.

A limitation of single-arm observational studies like TOP versus randomized clinical trials is the lack of control groups and randomized treatment assignment. However, the selection of an external patient cohort that matches the TOP patient population may allow a reliable comparison with TOP patients, if adjustments are made. Propensity score analysis, which relies on determining baseline characteristics of individual patients, is used in retrospective or observational studies to compensate for non-random assignment of treatment groups.

An independent, observational, multinational, and multicenter study in a subset of centers participating in MSBase has been set up to collect prospective clinical efficacy data in patients treated for active RRMS with β-interferon or glatiramer acetate. The propensity score technique will allow individual TOP patients to be matched with individual patients in this MSBase study. As this procedure can be applied stepwise, if a change in the distribution of baseline characteristics in TOP patients occurs over time it allows for compensation.

## 6.1. Primary Endpoint

- Long-term safety (incidence and pattern of SAEs) in patients receiving Tysabri

## 6.2. Secondary Endpoints

- MS disease activity as determined by the occurrence of clinical relapses (annualized relapse rate, distribution of the total number of relapses over a period of up to 15 years, time to first relapse, proportions of patients with and without relapse)
- Disability progression as determined by EDSS (based on neurological examination, "physical EDSS")

- Evaluation of baseline disease characteristics as prognostic indicators for disease activity and disability progression over time. Such baseline disease characteristics will be:
  - EDSS
  - Disease duration at baseline
  - Number of relapses during 1 and 2 years before baseline
  - Previous use of disease modifying therapy
  - Age, gender, and any other characteristics available for the total population or sufficiently large subgroups to be defined by the Study Steering Committee as putative prognostic indicators to be studied
- Evaluation of short-term (1 year) disease outcomes as prognostic indicators for disease activity and disability progression over time. Such short-term outcomes will be:
  - EDSS progression during first 12 months
  - Occurrence of relapses during first 12 months
  - Others to be defined by the Study Steering Committee as putative prognostic indicators to be studied

[redacted]

[redacted]

# 7. PATIENT CHARACTERISTICS AND PRINCIPLES OF INCLUDING PATIENTS INTO TOP

## 7.1. Number and Characterization of Patients

At least 4500 patients with RRMS, who are naïve to Tysabri at initiation of Tysabri treatment, and who meet the criteria defined in the indication statement for prescription in the respective country will be enrolled. Patients will be enrolled as soon as possible after the decision to start Tysabri treatment, but before their fourth dose at the latest.

The patient characteristics listed below reflect the terms of the marketing authorization for Tysabri (see SmPC or prescribing information for a particular country). With the exception of written informed consent for TOP and the inclusion of Tysabri-naïve patients only, these criteria represent a checklist for patients eligible to receive Tysabri, rather than selection criteria for inclusion or exclusion from TOP.

To participate in this observational study, patients must fulfill **ALL** the following enrollment principles and patient characteristics at the Enrollment Visit:

## 7.2. Principles of Enrollment Into TOP

1. Must give written informed consent and provide all authorizations required by local law
2. Decision to treat with Tysabri must precede enrollment
3. Must have had no more than 3 Tysabri doses prior to enrollment

## 7.3. Patient Characteristics and Contraindications to Treatment With Tysabri in Accordance With Prescribing Information

1. Documented diagnosis of RRMS
2. Must have had at least one relapse in the previous year and must satisfy the locally approved therapeutic indications for Tysabri
3. Males or females whose age is within the Tysabri indication statement
4. Must not have a history of positive anti- Tysabri antibodies
5. Must not have a history of PML or other opportunistic infections, or an increased risk for such infections
6. Must not receive concomitant immunomodulatory or immunosuppressive therapy during therapy with Tysabri
7. Must not be immunocompromised at the time of enrollment
8. Must not suffer from known active malignancies (patients with cutaneous basal cell carcinoma that has been completely excised prior to study entry remain eligible)
9. Must not show a known hypersensitivity to Tysabri or to any of the excipients

10. Female patients must be postmenopausal for at least 1 year, surgically sterile (does not include tubal ligation), or willing to practice effective contraception (as defined by the treating physician) while receiving Tysabri
11. Women must not be breastfeeding or pregnant

The Investigator should refer to the approved local label for guidance if female patients become pregnant or are considering becoming pregnant during the study.

At each routine visit, female patients of childbearing potential will be asked about their pregnancy status and possible pregnancies/spontaneous abortions since the last visit or contact. Spontaneous abortions are considered to be SAEs and must be reported as such.

# 8. STUDY MEDICATION

This study will follow patients who are prescribed Tysabri according to the local prescribing information (300 mg IV or subcutaneously [SC] Q4W).

# 9. STUDY PROCEDURES

## 9.1. Overview

TOP (TYSABRI Observational Program) is a multinational, multicenter, observational study of the efficacy and safety of Tysabri in at least 4500 patients. The TOP population consists of patients who are naïve to Tysabri at initiation of Tysabri treatment, i.e., patients who have received Tysabri previously (including clinical Tysabri studies) are not eligible for TOP. Patients may be permitted to participate in TOP while enrolled in another clinical study, provided that the other study is non-interventional in nature. In addition, the patients in TOP need to fulfill criteria for treatment according to the local prescribing information.

Those patients who complete their 10-year period of observation were permitted by further informed consent to extend their follow-up period, thereby allowing for up to 15 years of observation.

All source data will be kept at the Prescribing Physician's site. All information received by Biogen will be stored in a secure database.

## 9.2. Enrollment Visit

The decision to treat with Tysabri must be made prior to and independently of enrollment into TOP. Prescribing Physicians inform patients who start Tysabri treatment about TOP. If a patient agrees to participate in TOP, she/he will read and sign the informed consent form. Enrollment should occur before the fourth dose of Tysabri.

The Prescribing Physician will collect the following data at the enrollment visit:

- Consent for TOP participation
- Demographic data
- Medical history (in reference to the time prior to enrollment), including:
  - History of serious opportunistic infection, malignancy, organ transplant (excluding corneal transplant), and HIV infection
  - Date of first MS symptoms
  - Number of Tysabri doses prior to enrollment, date of first dose given
  - Last EDSS score prior to treatment with Tysabri
  - Most recent MRI data prior to enrolment in TOP
  - Number and description (use of steroids, hospitalizations) of relapses during 1 and 2 years prior to enrollment
  - Prior use and duration of disease-modifying, anti-neoplastic, or other immunosuppressive medication
- EDSS score
  - Based on neurological exam

During enrollment, the Prescribing Physicians will inform female patients of childbearing potential about the importance of reporting pregnancy status or spontaneous abortions since the last visit.

Where permitted by local regulatory authorities, patients may be asked to provide information on their employment status prior to treatment with Tysabri, including responses to simple questions regarding the nature of any employment and the effect that MS may have had on their ability to work.

## 9.3. Regular Clinical Practice Visits

According to the SmPC or local prescribing information, Tysabri patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs. Thus, data will be collected at regular clinical visits at 6-monthly intervals (± 1 month), starting 6 months after the enrollment visit and taking place throughout the entire study period.

The Prescribing Physician will collect the following data at the regular clinical practice visits using standard data collection tools:

- Status of treatment with Tysabri (including reason for and date of possible discontinuation)
- Use of concomitant disease-modifying, anti-neoplastic, or immunosuppressive medications, and systemic steroids
- SAEs (as described in Section 9.4 and Section 11)
- EDSS score
  - Based on neurological exam
- Occurrence and description of relapses
  - Use of steroids
  - Hospitalizations

At each study visit, female patients of childbearing age will be asked about pregnancy status and possible pregnancies/spontaneous abortions since the last visit. If pregnant patients receive Tysabri within 3 months of conception or during pregnancy, the pregnancy should be reported to Biogen. Spontaneous abortions are considered to be SAEs and must be reported as such in TOP.

Where permitted by local regulatory authorities, patients may also be asked to provide information on their current employment status, including responses to simple questions regarding the nature of any employment and any effect that their MS may have had on their ability to work.

If the Data Compilation Center (DCC) does not receive a completed data set from the Prescribing Physician on a patient for whom 6-month follow-up is expected, the DCC will contact the site to remind them to complete the required data.

## 9.4. Discontinuation of Tysabri and Continued Participation in TOP

If a patient discontinues Tysabri treatment, but continues to participate in TOP, data will be collected on the reasons for Tysabri discontinuation 6 months after the last dose. The Prescribing Physician will contact the patient by telephone or at their next clinic visit to discuss their MS disease activity, all SAEs (including serious infections and malignancies), the use of immunomodulatory or immunosuppressive agents and corticosteroids, and pregnancy (if applicable). Thereafter, every reasonable attempt should then be made to collect information from the patient about MS disease activity, disability progression, data on serious opportunistic infections and malignancies, and the MS therapy to which the patient has been switched every 6 months throughout the entire study duration.

## 9.5. TOP Study Drop-out Visit

If participation in TOP is discontinued, the Prescribing Physician shall make every reasonable attempt to contact the patient in order to collect information about the reason for study discontinuation. If the patient agrees to attend a Drop-out Visit, information collected will include vital status and status of treatment with Tysabri, disease activity, disability progression, and SAEs. No further information will be collected on the patient after the TOP Drop-out Visit with the exception of PML cases. Following the Drop-out Visit, Biogen Idec will continue to request follow-up information on PML patients until the final outcome is established.

Information collected if the patient is treated with Tysabri but discontinues from TOP and agrees to attend a Drop-out Visit will be:

- Vital status
- Confirmation of last Tysabri dose
- Reason for and date of study discontinuation
- Status of treatment with Tysabri (including reason for and date of possible discontinuation)
- Use of concomitant disease-modifying, anti-neoplastic, immunosuppressive medications, and systemic steroids
- SAEs, as described in Section 11
- EDSS score
  - Based on neurological exam
- Occurrence and description of relapses
  - Use of steroids
  - Hospitalizations
- Employment status (where permitted by local authorities)

## 9.6. Visits for the Evaluation of New or Worsening Neurological Symptoms (as Described in the SmPC and/or Prescribing Information)

Prescribers of Tysabri should be aware of the possibility that PML and other opportunistic infections may occur during this therapy. Therefore, they should consider these opportunistic infections in their differential diagnosis of all infections and of any new or worsening neurological symptoms that occur in Tysabri treated patients. For this purpose, Biogen has established Tysabri MS patient management algorithms ("Physician Information and Management Guidelines for MS patients on Tysabri therapy"). The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are typical of MS or possibly suggestive of PML or other opportunistic infections. If they are suggestive of PML, or if any doubt exists, further evaluation, including MRI scan (compared with MRI prior to therapy), CSF testing for [redacted] and repeat neurological assessments, should be considered. If new neurological symptoms occur, further Tysabri dosing is to be suspended until PML has been excluded. Once the clinician has excluded PML, dosing of Tysabri may resume.

**Patients who are experiencing new or worsening neurological symptoms or symptoms of potential opportunistic infections should contact the Prescribing Physician within 48 hours of the onset of symptoms.** At the treating physician's discretion, the patient can be asked to come in for an office visit, which may occur outside of routine clinical practice visits.

Information collected at the neurological evaluation visits:

- Status of treatment with Tysabri (including reason for and date of possible discontinuation)
- Use of concomitant disease-modifying, anti-neoplastic, or immunosuppressive medications, and systemic steroids
- SAEs as described in Section 11
- Occurrence and description of relapses
  - Use of steroids
  - Hospitalizations

### 9.6.1. Definition of Relapse

A clinical relapse is defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 hours, and followed by a period of 30 days of stability or improvement. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse.

[redacted]

## 9.8. Lost to Follow-Up

A patient will be considered lost to follow-up if no more data can be obtained on the patient.

## 9.9. Sponsor Discontinuation of TOP

Biogen may terminate TOP at any time.

# 10. DATA COLLECTION

The data collection shall be performed at the different study sites using the web-based, TOP electronic case report form (eCRF). The collection of data in this specific format allows efficacy comparison of the patients treated with Tysabri in TOP with matched controls from an established multiple sclerosis patient database (MSBase).

## 10.1. MRI Baseline Characteristics

MRI baseline data may play an important role in the decision to treat with Tysabri and may be an important prognostic factor. It is therefore justified to collect data on the most recent MRI prior to the start of TOP.

The baseline MRI should not have been carried out more than 6 months prior to commencing Tysabri. The following baseline MRI data will be collected:

- MRI date, if available
- Semi-quantitative load of T2 hyperintensive lesions > 3 mm (0, 1-2, 3-8, ≥ 9)
- Semi-quantitative load of T1-Gadolinium+ lesions (0, ≥ 1, NA)

## 10.2. EDSS

In order to assure high reliability of assessments it is essential to have standardized examinations and consistent definitions for the Kurtzke Functional System scores [Kurtzke 1983]. The physicians participating in TOP are therefore provided with a copy of the interactive Neurostatus Training DVD-ROM edited by L Kappos and S Wu, Basel – Switzerland.

Neurostatus certification is highly recommended for all participating physicians. Investigators are therefore asked to provide their certification information. If they are not yet certified, they are offered a free-of-charge online certification training (www.neurostatus.net).

The TOP eCRF provides the investigators with context-related on-screen help when entering the different functional system scores.

# 11. SAFETY DEFINITIONS, MONITORING, AND REPORTING

## 11.1. Definitions

### 11.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value, vital sign result, and/or electrocardiogram result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the patient to receive specific corrective therapy
- The result is considered by the Investigator to be clinically significant

### 11.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death.
- in the view of the Investigator, places the patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- requires inpatient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability/incapacity.
- results in a congenital anomaly/birth defect.
- is a medically important event.

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

MS relapses fulfilling the criteria of an SAE should not be considered SAEs in this study.

## 11.2. Monitoring and Recording Events

Nonserious AEs will not be collected as part of this study and should follow spontaneous postmarketing reporting rules as per local regulations.

### 11.2.1. Serious Adverse Events

Any SAE that occurs during treatment with Tysabri, or within 6 months of the discontinuation of treatment with Tysabri, should be recorded on an SAE Form, regardless of severity or relationship to study treatment. In addition, malignancies and opportunistic infections that occur in any patient participating in TOP, even if Tysabri treatment has been discontinued for more than 6 months, should be treated as an SAE and recorded on an SAE form. SAEs must be reported to the Sponsor or designee. Refer to the Study Reference Guide for details.

Any SAE experienced by a patient after the patient signs the ICF and before study completion or premature study withdrawal is to be recorded on an SAE Form and the CRF, regardless of the event relationship to Tysabri. The site must formally notify Biogen within 24 hours of becoming aware of the SAE, or according to national law, by submitting the SAE Form. Thereafter, the event should be reported to Biogen on an SAE Form only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the patient completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

### 11.2.2. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 11.1.2
- The relationship of the event to study treatment as defined in Section 11.3.1
- The severity of the event as defined in Section 11.2.3

### 11.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of SAEs:

| **Severity of Event** | |
|---|---|
| Mild | Symptom(s) barely noticeable to patient or does not make patient uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of patient. |
| Moderate | Symptom(s) of a sufficient severity to make patient uncomfortable; performance of daily activity is influenced; patient is able to continue in study; treatment for symptom(s) may be needed. |
| Severe | Symptom(s) causes severe discomfort; symptoms cause incapacitation or significant impact on patient's daily life; severity may cause cessation of treatment |

| Severity of Event | |
|---|---|
| | with study treatment; treatment for symptom(s) may be given and/or patient hospitalised. |

### 11.2.4. Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen or designee as soon as possible, preferably within 24 hours of the study site staff becoming aware of the SAE (refer to the Study Reference Guide for details), or according to national law. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

| Reporting Information for SAEs |
|---|
| Any SAE that occurs from the time that the patient has signed informed consent and occurs either during treatment with Tysabri or within 6 months of discontinuation should be treated as an SAE and must be reported to Biogen or designee as soon as possible, preferably within 24 hours of the study site staff becoming aware of the event (refer to Study Reference Guide for details). If a patient is off Tysabri for more than 6 months and continues to participate in TOP and experiences malignancy or opportunistic infection, this must be reported to Biogen or designee as soon as possible, preferably within 24 hours of the study site staff becoming aware of the event (refer to Study Reference Guide for details).<br>A report ***must be submitted*** to Biogen or designee regardless of the following:<br>• Whether or not the patient has undergone study-related procedures;<br>• Whether or not the patient has received study treatment;<br>• The severity of the SAE; and<br>• The relationship of the event to study treatment.<br>To report initial or follow-up information on an SAE, refer to the Study Reference Guide. |

### 11.2.5. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported as an SAE within 24 hours of the site becoming aware of the event, or according to national law. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen or designee. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

## 11.3. Safety Classifications

### 11.3.1. Relationship of Events to Tysabri

The following definitions should be considered when evaluating the relationship of SAEs to Tysabri:

| Relationship of Event to Commercial Drug | |
|---|---|
| Not related | An SAE will be considered "not related" to the use of Tysabri if there is not a possibility that the event has been caused by it. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the SAE (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the SAE. |
| Related | An SAE will be considered "related" to the use of Tysabri if there is a possibility that the event may have been caused by it. Factors that point toward this assessment include, but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the SAE, or a lack of an alternative explanation for the SAE. |

### 11.3.2. Expectedness of Events

Expectedness of all SAEs will be determined by Biogen according to the approved local label.

## 11.4. Procedures for Handling Special Situations

### 11.4.1. Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care.

### 11.4.2. Pregnancy

The Investigator should refer to the approved local label for guidance if female participants become pregnant or are considering becoming pregnant during the study.

At each routine visit, female patients of childbearing potential will be asked about their pregnancy status and possible pregnancies/spontaneous abortions since the last visit or contact. Spontaneous abortions are considered to be SAEs and must be reported as such.

Congenital abnormalities/birth defects in the offspring of male or female patients should be reported if conception occurred after administration of Tysabri.

### 11.4.3. Regulatory Reporting

Biogen will report SAEs to the appropriate regulatory authorities and Investigators as required, according to local law.

## 11.5. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Review all AEs to determine seriousness and fulfillment of collection criteria defined in Section 11.1.2.

- Monitor and record all SAEs regardless of the relationship to Tysabri.
- Determine the relationship of each SAE to Tysabri.
- Determine the onset and resolution dates of each SAE.
- Complete the appropriate form for each SAE, overdose, and pregnancy, when applicable, and fax or email it to Biogen within 24 hours of the site staff becoming aware of the event, or according to national law.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen within 24 hours of the site staff becoming aware of new information, or according to national law.
- Ensure all SAE reports are supported by documentation in the patients' medical records.
- Report SAEs to local ethics committees, as required by local law.

## 11.6. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before site activation and patient enrollment, the Clinical Monitor or designee is responsible for reviewing with site staff the definition of an SAE, as well as the instructions for monitoring, recording, and reporting SAEs.
- Determine the expectedness of all SAEs.
- Notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

# 12. STATISTICAL CONSIDERATIONS

## 12.1. Sample Size

At least 4500 patients will be enrolled into this study. Because the primary objectives are to observe and estimate incidence and pattern of SAEs in patients receiving Tysabri, the sample size is not based on the statistical power considerations.

## 12.2. Analysis Population

All patients who are enrolled into TOP and have at least 1 dose of Tysabri will be included in the evaluation of safety and impact of Tysabri on disease activity and progression, irrespective of their treatment duration and/or possible treatment discontinuation**.** However, the impact of treatment discontinuation and differences in treatment duration will be evaluated.

## 12.3. External Control Population

In order to have a control group with significant overlapping of disease characteristics allowing for valid comparisons with TOP patients, a patient sampling technique based on the propensity score will be used [Rosenbaum and Rubin 1985]. Propensity scores will be estimated based on patients enrolled into TOP and all eligible control patients. Control patients will then be selected through matching to TOP patients using the nearest propensity score.

## 12.4. Statistical Methods

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

Differences from baseline will be assessed using statistical methods for paired data (i.e., paired t-test, Wilcoxon signed-rank test, McNemar's test). Stratified, correlation, graphical, and regression analyses will be performed to explore the association between baseline characteristics and disability progression/disease activity while on Tysabri.

Propensity analysis will be used in the comparison of TOP patients with a cohort from the independent MSBase comparator group study to compensate for non-random assignment of treatment groups [Butzkueven 2006]. Propensity score analysis relies on pre-treatment variables (baseline characteristics) of individual patients that influence treatment decisions. It reduces the entire collection of baseline characteristics to a single composite that appropriately summarizes the individual patient's conditional probability to be assigned to a specific treatment [Rubin 1997]. The reduction to one composite characteristic (the propensity score) also allows the assessment of whether the evaluated treatment groups overlap enough with respect to baseline characteristics to allow a sensible estimation of treatment effects from the datasets. This type of analysis has been successfully applied to RRMS patients [Trojano 2007] where long-term disability outcomes were compared in non-randomly assigned groups of interferon treated and untreated patients.

A logistic regression model will be used to obtain the propensity score. Covariates for consideration will be all observed baseline characteristics. Treatment effects will be examined using the following analyses:

a. Estimate the treatment effect within strata defined by the propensity score
b. Estimate the treatment effect using propensity score inverse weighting
c. Estimate the treatment effect by including the propensity score in a regression analysis

The data will also be analyzed by subgroups (e.g., age, gender, previous treatment, EDSS classification, disease duration, number of past relapses at enrollment, and any other factors that the Steering Committee deems to be appropriate as prognostic indicators for disease activity and disability progression over time). If there are heterogeneities among the groups in any of the patient characteristics that are of clinical importance, the impact of the imbalances will be investigated and, if appropriate, adjustments will be made in the comparison to the matched treated external cohort and the analysis of the impact of the drug on disease activity and progression. All proportions associated with time to an event will be calculated using Kaplan-Meier estimate, and compared, if necessary, among different subgroups using log-rank test or a proportional hazards model adjusting for clinically important baseline factors. Frequency distributions resulting from discrete data will be compared, if necessary, using a Chi-Square test, or logistic regression model, or proportional odds model if data is ordinal. Continuous data will be analyzed using either a simple t-test or a nonparametric test if data deviates severely from normality. Analysis of variance model or the nonparametric one will be employed if adjusting for baseline factors is necessary. A Poisson regression or negative binomial model will be used for analysis of annualized relapse rates.

Safety will be analyzed using the incidence of SAEs, which will be estimated with percentage of patients experiencing at least 1 SAE. Patterns of the SAEs will also be investigated.

Disability progression will be assessed by evaluating EDSS evolution over time. These analyses include:

- Proportion of patients that progress at least 1 point on EDSS and sustained over 6 months
- Proportions of patients that reach EDSS milestones such as 4.0, 6.0, and 7.0 sustained after 6 months
- Proportions of patients whose disability status worsened, stabilized, or improved will also be estimated (values sustained after 6 months)

MS disease activity will be assessed by evaluating the frequency of relapses over time:

- Annualized relapse rate
- Distribution of the total number of relapses over a period of up to 15 years
- Time to first relapse
- Proportions of patients with relapse

Prognostic factors for disability progression and MS disease activity will be assessed in different patient cohorts stratified according to their baseline characteristics:

- EDSS
- Disease duration
- Number of relapses in previous 1 and 2 years
- Previous use of disease modifying therapies
- Age, gender, and any other factors that the Steering Committee will deem to be appropriate

[redacted]

## 12.5. Interim Analyses

Interim analyses will be performed when the following milestones are achieved:

- The first 500 patients have completed 1 year of observation
- The first 1000 patients have completed 1 year of observation

Data analyses will be performed on an annual basis thereafter.

# 13. ETHICAL, REGULATORY, AND ADMINISTRATIVE REQUIREMENTS

Biogen and all Investigators agree to comply with this protocol and to conduct TOP according to local law, regulations, and agreements and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines. The patient's privacy, physical and mental integrity, personality as well as confidentiality will be strictly respected in accordance to the principles set forth by the Declaration of Helsinki.

## 13.1. Informed Consent and Confidentiality

Prior to any data collection under this protocol, the patient, in accordance with local practice and regulations, must sign a written informed consent. Information about TOP will be explained to the patient. The DCC will receive the data of each study visit, as a rule in 6-monthly intervals, as well as after every visit that might take place in order to evaluate new or worsening neurological symptoms. All reported data must be documented in the patient's medical record. A copy of the informed consent form, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must be documented in the patient's medical record prior to any data collection under this protocol. The informed consent form must not be altered without the prior agreement of the relevant ethics committee and Biogen.

In order to ensure patient confidentiality, patients will be assigned a unique identifying number. The transmitted data sets use this identifying number plus the patient's initials but are otherwise anonymized.

In any presentations or in publications of TOP results, the patients' identities will remain anonymous and confidential. Biogen, its designee(s), and various government health agencies may inspect the records of TOP. Every effort will be made to keep the patients' personal medical data confidential.

## 13.2. Competent Authorities and Ethics Committees

As regulations for observational studies differ among participating countries, Competent Authorities and Ethics Committees will be consulted as dictated by local country regulations.

## 13.3. Changes to the Protocol

Ethics Committees and appropriate regulatory authorities will be contacted, as applicable, if changes to the protocol need to be applied.

## 13.4. Operational Aspects

### 13.4.1. Data Compilation Center

Biogen has chosen [redacted] ([redacted], Switzerland) as the contract research organization responsible for the development, maintenance, and support of the Data Collection platform. Data will be entered at the study sites into an MSBase compatible central database using a web-based eCRF.

### 13.4.2. Clinical Research Organization

Biogen has chosen [redacted] as the contract research organization for TOP. [redacted] will be responsible for study site instruction, data management, and follow-up of data generated in TOP. [redacted] ([redacted], Switzerland) will manage data collection.

### 13.4.3. Internal Safety Review

Applicable personnel at Biogen will review all SAEs on a regular basis.

## 13.5. Completion of TOP

Regulatory Agencies and Ethics Committees approving the study will be notified of completion or termination of TOP, as applicable.

# 14. REFERENCES

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# 15. APPENDIX I: SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, entitled: “TOP: TYSABRI Observational Program” and agree to conduct the study as detailed herein and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print) Date

_____

Investigational Site (Print)

# 16. APPENDIX II: QUESTIONS REGARDING EMPLOYMENT STATUS

The following questions will be asked of patients where permitted by local regulatory authorities.

Before Tysabri (Asked at visit when patient signs new informed consent):

What was your employment status in the year before starting Tysabri? Check one:

| **__ Working full-time** | | **__ Student full-time** | | **___ Other - Please specify** |
|---|---|---|---|---|
| __ Working part-time | | __ Student part-time | | _____ |
| __ Self-employed | | __ Unemployed | | _____ |
| __ Homemaker | | __ Retired | | _____ |

If you were not a full-time worker (employed or self-employed), full-time student, or full-time homemaker in the year before starting Tysabri, was that because of your MS? Yes / No

If you were employed or self-employed (working for pay) in the year before starting Tysabri, did you have to take sick leave because of your MS? Yes / No

Since Initiation of Tysabri (Asked at visit when patient signs new informed consent)

What has your employment status been since you started Tysabri? Check all that apply and indicate time (in years) for each:

| **__ Working full-time** | **___ yr** | **__ Student full-time** | **___ yr** | **___ Other - Please specify** |
|---|---|---|---|---|
| __ Working part-time | ___ yr | __ Student part-time | ___ yr | ___ yr _____ |
| __ Self-employed | ___ yr | __ Unemployed | ___ yr | _____ |
| __ Homemaker | ___ yr | __ Retired | ___ yr | _____ |

If you have not been a full-time worker (employed or self-employed), full-time student, or full-time homemaker since you started Tysabri, is that because of your MS? Yes / No

Currently on Tysabri (Asked at each clinic visit)

What is your current employment status? Check one:

| **__ Working full-time** | | **__ Student full-time** | | **___ Other - Please specify** |
|---|---|---|---|---|
| __ Working part-time | | __ Student part-time | | _____ |
| __ Self-employed | | __ Unemployed | | _____ |
| __ Homemaker | | __ Retired | | _____ |

If you are not currently a full-time worker (employed or self-employed), full-time student, or full-time homemaker, is that because of your MS? Yes / No

If you are currently employed or self-employed (working for pay), how many days did you have to take sick leave during the past 6 months because of your MS? ___ days