Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR TYSABRI® (NATALIZUMAB)

RMP version number:	33.0
Data lock point (DLP) for this RMP:	18 Oct 2024
Date of final sign off:	12 May 2025

QPPV name: Jana Hyankova, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

EU RMP v32.2 is currently under evaluation.

Details of currently approved RMP

Version number:	32.0
Approved with procedure:	EMEA/H/C/000603/IB/0146
Date of approval:	28 Aug 2024

Rationale for submitting an updated RMP

Version 33.0 of this EU RMP has been prepared to include an update of Part V and Annex 6 in support of a proposed amendment to the EU Labelling to allow Tysabri subcutaneous (SC) to be self-administered by the patient or administered by a caregiver as an option.

The checklist for health care professionals (HCPs) administering Tysabri SC outside of the clinical setting (OCS) is proposed to be replaced by a Pre-Administration Checklist for both, HCPs administering Tysabri SC OCS and patients and caregivers administering Tysabri SC.

The addition of the following key element to the Patient Alert Card is proposed: Reminder to patients self-administering and caregivers administering Tysabri SC to review the Pre-Administration Checklist for signs and symptoms of PML prior to each administration of Tysabri SC. If any signs or symptoms of PML are noted, Tysabri SC may not be administered, and the prescriber needs to be informed immediately.

Summary of significant changes in this RMP

In consideration of the above rationale, a summary of the significant changes implemented in Version 33.0 of this RMP is provided in the table below:

Module	Rationale for update	Summary of significant changes
Part I	Not applicable	No significant changes made.
Part II Module SI	Not applicable	No significant changes made.
Part II Module SII	Not applicable	No significant changes made.
Part II Module SIII	Not applicable	No significant changes made.
Part II Module SIV	Not applicable	No significant changes made.
Part II Module SV	Not applicable	No significant changes made.
Part II Module SVI	Not applicable	No significant changes made.
Part II Module SVII	Not applicable	No significant changes made.
Part II Module SVIII	Not applicable	No significant changes made.
Part III	Not applicable	No significant changes made.
Part IV	Not applicable	No significant changes made.
Part V	To provide guidance beyond the Patient Alert Card and package leaflet to patients self-administering at home and to caregivers administering at home, to make them aware of the signs and symptoms of PML, simplification of educational tool.	Pre-Administration Checklist for HCPs administering Tysabri SC OCS and for patients and caregivers administering Tysabri SC included as an educational tool under additional risk minimisation measures for PML.
Part VI	Updates in Part V	Pre-Administration Checklist for HCPs administering Tysabri SC OCS and for patients and caregivers administering Tysabri SC included as an educational tool under additional risk minimisation measures for PML. Link to EMA EPAR updated.

TABLE OF CONTENTS

PART I: PRODUCT OVERVIEW 9
PART II: SAFETY SPECIFICATION 11
PART II, MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) 11
II: 1.1 Indication 11
II: 1.1.1 Epidemiology of the disease 11
II: 1.1.2 Important co-morbidities found in the target population 14
PART II, MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION 16
II: 2.1 Summary of key safety findings from non-clinical data 16
PART II, MODULE SIII – CLINICAL TRIAL EXPOSURE 21
II: 3.1 Integrated clinical trial exposure (IV route of administration) 21
II: 3.2 Exposure to Tysabri SC (Study 101MS102 and Study 101MS206) 23
PART II, MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS 24
II: 4.1 Exclusion criteria in pivotal clinical studies within the development programme 24
II: 4.2 Limitations to detect adverse reactions in clinical trial development programmes 26
II: 4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes 26
PART II, MODULE SV – POST-AUTHORISATION EXPERIENCE 28
II: 5.1 Post-authorisation exposure 28
II: 5.1.1 Method used to calculate exposure 28
II: 5.1.2 Exposure 28
PART II, MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION 29
II: 6.1 Potential for misuse for illegal purposes 29
PART II, MODULE SVII – IDENTIFIED AND POTENTIAL RISKS 30
II: 7.1 Identification of safety concerns in the initial RMP submission 30
II: 7.2 New safety concerns and reclassification with a submission of an updated RMP 30
II: 7.3.1 Presentation of important identified risks 30
II: 7.3.2 Presentation of important potential risks 36
II: 7.3.3 Presentation of missing information 37

PART II, MODULE SVIII – SUMMARY OF SAFETY CONCERNS 39
PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES) 40
III: 1 Routine pharmacovigilance activities 40
III. 2 Additional pharmacovigilance activities 40
III. 3 Summary table of additional pharmacovigilance activities 41
PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES 44
PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) 45
V: 1 Routine risk minimisation measures 45
V: 2 Additional Risk Minimisation Measures 47
V: 2.1 Progressive multifocal leukoencephalopathy 47
V: 2.1.1 Educational tools targeting healthcare professionals 47
V: 2.1.2 Educational tools targeting patients and/or carers 49
V: 3 Summary table of risk minimisation measures 50
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 52
VI: 1 The medicine and what it is used for 53
VI: 2 Risks associated with the medicine and activities to minimise or further characterise the risks 53
VI: 2.1 List of important risks and missing information 54
VI: 2.2 Summary of important risks 54
VI: 2.3 Post-authorisation development plan 58
VI: 2.3.1 Studies that are conditions of the marketing authorisation 58
VI: 2.3.2 Other studies in post-authorisation development plan 59

PART VII – ANNEXES

Annex 1 EudraVigilance Interface
Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme
Annex 3 Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan
Annex 4 Specific adverse drug reaction follow-up forms
Annex 5 Protocols for proposed and ongoing studies in RMP part IV
Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Annex 7 Other supporting data (including referenced material)

Annex 8 Summary of changes to the risk management plan over time

LIST OF TABLES

Table 1: Product Overview 9

Table 2: Pneumonia 14

Table 3: Urinary Symptoms 14

Table 4: Pain 15

Table 5: Key safety findings from non-clinical studies and relevance to human usage 16

Table 6: Clinical study exposure by indication, as of suspension and from reintroduction of Tysabri (07 August 2020) 21

Table 7: Cumulative subject exposure to Tysabri from completed and ongoing clinical trials by age and sex from reintroduction to 07 Aug 2020 22

Table 8: Cumulative subject exposure to Tysabri from completed and ongoing clinical trials by racial group from reintroduction to 07 Aug 2020 22

Table 9: Exposure to subcutaneous Tysabri in Studies 101MS102 and 101MS206, by indication and dose 23

Table 10: Exclusion criteria that remain as contraindications in relation to the assessment of missing information 24

Table 11: Discussion of exclusion criteria not remaining as contraindications in relation to the assessment of missing information 25

Table 12: Limitations common to clinical trial development programme 26

Table 13: Exposure of special populations included or not in the clinical trial development programme 27

Table 14: Estimated Post-marketing Patient Exposure by Region, International Birth Date Through 31 Jul 2023 28

Table 15: Summary of safety concerns 39

Table 16: Ongoing and planned additional pharmacovigilance activities 42

Table 17: Description of routine risk minimisation measures by safety concern 45

Table 18: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern 50

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AED	Antiepileptic drugs
ANA	Anti-natalizumab antibody
ARN	Acute retinal necrosis
AUC	Area under the concentration time curve
CD	Crohn’s disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMQ	Customized MedDRA Query
CMV	Cytomegalovirus
CNS	Central nervous system
DCT	Data collection tools
DHPC	Direct Healthcare Professional Communication
DMF	dimethyl fumarate
DMT	Disease modifying therapy
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EID	Extended interval dosing
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GA	Glatiramer acetate
GCN	Granule cell neuronopathy
HCP	Healthcare Professional
IFN	Interferon
IA	immunoadsorption
Ig	Immunoglobulin
IV	Intravenously
IRIS	Immune Reconstitution Inflammatory Syndrome
IS	Immunosuppressant

Abbreviation	Definition
JCV	John Cunningham virus
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
OCS	Outside a clinical setting
PIL	Patient information leaflets
PD	Pharmacodynamic
PK	Pharmacokinetic
PL	Package Leaflet
PLEX	Plasmapheresis
PML	Progressive multifocal leukoencephalopathy
PT	Preferred Term
PSUR	Periodic safety update report
PY	Patient-years
Q4W	Once every 4 weeks
Q6W	Once every 6 weeks
RBC	Red blood cell
RMP	Risk Management Plan
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
SC	Subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SID	standard interval dosing
SmPC	Summary of Product Characteristics
SPMS	Secondary progressive multiple sclerosis
TOP	Tysabri Observational Programme
US	United States
UTI	Urinary tract infection
WBC	White blood cell

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Natalizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AA23
Marketing Authorisation Holder	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Tysabri®
Marketing authorisation procedure	Centralised
Brief description of the product including: • **chemical class** • **summary of mode of action** • **important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)**	Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant Deoxyribonucleic acid technology. Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4 subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule 1, and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment 1. Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule 1. Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4 expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site and inhibit further recruitment of immune cells into inflamed tissues.
Hyperlink to the EU Product Information (PI)	https://www.ema.europa.eu/en/medicines/human/EPAR/tysabri

Indication(s) in the European Economic Area (EEA)	**Current:** Tysabri is indicated as a single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see Sections 4.4 and 5.1 of the SmPC) or • Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.
Dosage in the EEA	300 mg by intravenous infusion or subcutaneous injection once every 4 weeks.
Pharmaceutical form(s) and strengths	*Form:* Concentrate for solution for infusion *Strength:* 300 mg *Form:* solution for injection in pre-filled syringe *Strength:* 150 mg (dose is 300 mg)
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II, MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

II: 1.1 Indication

Tysabri is indicated as a single disease modifying therapy (DMT) in adults with highly active relapsing-remitting multiple sclerosis for the following patient groups: Patients with highly active disease despite a full and adequate course of treatment with at least one DMT (for exceptions and information about washout periods see Sections 4.4 and 5.1 of the Summary of Product Characteristics [SmPC])

Or

Patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

II: 1.1.1 Epidemiology of the disease

Epidemiology data for the indicated patient population is provided in the sections below.

II: 1.1.1.1 Incidence and prevalence

The worldwide incidence of MS in 2016 was estimated to be 0.9 per 100,000 [Clarivate ; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017]. Kingwell et al. [Kingwell 2013] conducted a systematic review of studies of the incidence and prevalence of MS in Europe, and discovered significant heterogeneity in incidence rate and prevalence estimates between and within regions as well as across time (e.g., increasing incidence in more recent years). Some of the observed heterogeneity in more recent years could be explained by advances in methodology and study design, but increasing latitude was also a potential explanation for regional variance. The prevalence and incidence estimates tended to be higher in the Northern regions of the United Kingdom and in the Nordic countries, implicating the role of latitude and the more recent studies (after year 2000) reported higher MS prevalence and incidence estimates. The annual incidence rate of MS in Europe is estimated to range from 0.7 to 12.2 per 100,000 persons, with country-specific variations [Dean 2002; Kingwell 2013; Nicoletti 2005; Pugliatti 2006].

The total number of people living with MS worldwide is approximately 2 – 2.5 million [Compston and Coles 2002; Reich 2018; Wallin 2019]. The disease is unevenly distributed throughout the world with prevalence varying between < 5 cases per 100,000 people in tropical areas and Asia and > 100 - 200 cases per 100,000 in temperate areas especially those with large populations of Northern European origin [Milo and Kahana 2010; Rosati 2001]. In 2015, the age-standardized global prevalence was estimated to be 26 per 100,000 (95% CI: 26-30) and in 2016, the age-standardized global prevalence was estimated to be 30 per 100,000 (95% CI: 28 - 33) [Clarivate ; Feigin 2019; Feigin 2017]. The highest age-standardized prevalence (164 per 100,000) was noted in high-income areas of North America and the lowest age-standardized prevalence was noted in Oceania (2.0 per 100,000) [Wallin 2019].

II: 1.1.1.2 Demographics of the target population in the authorised indication

The mean age of MS diagnosis is 30 years old, with twice as many women affected as men [Reich 2018; Wallin 2019].

II: 1.1.1.4 Risk factors for the disease

MS is an inflammatory disease of the brain and spinal cord characterized by focal areas of inflammation that lead to destruction of the myelin sheath and varying degrees of axonal injury. While researchers do not know the exact causes of the disease, both genetic (e.g., family history of disease) and environmental (e.g., smoking, Epstein-Barr virus, latitude, vitamin D) risk factors are suspected etiologies of the disease [Ramagopalan 2010].

II: 1.1.1.5 Main existing treatment options

Therapies for MS include symptomatic treatments (e.g., steroids) and DMTs. The available therapies entail difficult trade-offs in efficacy, safety, tolerability, and convenience that make RMS a challenging condition to treat successfully, and that result in a substantial need to provide new options that can improve these trade-offs for some patients.

Commonly used DMTs in patients with RMS or RRMS include interferon-β (IFN-β) therapies and GA, which require either intramuscular or subcutaneous injections from as few as every 2 weeks to as many as 7 times a week [Calabresi 2014; Jacobs 1996; Johnson 1995; Li and Paty 1999; PRISMS Study Group 1998]. While these treatments have a well-established safety and efficacy profile, many subjects continue to experience significant MS disease activity while on treatment. Furthermore, these therapies are associated with known side effects, including flu-like symptoms for the IFN-β therapies, and lipoatrophy and other injection site pathologies for GA, which can be a significant burden for some patients.

Oral DMTs that are approved for the treatment of RRMS include DMF, fingolimod, and teriflunomide [Cohen 2010; Confavreux 2014; Fox 2012; Gold 2012; Kappos 2010; O'Connor 2011]. While these therapies may offer an improved route of administration for some patients, they nonetheless require daily administration. Furthermore, some patients may not tolerate them or may continue to experience disease activity while on treatment. These therapies have also been associated with serious side effects, such as lymphopenia for DMF; bradycardia, atrioventricular block, and macular oedema for fingolimod; and hepatotoxicity and leukopenia (including lymphopenia and neutropenia) for teriflunomide. These risks may necessitate exclusion of vulnerable patients and specialized monitoring both during and prior to initiation of therapy.

Other available DMTs include alemtuzumab and mitoxantrone, which are administered intravenously (IV) [Cohen 2012; Polman 2006; The Medical Letter 2012]. Alemtuzumab is a monoclonal antibody that has shown superior efficacy to IFN β-1a but entails risks of life-threatening autoimmune disorders, including fatal thrombocytopenia and nephropathies; additionally, autoimmune thyroid disease is common during treatment. For these reasons, in the European Union (EU) and some other regions, its use is restricted to those patients who have failed other therapies or is not approved for patients with inactive disease. Mitoxantrone is associated with significant risks including cardiotoxicity, which increases with cumulative dose, as well as myeloid leukaemia. Therefore, mitoxantrone is mainly used as a third-line therapy in patients with severe MS that has failed to improve with other therapies. Cladribine is an immunosuppressive

agent that is reported to reduce clinical and radiological measures of disease activity in patients with relapsing remitting multiple sclerosis but is associated with a increased risk of lymphopenia.

Anti-CD-20 antibodies (ocrelizumab, ofatumumab, ublituximab) have recently become available as DMTs for RRMS. The long-term safety of these drugs has not yet been established [F. Hoffmann-La Roche Ltd 2022; Neuraxpharm 2021; Novartis 2021].

In summary, while a number of DMTs are currently available, MS patients face difficult trade-offs between benefits and risks when selecting a therapy, including inadequate disease control, life-threatening AEs, need for frequent injections or pills, and/or tolerability problems that reduce treatment adherence and quality of life. Given the heterogeneity of MS and patients' response to therapy, disease control is frequently incomplete after initiation of treatment, and patients must often switch from one treatment to another as their disease progresses or their response to a given treatment proves to be unsatisfactory based on safety, efficacy or tolerability.

Therefore, a substantial unmet medical need exists for well-tolerated MS treatments that offer greater efficacy while still offering convenience.

II: 1.1.1.6 Natural history of the indicated condition in the untreated population, including mortality and morbidity

MS is a chronic autoimmune and neurodegenerative disorder of the CNS that is characterized by inflammation, demyelination, and neuronal loss. The pathological changes underlying MS are believed to be mediated by activated, autoreactive lymphocytes, which cross the blood-brain barrier and initiate an immune-mediated cascade of events that injures both the grey and white matter of the brain [Frohman 2006].

RMS is the most common clinical presentation of the disease [Lublin and Reingold 1996]. The diagnosis of relapsing MS is usually made on the basis of both clinical and radiographic criteria, and it requires that a patient experience at least 2 neurological events that are consistent with demyelination and separated both in time and in location in the CNS [McDonald 2001; Polman 2011; Polman 2005; Poser 1983]. Patients with RMS experience discrete episodes of neurological dysfunction (referred to as relapses, exacerbations, or attacks), each lasting several days to several weeks, which occur intermittently over many years. Typical symptoms of relapse include weakness, sensory loss, visual loss, and imbalance.

Early in the course of the disease (the RRMS phase), the physical symptoms of relapse tend to subside completely after each attack. However, the CNS inflammatory process that accompanies the clinical relapses during the RRMS phase results in lasting brain injury as detected by early grey-matter atrophy and increased lesion load on MRI that predispose individuals to long-term disability [Dalton 2004; Fisniku 2008]. Over time, the clinical recovery from relapses tends to be incomplete, leading to the accumulation of functional disability and the frequent onset of secondary progressive MS.

The prevention of clinical relapses and disability progression as well as the subclinical brain injuries that occur during the relapsing phase of MS are recognized as important therapeutic benefits for MS patients. Clinical relapses impair essential activities of daily life and frequently result in hospitalization. An estimated 42% to 57% of relapses are associated with residual neurological deficits [Hirst 2008; Lublin 2003]. The goal of relapse prevention applies to patients with both RRMS and other forms of relapsing MS (such as secondary progressive MS). Consensus

panels on the treatment and classification of MS have underscored the importance of inflammatory activity (as defined by the presence of clinical relapses and new MRI lesions) in both relapsing and progressive forms of MS as an indication for disease-modifying treatment [Costello 2014; Lublin 2014]. Without effective treatment, approximately half of all RMS patients are unable to walk without assistance within 15 years of their diagnosis, and more than half may eventually die from disease-related complications [Brønnum-Hansen 2004; Runmarker and Andersen 1993; Weinshenker 1989].

II: 1.1.2 Important co-morbidities found in the target population

Table 2: Pneumonia

MS Comorbidity	Pneumonia
Incidence	Estimated to be twice that of the general population
Co-prescribed medication	Antibiotics

Pulmonary morbidity has been described in MS, especially among patients with more severe disease. Respiratory muscle function is affected by disease severity [Gosselink 1999]. Complications from a respiratory illness are also a common cause of death among patients with MS. A cohort study that used prospectively collected data from the United Kingdom General Practice Research Database found that pneumonia was the second most commonly recorded cause of death amongst this cohort across all age groups [Jick 2014]. Utilizing patient records from the Manitoba Vital Statistics Death Database and Manitoba provincial health department, Marrie and colleagues found respiratory disease to be one of the most common causes of death for MS patients [Marrie 2015]. This finding supported a previous finding by Goodin and colleagues that pulmonary disease is a leading cause of death among persons with MS (Goodin, 2014). A population-based study using the Danish Multiple Sclerosis Registry found that the presence of a pulmonary illness resulted in diagnostic delays for MS [Thormann 2017]. A study of the Danish MS Registry (1998) found that patients with MS were more likely to die from respiratory and infectious diseases than the general population [Koch-Henriksen 1999]. Patients appear to have an increased history of respiratory tract infections prior to MS onset [Marrie 2000]. A crude estimate, based on the MS Danish registry results, suggests that the infection rate in patients with MS may be at least 2 times greater than the general population.

At this time, no estimates of pneumonia incidence rates within patients with MS were found. Hill and colleagues conducted a large EMR study in which they evaluated the prevalence of asthma among persons with MS (n = 141,800) compared to persons without MS (n = 56,416,790) and observed that the prevalence of asthma was significantly greater among those with MS compared to the control cohort (PR 2.97, 95% CI 2.96-2.97) [Hill 2019]. Even after adjusting for age and sex, asthma was three times more common among the MS cohort compared to the controls [Hill 2019].

Table 3: Urinary Symptoms

MS Comorbidity	Urinary Symptoms
Incidence	10% at diagnosis

MS Comorbidity	Urinary Symptoms
Prevalence	64%-68%
Co-prescribed medication	Antibiotics and anticholinergic agents

Urinary symptoms are very common in patients with MS. One in 10 patients may already have urinary symptoms at the time of initial diagnosis of MS, but on average, symptoms will appear about 6 years after the onset of disease [de Sèze 2007] and are estimated to be present in 64%-68% of patients with MS [Mahajan 2010]. Symptoms include frequency, urgency, and urinary incontinence, which together are described as overactive bladder syndrome. UTIs are common in patients with MS and are likely to be present in 30% of patients with MS. The incidence of urinary symptoms increases with disease duration. Treatment options for overactive bladder include anticholinergic agents, but none of the newer drugs in this class, which are also likely to be better tolerated, have been specifically studied in patients with MS. Infection needs to be excluded in any patient presenting with urinary symptoms.

Table 4: Pain

MS Comorbidity	Pain
Prevalence	50% in patients with MS in an outpatient department
Co-prescribed medication	See below

A 2008 systematic review found the point prevalence of pain in persons with MS to be nearly 50% and about 75% of persons with MS reported having pain within one month of assessment [O'Connor 2008]. O'Connor and colleagues found that nearly 20% of patients were experiencing pain at disease onset and there are several types of pain associated with MS, such as central neuropathic pain, musculoskeletal pain, intermittent central neuropathic pain, and mixed neuropathic and non-neuropathic pain [O'Connor 2008]. Nearly 50% of persons with MS are reported to have central neuropathic pain, which makes it the most common pain syndrome among this population [Solaro 2013]. Severe spasticity may be treated with botulinum toxin or intrathecal baclofen [Pöllmann and Feneberg 2008].

PART II, MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II: 2.1 Summary of key safety findings from non-clinical data

All toxicology studies were carried out using the humanized antibody (i.e., natalizumab). The studies performed included an acute study in guinea pigs and mice, a 4-week study in primates (rhesus monkeys), 6-month chronic studies in adult and juvenile primates (cynomolgus monkeys, juvenile cynomolgus monkeys), an embryo/foetal development study in primates, a combination toxicity study of natalizumab with Avonex (IFN β-1a) in primates, and an immunotoxicity study in primates. Genotoxicity and tissue cross-reactivity studies were also performed. Special toxicology studies included a dog cardiovascular study and an in vitro study to assess potential immunomodulatory effects of natalizumab. Toxicology studies in guinea pigs, mice, and rhesus and cynomolgus monkeys have not demonstrated any specific risks likely to be associated with the use of natalizumab in human subjects. All studies have demonstrated expected increases in white blood cell counts likely due to the demargination of lymphocytes and monocytes. Key safety findings from these studies with potential relevance to human usage are described in Table 5.

Table 5: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity studies	
Antibody formation In a 6-month multiple dose study in cynomolgus monkeys, natalizumab was administered IV to male and female animals at 3, 10, 30, or 60 mg/kg/week and compared with a vehicle control group. Approximately 50% of the animals in the 30 and 60 mg/kg/week groups had detectable antibodies to natalizumab. Of the 32 natalizumab-treated animals, 22 animals were positive for anti-natalizumab antibodies, but only 5 showed signs of glomerulonephritis at necropsy. Laboratory tests indicated that these animals had activation of complement and/or evidence of circulating immune complexes. In a 6-month multiple dose study in juvenile cynomolgus monkeys natalizumab was administered IV to male and female animals at 10, 30, or 60 mg/kg/week and compared with a vehicle control group. Antibodies to natalizumab were found in 10 of 22 natalizumab-treated animals. Development of antibodies occurred between Day 22 and 50 and had an inverse relationship to dose. The presence of antibodies was correlated with decreases in total serum complement activity and the development of immune complexes in the serum immediately post-infusion.	Antibody formation is expected due to injection of foreign protein. A similar effect was seen in humans and is included in Section 4.4 (Special warnings and precautions for use) of the SmPC. Hypersensitivity reactions were also seen in humans and are included in Section 4.4 (Special warnings and precautions for use) of the SmPC.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Anti-natalizumab antibody analysis Liquid high concentration or lyophilized high concentration natalizumab formulations after subcutaneous or intramuscular injections at doses of 150 (liquid formulation) or 120 mg (lyophilized formulation) were well tolerated in cynomolgus monkeys, and produced expected pharmacologic-related increases in peripheral blood lymphocyte counts that were comparable to, but of slightly greater persistence than after a single 30 mg intravenous dose of the commercial liquid formulation. Immunogenicity was relatively consistent across all dose groups and did not appear to be greater following extravascular dosing when compared to the commercial liquid IV route. No anti-natalizumab antibodies were detected prior to dosing in any group. On Day 28, all animals were antibody-positive in commercial liquid IV group and between 3 of 6 and 4 of 6 animals were antibody positive in the remaining groups. Day 28 antibody titers ranged from 11 μg/mL to 125 μg/mL. On Day 36, all animals remained positive in commercial liquid IV and between 4 of 6 and 5 of 6 animals were positive in the remaining groups. Day 36 titers were greater than those observed on Day 28 and ranged from 116 μg/mL to 303 μg/mL. Immunogenicity was relatively consistent across all dose groups and did not appear to be greater following extravascular dosing when compared to the IV route	Consistent with findings observed in Phase 1 (DELIVER) and Phase 2 (REFINE) studies for Tysabri SC administration. Antibody formation is expected due to injection of foreign protein. A similar effect was seen in humans and is included in Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) of the SmPC.
<u>Effects on white blood cells</u> In a 6-month multiple dose study in juvenile cynomolgus monkeys natalizumab was administered IV to male and female animals at 10, 30, or 60 mg/kg/week and compared with a vehicle control group. Expected increases in total WBCs, resulting primarily from increases in lymphocytes, were seen in natalizumab treated animals and consisted of increases in both T and B cells. Higher spleen weights and spleen weight ratios were observed in the natalizumab-treated groups. Histologically, the higher spleen weights correlated to an increased frequency and severity of splenic follicular hypertrophy and hyperplasia (graded as minimal to mild). There were no gross necropsy findings, effects on organ weights, or spleen findings in the 17-week recovery animals indicating reversibility of these findings.	Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was apparent as WBC increases as well as increased spleen weights in most in vivo studies. Although some dose-dependency was observed in both parameters in terms of the incidence of the observation per group, the extent of changes when observed was generally unchanged with dose. These changes do not appear to have any adverse toxicological consequences, and can be expected to occur at the clinical dose level. Hyper eosinophilia without symptoms has been observed in patients treated with Tysabri in the post-marketing setting.

SAFETY FINDING	RELEVANCE TO HUMAN USE
In a 6-month multiple dose study in cynomolgus monkeys, natalizumab was administered IV to male and female animals at 3, 10, 30, or 60 mg/kg/week and compared with a vehicle control group. Dose-related increases in WBC counts were observed in this study, primarily due to increases in circulating lymphocyte counts, in the natalizumab 30 and 60 mg/kg/week groups.	
Reproductive/developmental toxicity	
Effects of natalizumab on male and female fertility have been evaluated in guinea pigs, and on embryo/foetal development in guinea pigs and cynomolgus monkeys. Fertility studies in guinea pigs demonstrated no treatment-related effects on male fertility at doses up to 30 mg/kg every other day, which results in 38-fold greater exposure (based on cumulative AUC) than the anticipated human exposure. Female guinea pigs showed a reduction in fertility in 1 of 2 studies at a dose of 30 mg/kg every other day, which results in 40-fold greater exposure (based on cumulative AUC) than the anticipated human exposure. Doses below 30 mg/kg did not result in a reduction in female fertility. Embryo/foetal development studies in guinea pigs and cynomolgus monkeys at doses up to 30 mg/kg every other day, which results in 26-fold and 213-fold greater exposure (based on cumulative AUC), respectively, than the anticipated human exposure, did not reveal any teratogenic effects. There was an increased incidence of abortions in natalizumab-treated groups in 1 primate study (13% for controls versus 29% natalizumab-treated animals); however, no increased incidence was observed in 4 other studies that evaluated this endpoint in the 2 species. Therefore, although a treatment-related effect on abortion cannot be ruled out, it is unlikely that natalizumab treatment significantly increases the risk of abortion.	An increased incidence of abortions with natalizumab treatment was noted in 1 cohort of the developmental cynomolgus monkey study, but was not observed in the second cohort of animals in the same study, or in separate primate or guinea pig embryo/foetal development studies. In addition, the incidence of abortion was within the rather large historical range reported by the laboratory facility that conducted the developmental study. The potential abortifacient activity of natalizumab is probably best judged on the cumulated body of data from 4 studies, in 2 species that exposed pregnant animals to the drug. Based on the observation of an increased rate in only part of 1 of 4 studies, it seems reasonable to conclude that natalizumab does not have clear abortifacient activity.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Data from the developmental reproductive toxicology study in cynomolgus monkeys indicate no changes in infant survival, growth, in-life clinical observations, or clinical chemistry parameters in infants from dams treated with 30 mg/kg natalizumab on alternate days from Gestational Day 20 to 70 or Gestational Day 20 to term. Haematology results demonstrated the presence of increased lymphocytes in the circulation of infants from dams treated with natalizumab until parturition, a finding that is consistent with the measurement of natalizumab in the sera of these infants. No changes in RBC parameters were evident, indicating that the anaemia seen in the embryo/foetal development study was reversible by 1 month of age. Serum levels of IgG, IgM, and Ig A, primary and secondary immune responses following immunization, immunohistochemistry (for lymphocyte markers) and histopathology of immune organs were unaffected in the infants of natalizumab treated dams. In summary, treatment with 30 mg/kg natalizumab to pregnant cynomolgus monkeys either through organogenesis (Gestational Day 20 to 70) or through the full pregnancy (Gestational Day 20 to term) did not have adverse effects on the general health, survival, development, or immunological function of infants born to these dams.	There was a greater reduction in platelets in foetuses than in offspring, but no effects on platelets in juvenile or adult animals. This suggests that inhibition of α4 by natalizumab treatment during pregnancy may affect platelet precursors in the developing bone marrow, an effect that is reversible and to which juvenile and adult animals are not susceptible. There were no apparent adverse effects observed in the offspring of natalizumab treated dams, including no findings of anaemia in offspring. The clinical significance of the effect of natalizumab on foetal lymphoid organs has been evaluated in the developmental study through antigen challenges. These data indicated no differences in the immune responses of infants born to natalizumab-treated dams versus control-treated dams. The possibility that natalizumab may have effects on the developing immune system and haematopoiesis, dictates that caution should be exercised if natalizumab is considered for use during pregnancy and lactation.
Genotoxicity and Carcinogenicity	
Two in vitro studies were conducted to assess the potential genotoxicity of natalizumab. Natalizumab at concentrations of 48 to 1,530 g/mL was negative in the L5178Y tyrosine kinase mouse lymphoma forward mutation. Natalizumab at concentrations of 191 to 2,040 g/mL did not induce chromosomal aberrations in cultured human whole blood lymphocytes in both the absence and presence of metabolic activation. No proliferative effects were seen with any one of 11 α4+ tumour cell lines. No increases in tumour take, growth, or metastasis resulted from natalizumab treatment in either graft system (2 different α4+ human tumour cell lines (a leukaemia and a melanoma).	These observations, together with a review of the literature regarding the role of alpha 4 integrins in cancer, suggest that natalizumab treatment is unlikely to increase the risk of cancer in humans.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Safety Pharmacology studies	
Cardiovascular Safety To assess potential effects of natalizumab on the cardiovascular system, beagle dogs were given a 30 minute single IV infusion at doses of 0.3, 3, and 30 mg/kg followed by a 2.5-hour monitoring period. An apparent dose-related effect on hemodynamic parameters was observed in several of the dogs in the mid- and high-dose groups. In the 3 mg/kg dose group, 1 out of 3 dogs showed decreases in mean arterial blood pressure, left ventricular systolic pressure, and cardiac output, and increases in heart rate and total peripheral resistance. These hemodynamic effects were also observed in 2 out of 3 dogs at the 30 mg/kg dose group. This study did not include a nonspecific humanized IgG4 antibody control.	Potential treatment-related changes were observed only in the dog study, where doses of 3 mg/kg were associated with transient decreases in systemic and left ventricular pressure in 1 dog. The finding that these were transient effects, together with the lack of development of any significant cardiovascular changes following 6 months of dosing in primates, indicates that natalizumab is unlikely to have cardiovascular effects in humans. Furthermore, the lack of effect in 2 monkey species and also absence of alpha 4 integrins on cardiac tissue make it unlikely that this single finding is of relevance to humans.
Other toxicity-related information	
Immunotoxicity A retrospective analysis of serum and tissues samples from the two 6-month cynomolgus monkey toxicity studies and the 4-week combination toxicity study in rhesus monkeys was performed to determine whether any changes after treatment with natalizumab or natalizumab plus IFNβ-1a occurred in SV40, an endemic and usually benign polyomavirus in macaque populations. The study was undertaken to help understand the case of patients who developed PML, generally caused by recrudescence of the polyomavirus, JC. Like JCV in humans, SV40, which has 69% genomic homology to JCV, naturally infects rhesus monkeys and becomes latent. In immunocompromised monkeys, SV40 can cause a demyelinating disease pathologically and epidemiologically very similar to human PML. No treatment-related changes in the level of anti-SV40 antibodies were identified in samples from the toxicity studies. In addition, none of the organs (brain, kidney, lung, or lymphoid tissues) from any of the animals showed evidence of expression of SV40 T or VP1 proteins. Furthermore, results from a murine CMV reactivation host resistance model indicated that treatment with a rat anti-mouse 4 integrin mAb or a combination of rat anti-mouse 4 integrin mAb with murine IFN did not result in reactivation of CMV.	The administration of natalizumab, a humanized protein, to non-human species results in an immune response to the antibody. The overall incidence of antibody formation in the programme is difficult to establish due to the limitations of the assay to detect antibodies in the presence of circulating levels of natalizumab that are generally present at necropsy. However, where washout periods have been allowed, the incidence of antibody formation is up to 100%. Antibody-related effects were observed in 3 areas; apparent immune-mediated hypersensitivity in some guinea pigs and monkeys, evidence of glomerulonephritis in some antibody positive monkeys and, reduced exposure of natalizumab in some animals.

PART II, MODULE SIII – CLINICAL TRIAL EXPOSURE

II: 3.1 Integrated clinical trial exposure (IV route of administration)

The efficacy of natalizumab in relapsing MS patients has been established in 3 controlled studies: a Phase 2 dose-comparison study (Study C-1803) plus two Phase 3 efficacy and safety studies (Study C-1801 and Study C-1802). In Study C-1801 natalizumab was compared to placebo in untreated MS subjects, whereas in Study C-1802, natalizumab was compared to placebo in subjects who were being treated with IFN beta-1a (Avonex®). Although there were some differences in the characteristics of the subjects enrolled in these Phase 3 studies, both studies showed that treatment with natalizumab delayed the time to sustained progression in disability, substantially reduced the frequency of relapse, and markedly attenuated brain MRI measures of inflammation and tissue destruction in subjects with relapsing MS.

The overall evaluation of the safety profile of Tysabri presented in this EU RMP (in support of the overall benefit-risk assessment) originally focused primarily upon the review of integrated data available in the original pivotal clinical development programme in 2006 from 8 placebo-controlled studies (MS200, MS201, MS202, MS221, MS231, C-1801, C-1802, C-1803) to form a database of 2,752 patients 1,617 who received natalizumab and 1,135 who received placebo. Crohn's disease studies (4 short-term – CD201, CD202, CD301 and CD307, and 5 long-term – CD251, CD351, CD303, CD305, and CD352), which extended up to a maximum dosing duration of 3 years have involved 1563 natalizumab treated patients with 33% receiving over one year- treatment and 18% over two years treatment. It is noted that Tysabri was originally developed for infusion by IV administration and therefore all studies in the original pivotal pooled safety dataset investigated the administration of Tysabri via the IV route. Since this time, Tysabri has been investigated in further studies and in additional indications (using the IV formulation), with all safety data routinely reviewed in order to inform the ongoing safety profile of Tysabri.

As of 07 August 2020, a total of 6720 participants have been enrolled into the Tysabri clinical program and exposed to Tysabri since the DIBD (01 January 1996), of which 4193 participants have received Tysabri as of suspension and 3564 participants have received Tysabri from reintroduction. Please note some participants in the STRATA study received Tysabri before suspension and after reintroduction. Clinical study data by indication are presented in Table 6.

Table 6: Clinical study exposure by indication, as of suspension and from reintroduction of Tysabri (07 August 2020)

Indication	As of Suspension		From Reintroduction [b,c] (March 2006)	
	Patients[a]	Patient-Years	Patients[a]	Patient-Years
Multiple sclerosis	2323	3297	3238	6756
Crohn's disease	1639	1406	0	0
Rheumatoid arthritis	231	75	0	0
Multiple myeloma	0	0	6	1
Ischemic stroke	0	0	257	20

Indication	As of Suspension		From Reintroduction [b,c] (March 2006)	
	Patients[a]	Patient-Years	Patients[a]	Patient-Years
Epilepsy	0	0	63	41
Total	**4193**	**4778**	**3564**	**6818**

[a] Includes subjects who received at least 1 dose of natalizumab from interventional clinical trials

[b] Includes all completed studies plus Epilepsy Study 101EP201, and Study 101MS329.

[c] 2074 subjects in the STRATA study were dosed in both pre-suspension and post-reintroduction periods

Exposure data are presented by age and gender (Table 7) and by racial group (Table 8) from interventional clinical trials since reintroduction.

Table 7: Cumulative subject exposure to Tysabri from completed and ongoing clinical trials by age and sex from reintroduction to 07 Aug 2020

Age Range	Male	Female	Total[a]
< 18	3	10	13
18 to 29	134	286	420
30 to 39	309	660	969
40 to 49	379	815	1194
50 to 59	206	482	688
≥ 60	115	102	217
Total	**1146**	**2355**	**3501**

[a] Only includes subjects who received at least one dose of Tysabri (natalizumab) from interventional clinical trials. Includes all completed studies plus the ongoing Epilepsy Study 101EP201, and Study 101MS329. 1037 subjects in STRATA were dosed in both pre-suspension and post-reintroduction periods. Age range calculated based on age of subject at first dose of Tysabri in parent study.

Table 8: Cumulative subject exposure to Tysabri from completed and ongoing clinical trials by racial group from reintroduction to 07 Aug 2020

Racial Group	Number of Subjects[a]
White	2446
Black or African American	101
Asian	116
American Indian or Alaska Native	3
Hispanic	26
Native Hawaiian or Other Pacific Islander	1
Other	23

Racial Group	Number of Subjects[a]
Not reported	785
Total	**3501**

[a] Only includes subjects who received at least one dose of Tysabri (natalizumab) from interventional clinical trials. Includes all completed studies plus the ongoing Epilepsy Study 101EP201, and Study 101MS329. 1037 subjects in STRATA were dosed in both pre-suspension and post-reintroduction periods.

II: 3.2 Exposure to Tysabri SC (Study 101MS102 and Study 101MS206)

The assessment of the safety of Tysabri in support of the SC route of administration was based on data obtained from 2 completed clinical studies – Study 101MS102 (DELIVER) conducted in adult patients with RRMS and secondary progressive multiple sclerosis (SPMS), and Study 101MS206 (REFINE) conducted in adult patients with RRMS.

In these 2 completed clinical studies, a total of 162 patients with RRMS or SPMS were exposed to all doses and treatment regimens of Tysabri treatment via SC administration (Table 9). Of these, a total of 71 patients (57 RRMS patients and 14 SPMS patients) have received Tysabri SC at the treatment regimen of 300 mg Q4W.

Table 9: Exposure to subcutaneous Tysabri in Studies 101MS102 and 101MS206, by indication and dose

Indication Dose	Study 101MS102	Study 101MS206	Total
Relapsing remitting multiple sclerosis (RRMS)			
300 mg SC Q4W	12	45	57
300 mg SC Q12W	-	53	53
150 mg SC Q12W	-	38	38
Secondary progressive multiple sclerosis (SPMS)			
300 mg SC Q4W	14	-	14
Total	**26**	**136**	**162**

PART II, MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II: 4.1 Exclusion criteria in pivotal clinical studies within the development programme

The Tysabri clinical development programme has employed specific exclusion criteria which were either related to the evaluation of efficacy (to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), or were related to safety (in order to protect trial patients from potential risks associated with investigational product administration), or were good clinical practice related (e.g., to ensure that proper follow-up was possible).

When evaluating the impact of these exclusion criteria in relation to the impact on the safety of patients receiving treatment with Tysabri in the post-marketing setting, key exclusion criteria pertaining to safety from pivotal studies included in the primary pooled safety dataset are addressed by the 'Contraindications' and 'Warnings and precautions for use' sections of the Tysabri SmPC. Exclusion criteria from these pivotal studies that are considered as contraindications in the SmPC, and their rationale for not being considered as missing information, are discussed in Table 10.

Table 10: Exclusion criteria that remain as contraindications in relation to the assessment of missing information

Exclusion Criteria	Reason for being an exclusion criterion	Considered to be missing information?	Rationale
Hypersensitivity to medicinal product	Standard exclusion criterion in order to ensure patient safety	No	The current SmPC contraindicates the use of Tysabri in patients with hypersensitivity to the active substance or to any of the excipients (as listed in SmPC Section 6.1). Considering this contraindication, use in this patient population is not considered to be relevant for inclusion as missing information.
Concomitant treatment with beta IFNs or GA or any other MS disease modifying therapy	This was an exclusion criterion for efficacy reasons and for added toxicity due to the mechanism of action of DMTs	No	Tysabri is indicated as a monotherapy only for the treatment of RRMS, and therefore use in combination with other DMTs contraindicated. Considering this contraindication, use in this patient population is not considered to be relevant for inclusion as missing information.

Exclusion Criteria	Reason for being an exclusion criterion	Considered to be missing information?	Rationale
History of malignancy	Natalizumab is an immune-suppressant	No	It has been hypothesised that an increase in the rate of malignancies may theoretically occur due to the effect of Tysabri on interfering with lymphocyte trafficking, and consequently Tysabri is contraindicated in patients with known active malignancies (except for cutaneous basal cell carcinoma). Considering this contraindication, use in this patient population is not considered to be relevant for inclusion as missing information.

A review of the key exclusion criteria in the pivotal studies which do not remain as contraindications for use, and the appropriate justifications in relation to their relevance to be considered as missing information are presented in Table 11.

Table 11: Discussion of exclusion criteria not remaining as contraindications in relation to the assessment of missing information

Exclusion Criteria	Reason for being an exclusion criterion	Considered to be included as missing information?	Rationale
A clinically significant infectious illness	Natalizumab is an immunosuppressant	No	In clinical trials the rate of infection was similar in treatment and placebo arms. Majority of patients did not interrupt treatment during infections and recovery occurred with appropriate treatment. Patients with increased risk for opportunistic infections remains a contraindication.
History of, or abnormal laboratory results	To be able to assess impact of drug administration	No	Contraindication for patients that are immunocompromised remains.
Prior treatment with various medicinal products	Prior use of disease modifying therapies	No	Tysabri is a second line treatment for MS and patients must have failed treatment with at least one DMT to be eligible for Tysabri.
Positive for anti-natalizumab antibodies at screening	To be able to assess immunogenicity potential of drug	No	Persistent positive anti-natalizumab antibody formation may be associated with decreased efficacy of drug

II: 4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure; however, a review of the limitations of exposure to Tysabri in the clinical development programme, and the ability to detect specific categories of adverse reactions, is provided in Table 12 below.

Table 12: Limitations common to clinical trial development programme

Ability to detect adverse reactions	Level of adverse reaction detection for the clinical trial programme and implications for target population
Which are rare	As of 07 August 2020[a], a total of 6720 subjects (total of 11596 person-year exposure) were exposed to Tysabri in the clinical development programme. Of these, 4524 were patients with MS (total of 10053 person-year exposure). The clinical trial database remains too small to exclude Adverse Drug Reactions (ADRs) occurring at rates below about 1/700 patients.
Due to prolonged exposure, cumulative effects, and/or which have a long latency	In clinical trials since March 2006 up to a DCO of 07 August 2020[b], 1763 patients have been exposed to Tysabri for 1 year (≥ 12 doses), 1009 for 2 years (≥ 24 doses), 804 for 3 years (≥ 36 doses), 564 for 4 years (≥ 48 doses), 506 for 5 years (≥ 60 doses), 458 for 6 years (≥ 72 doses), 415 for 7 years (≥ 84 doses) and 153 for 8 years (≥ 96 doses). There were no new safety findings from the long-term extension studies in patients with MS. A small number of patients have been treated beyond 6 years and therefore, rare ADRs with long latency may not be detected.

[a] Includes subjects who received at least one dose of natalizumab from interventional clinical trials up to the DCO of 07 August 2020. Includes all completed studies before suspension and after reintroduction plus the ongoing epilepsy Study 101EP201, and Study 101MS329.

[b] Includes participants who received at least one dose of natalizumab from interventional clinical trials up to the DLP of 07 August 2020. Includes all completed studies from reintroduction in March 2006 plus the ongoing epilepsy Study 101EP201, and Study 101MS329.

II: 4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 13. Tysabri was not studied in special populations, age groups, or specific disorders in the clinical development program for the SC formulation.

Table 13: Exposure of special populations included or not in the clinical trial development programme

Type of special population	Exposure
Children (< 18 years)	13 patients in total[a]; comprising 3 male patients, and 10 female patients
Elderly patients (≥ 60 years)	217 patients in total in completed and ongoing clinical trials[a]; comprising 115 male patients and 102 female patients
Pregnant women	Not included in pre-authorisation clinical development programme.
Breast feeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Hepatic impairment	Not included in the clinical development programme. No formal pharmacokinetic (PK) studies in patients with hepatic impairment have been performed, although given the nature and mechanism of clearance of natalizumab, no effects were anticipated, and none have been reported during post-marketing surveillance.
Patients with relevant comorbidities: • Renal impairment	Not included in the clinical development programme. No formal PK studies in patients with renal impairment have been performed, although given the nature and mechanism of clearance of natalizumab, no effects were anticipated, and none have been reported during post-marketing surveillance.
Patients with relevant comorbidities: • Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	N/A
Patients with relevant different ethnic origin	Although the majority of the subjects included in completed and ongoing clinical trials since reintroduction[a] are White (2446/3501), others include Asian (116), Black or African American (101), Hispanic (26), Other (23), American Indian or Alaska Native (3), Native Hawaiian or Other Pacific Islander (1). There are no data to suggest that there are important differences in the PK of natalizumab for patients with different racial or ethnic origins.

[a] Includes participants who received at least one dose of natalizumab from interventional clinical trials up to the DLP of 07 August 2020. Includes all completed studies from reintroduction in March 2006 plus the ongoing epilepsy Study 101EP201, and Study 101MS329.

PART II, MODULE SV – POST-AUTHORISATION EXPERIENCE

II: 5.1 Post-authorisation exposure

II: 5.1.1 Method used to calculate exposure

Exposure information for the EEA and ROW market settings is calculated using monthly sales data. For each month, an algorithm is used to calculate ongoing and new patients based on the estimated discontinuation percentage applied to the monthly sales patient numbers. These data are then summed across the months for the reporting of new patients for cumulative and/or interval reports. Infusions represent the sum of the amount of therapy equivalent to a single patient's infusion regardless of whether new or ongoing, in a given time period. PY are estimated by dividing the total number of sales patients for a given month by 12, and then summing the PY for the target time period. Exposure information for the US market setting, including number of patients and PY of exposure, are based of the data reported from the US Prescribing Program, in which all patients receiving Tysabri in the US are required to be enrolled.

II: 5.1.2 Exposure

Cumulative post-marketing exposure to Tysabri is presented in Table 14.

Table 14: Estimated Post-marketing Patient Exposure by Region, International Birth Date Through 31 Jul 2023

Region	Number of Patients	Person-Years
EEA (MS only)	91,110	491,282
Total Exposure Worldwide	**260,816**	**1,109,640**

PART II, MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

II: 6.1 Potential for misuse for illegal purposes

There is no known potential for misuse of natalizumab for illegal purposes.

PART II, MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

II: 7.1 Identification of safety concerns in the initial RMP submission

Not applicable, as this EU RMP update is not an initial submission.

II: 7.2 New safety concerns and reclassification with a submission of an updated RMP

II: 7.2.1 Newly identified safety concerns

Not applicable – no safety concerns were newly identified since the submission of the previous EU RMP.

II: 7.2.2 Reclassification of existing safety concerns

Not applicable – no existing safety concerns have been reclassified or removed from the current EU RMP.

II: 7.3.1 Presentation of important identified risks

II: 7.3.1.1 Progressive Multifocal Leukoencephalopathy

Relevant MedDRA terms: *CMQ PML*

It is noted that all data available to characterise PML risk are from the IV route of administration. Considering the similar pharmacodynamic profiles, the same PML risk and relevant risk factors are also assumed for the different routes of administration (eg, SC).

Potential mechanisms

PML is an opportunistic infection caused by the John-Cunningham virus (JCV).

Two general mechanisms have been suggested to explain the association between natalizumab treatment and PML. The first is that blocking alpha 4 integrin decreases lymphocyte trafficking, and the subsequent reduction in immune surveillance allows for the activation of a latent infection in the nervous system. The second suggested mechanism is associated with the finding that deletion of alpha4 integrin is associated with increased numbers of B cells and immature progenitor cells released from the bone marrow. Both of these cell populations may be reservoirs of latent JCV. Besides oligodendrocytes, JCV can also infect cerebellar granule cell neurons resulting in JCV GCN.

Evidence source(s) and strength of evidence

PML was reported in two patients in pre-authorization MS trials after about 2 years of combination treatment with natalizumab and beta-IFN 1a (Avonex®). A third case was reported in a patient from the Crohn's disease clinical trials, who had terminated use of immunosuppressants 2 to 3 months prior to starting natalizumab monotherapy.

In the post-marketing setting, Biogen utilises a framework that uses standardised criteria and case definitions to differentiate and classify reported cases of PML by levels of diagnostic certainty.

This objective adjudication process was developed with external PML expert input and has been used to evaluate PML case reports for natalizumab for several years.

PML case definitions (which categorize cases into Level 1 to Level 5) allow classification of cases based on various levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out (Level 5), includes a category for cases with insufficient data despite exhaustive due diligence (Level 4), as well as categories for high and low suspect cases (Levels 2 and 3, respectively).

Following this adjudication process, confirmed PML cases (Level 1) have been identified in association with natalizumab use. Consequently, PML was added as a listed ADR in Section 4.8 (Undesirable effects) of the natalizumab SmPC, and wording relating to the detection and management of PML was implemented in Section 4.4 (Special warnings and precautions for use).

Characterisation of the risk

From the reintroduction of natalizumab to the market in March 2006 through 07 August 2020, 839 confirmed cases of PML have been reported in addition to the 3 reported in the pre-authorisation studies. One hundred ninety-four cases were from clinical or observational studies, and 645 cases were reported spontaneously.

Pertinent data from the completed observational studies is provided below:

- *TYGRIS:* From the 6508 participants with 22,200 PY of exposure in the observational TYGRIS study, 44 cases with the PT Progressive multifocal leukoencephalopathy and 1 case with the PT JC Virus infection were reported, corresponding to an incidence rate per 1000 PY of 2.03 (95% CI 1.48 - 2.71) for all cases and 1.98 (95% CI 1.44 – 2.66) for cases with the PT Progressive multifocal leukoencephalopathy. Of the cases pertinent to the PT Progressive multifocal leukoencephalopathy, 20% (9/44) had history of prior immunosuppressant use and 95% (42/44) had received natalizumab for more than 24 infusions. In 5% (2/44) of the subjects, PML was diagnosed between 13 and 24 infusions.
- *STRATIFY-2:* 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].
- JCV-GCN events were not reported from the pivotal clinical trials with Tysabri. During the post-marketing period, there have been very rare reports of JCV GCN in patients receiving Tysabri [Agnihotri 2014; Schippling 2013].

Patients with confirmed PML in the post-marketing setting are followed up for up to 24 months following diagnosis. Of the 839 natalizumab-treated patients with confirmed PML from March 2006 through 07 August 2020, the survival rate was 76% (634 patients are alive), and the mortality rate was 24% (205 patients died).

As of 07 August 2020, 112 of 839 confirmed PML cases (13.3%) were clinically asymptomatic (defined as the absence of recognizable new symptoms attributable to PML at the time of PML diagnosis). The survival rate was higher in asymptomatic patients (92.0%) than in patients who were symptomatic at diagnosis (73.0%). JCV GCN can occur in isolation or in combination with PML. Symptoms of JCV GCN are similar to symptoms of PML (i.e., cerebellar syndrome).

In the confirmed cases of PML, the majority underwent either PLEX or immunoadsorption (IA) in order to remove natalizumab from the plasma and accelerate immune surveillance. In most cases, within days to weeks but generally about 4 to 6 weeks following PLEX or IA, there was evidence of the development of Immune Reconstitution Inflammatory Syndrome (IRIS) associated with worsening neurologic deficits which have been sometimes rapid, severe and at times fatal. Gd-enhancement on MRI was usually, but not always, present. Evidence suggests that high dose intravenous steroids with oral taper over relatively prolonged periods and sometimes repeated may be required to adequately control the inflammation of IRIS.

A retrospective analysis of the impact of PLEX on the clinical outcome of natalizumab-associated PML suggested that PLEX was not associated with a statistically significant effect on survival (based on 2-year observation period) and appeared to have no impact on improving post-PML outcomes. Physicians should use medical judgement when considering the use of PLEX to treat PML. The diagnosis and management of JCV GCN should follow guidance provided for PML.

Early diagnosis, clinical and MRI monitoring, and stopping Tysabri therapy may have improved the outcome of PML in affected Tysabri patients.

Risk factors and risk groups

PML can only occur in the presence of a JCV infection, with studies indicating that approximately 60%-70% of MS patients were seropositive when screened for anti-JCV antibody [Olsson 2013].

The following risk factors are associated with an increased risk of PML in natalizumab-treated patients:

- The presence of anti-JCV antibodies
- Treatment duration; especially beyond 2 years
- Immunosuppressant use prior to receiving natalizumab

Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of natalizumab therapy and have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive natalizumab-treated patients who have not used prior immunosuppressants, the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e., the risk is greater in those with a high antibody index compared to those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with natalizumab for longer than two years.

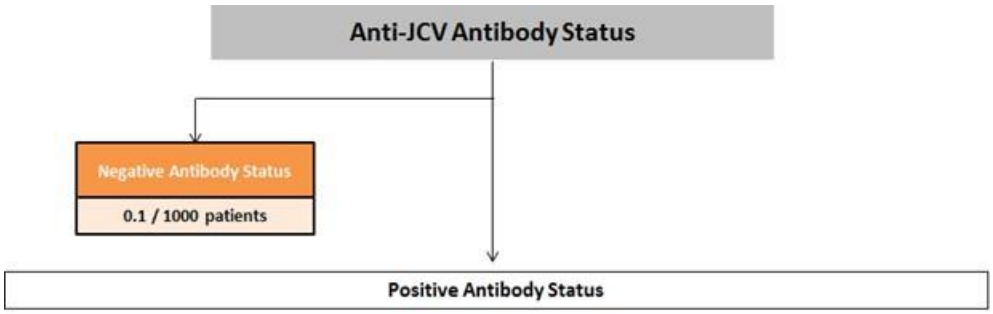
Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result.

Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results.

Using the 3 risk factors (JCV antibody status, prior immunosuppressant therapy use and duration of natalizumab therapy), and patients with high anti-JCV antibody index who have received more than 2 years of natalizumab therapy and without prior history of immunosuppressant

therapy, subgroups of patients with distinctly lower and higher risk for PML can be identified. Consequently, an algorithm containing these risk factors and the associated PML risk has been developed to allow physicians to assess the risk of patients for developing PML (see Figure 1). This algorithm is contained in the 'Physician Information and Management Guidelines for Multiple Sclerosis patients on Tysabri Therapy', which form an additional risk minimisation measure for Tysabri (see Part V:2 [*Additional risk minimisation measures*] for further details). The risk of PML persists for up to 6 months following discontinuation of natalizumab therapy.

Figure 1 PML risk factor assessment algorithm



Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Preventability

PML is not preventable, however early detection and stopping of natalizumab treatment may improve outcome. Anti-JCV antibody testing and increased frequency of MRI monitoring in high-risk patients may enable early detection including in patients who are asymptomatic.

For anti-JCV antibody positive patients with no history of prior immunosuppressant therapy use and low index, 6-monthly re-testing of these patients after 2 years of treatment for changes from low to high index is recommended to inform on appropriate patient MRI monitoring.

Extending the dosing interval of natalizumab (e.g., to 6 weeks) has been practiced by some physicians in anti-JCV antibody positive patients with the intention of improving the benefit/risk of natalizumab by reducing the exposure dependent risk of PML while maintaining efficacy.

A prespecified, retrospective analysis of anti-JCV antibody-positive patients treated with natalizumab in the US TOUCH (Tysabri® Outreach: United Commitment to Health) program demonstrated a clinically and statistically significant reduction in the risk of PML in patients treated with extended interval dosing (300 mg with an average dosing interval of approximately 6 weeks) as compared to approved dosing (300 mg every 4 weeks). The decrease in PML risk is

based on data from IV administration. No clinical data are available on either the safety or efficacy of dosing every 6 weeks with SC administration.

Study 101MS329 (NOVA), Part 1 showed that the safety profile in the Tysabri 300 mg IV Q6W group was similar to that in the Tysabri 300 mg IV Q4W group. No new safety findings were identified during this study, recognizing that this study was not designed to be informative on rare events such as PML. Of note, there was one event of asymptomatic PML reported in the Q6W group. This one case had additional known risk factors (anti-JCV antibody index > 1.5 and > 2 years of TYSABRI treatment) [Foley 2022].

Efficacy has been modelled for patients who switch to longer dosing after ≥ 1 year of approved dosing with this medicinal product under IV administration and who did not experience a relapse in the year prior to switching. Current PK/PD statistical modelling and simulation indicate that the risk of MS disease activity for patients switching to longer dosing intervals may be higher for patients with dosing intervals ≥ 7 weeks. No prospective clinical studies have been completed to validate these findings and the efficacy of EID has not been established.

Impact on the risk-benefit balance of the product

PML continues to be an uncommon event related to natalizumab use, and all reports of suspected PML are closely monitored and subject to rigorous follow-up to accurately adjudicate the cases according to level of evidence and to characterize any potential additional risk factors for PML.

The current natalizumab SmPC describes the risk of PML in Section 4.4 (Warnings and Precautions for use), which details specific clinical measures (in relation to the monitoring, diagnosis and management of suspected PML cases) in addition to guidance on risk factors, which should allow prescribers to make an adequate risk-benefit assessment for an individual patient. Furthermore, Biogen provides an additional risk minimisation guideline entitled ‘Physician Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI Therapy’ (see Part V [*Risk minimisation measures*] for further details) to convey further information on this important identified risk. These current label recommendations and additional risk minimisation measures are considered to be adequate to mitigate the risk of PML, and therefore the risk-benefit balance of the product remains favourable.

Public health impact

PML is not considered to have a major impact on public health.

II: 7.3.1.2 Serious herpes infections

Relevant MedDRA terms: *CMQ Serious herpes infection*

Potential mechanisms

As the herpes viruses lie latent in a large majority of the population in neuronal tissue, an effect of natalizumab on local tissue immunosurveillance may lead to increased risk of herpes viral reactivation and replication. This is particularly the case for the brain where the effect of natalizumab to reduce lymphocyte trafficking is well known. Pathological neuro-infection with herpes has been reported. A role for natalizumab to increase the risk of systemic herpes infection is less easily assessed. Natalizumab treatment does not lead to systemic immunosuppression in the classical sense of reduction of total or subtypes of circulating immunologically active cells, as might be seen with classical immunosuppressive agents, but local tissue depletion of

lymphocytes could possibly lead to a greater risk of more severe local herpes or a greater risk of systemic spread.

Evidence source(s) and strength of evidence

In clinical trials, herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab.

In post-marketing experience, rare cases of acute retinal necrosis (ARN) have been observed in patients receiving natalizumab, with some of these cases having occurred in patients with central nervous system herpes infections (e.g. herpes meningitis and encephalitis).

Characterisation of the risk

Herpes infection:

- **Clinical trials:** The overall incidence rate per 1000 PY of any herpes infection was 1.43 (95% CI 1.23 – 1.66), with 1.01 (95% CI 0.84 - 1.20) for PT Herpes simplex, 0.39 (0.29 - 0.52) for PT Herpes zoster, 0.03 (0.01, 0.08) for PT Varicella, and 0.01 (0.00, 0.05) for PT Pneumonia herpes viral. No events pertinent to the other PTs in the search strategy were reported.
- **Post-marketing data:** In the observational study TYGRIS, the incidence rate of events pertinent to the MedDRA CMQ Serious herpes infection was 1.22 (95% CI 0.80 - 1.77) per 1000 PY.

Encephalitis / meningitis:

- No cases of herpes encephalitis/meningitis were reported from the Tysabri pivotal clinical trials.
- In the observational study TYGRIS, the estimated incidence rate y for meningoencephalitic herpetic was 1 per 29,232 PY or 3.42 per 100,000 PY (95% CI: 0.087, 19.060).

Acute retinal necrosis:

- One case was reported from the observational study TYGRIS (PT Necrotising retinitis); the corresponding incidence rate was 0.05 (95% CI 0.00 - 0.25) per 1000 PY.
- At the DLP 07 Aug 2023, the cumulative postmarking reporting rate of ARN cases pertinent to the CMQ Serious herpes infections was 3.0 (95% CI 2.0 - 4.2) per 100,000 PY. Events with the following PTs were reported: Necrotising retinitis, Herpes zoster necrotising retinopathy, Necrotising herpetic retinopathy.

Risk factors and risk groups

No specific risk factors or groups have been identified.

Preventability

There are no preventability measures for the development of serious herpes infection; however, if herpes encephalitis or meningitis occurs, natalizumab should be discontinued, and appropriate

treatment should be administered. Additionally, early investigation of signs and symptoms indicative of ARN (such as decreased visual acuity, redness and painful eye) and stopping of natalizumab treatment may improve the outcome of this condition.

Impact on the risk-benefit balance of the product

There have been reports from post-marketing of serious, life-threatening and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex and varicella zoster and serious cases of ARN affecting one or both eyes which led to blindness in some patients.

Herpes encephalitis and meningitis can be serious, life-threatening, or fatal. ARN can be severe and lead to blindness.

Public health impact

Serious herpes infections is not considered to have a major impact on public health.

II: 7.3.2 Presentation of important potential risks

II: 7.3.2.1 Malignancies

Relevant MedDRA terms: *SMQ: Malignant or unspecified tumours*

Potential mechanisms

It has been hypothesised that an increase in the rate of malignancies may theoretically occur due to the effect of natalizumab on interfering with lymphocyte trafficking.

The majority of the medical literature on alpha 4 integrins and melanoma suggests that blocking the α4β1 integrin may inhibit the growth and metastasis of melanoma; however, there is also some data that indicate that α4β1 integrin blockage may have pro-tumour effects due to inhibiting the migration of Natural Killer cells into the tumour.

Evidence source(s) and strength of evidence

This risk is based on the class of product and based on scientific literature. No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded.

Characterisation of the risk

Clinical trials:

- The incidences of malignancies (excluding basal cell carcinomas) for MS/CD trials were 0.37 per 100 patient-years (PY) for natalizumab and 0.38 per 100 PY for placebo. The nature of the reported malignancies did not differ substantially between the natalizumab and placebo groups.

Post-marketing data:

- A cumulative review of malignancies from 24 November 2004 to 07 August 2018 indicate that the overall cumulative reporting rate of Healthcare Professional (HCP)-confirmed events is 337.87 (95% CI: 324.12 – 352.05) per 100,000 person-years, which is lower than the overall age-adjusted Surveillance, Epidemiology, and End Results (SEER) incidence rate

of 442.7 per 100,000 person-years. Review of any individual malignancies with a higher reporting rate and 95% CI of HCP-confirmed events did not highlight any specific concerns for those specific malignancies.

Additional pertinent data from the observational studies is provided below:

- TYGRIS: A total of 132 subjects (2%) reported a malignant event during the study. All emergent individual malignancies by site/type had incidence rates and 95% Cis that included incidence rates estimates for general population epidemiologic reference data for SEER and Globocan.

Risk factors and risk groups

None known for natalizumab. Based on the available epidemiological data and the review of malignancy cases, there is no evidence to suggest an increased risk for malignancy associated with long-term natalizumab therapy.

Preventability

None.

Impact on the risk-benefit balance of the product

As no evidence of a causal association between natalizumab and the development of malignancies has been identified, no impact on the risk-benefit balance of the product is currently considered.

Public health impact

As there is no evidence of increased risk of malignancy, there is no impact on public health.

II: 7.3.3 Presentation of missing information

II: 7.3.3.1 PML risk following switch from DMTs with immunosuppressant effect

Evidence source

At the time of the initial marketing authorization for natalizumab, the only other treatment options for patients with RRMS were the IFNs and GA. Immunosuppressant use prior to initiation of natalizumab has been identified as a risk for PML. This includes patients with prior use of mitoxantrone, methotrexate, cyclophosphamide, azathioprine or mycophenolate mofetil. Each of these immunosuppressants are mutagenic or are known intercollating agents. There are insufficient data available to inform whether patients switching from other DMTs other than the above with immunosuppressant effects are associated with an increased risk of PML. More recently an increasing number of alternative DMTs have been approved in the EU for patients with RRMS e.g. fingolimod, dimethyl fumarate (DMF) and teriflunomide. Some of these newer DMTs have immunosuppressive effects. While there are some data available from patients that have switched from these newer DMTs to natalizumab, the follow-up time on natalizumab for development of PML in patients who switched from these therapies is relatively short and therefore provides limited experience to inform on PML risk.

Anticipated risk/consequence of the missing information

Due to the paucity of data, the risk of PML following switch from DMTs with immunosuppressant effect is considered to be an area of missing information requiring further characterization, as prior treatment with a DMT may lead to an additive immunosuppressant effect, which may lead to a greater risk of developing PML.

Consequently, a post-authorization safety study (Study 101MS411) is ongoing to estimate the incidence of PML among patients who switch to natalizumab from newer DMTs (including fingolimod, DMF, teriflunamide) as well as among those patients switching from established DMTs (IFN beta, GA) using patients enrolled in the natalizumab TOUCH programme in the US as well as patients in various existing EU registries.

II: 7.3.3.2 Immunogenicity potential of subcutaneously administered Tysabri (ANA formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)

Evidence source

In the 32-week DELIVER study in MS patients with no prior exposure to natalizumab, persistent anti-natalizumab antibodies developed in 1 subject (4%) from 26 subjects who received natalizumab subcutaneously. Antibodies were detected on only one occasion in another 5 subjects (19%).

In the 60-week REFINE study in MS patients, no subjects (136 subjects) who switched from natalizumab intravenous administration to subcutaneous administration had detectable ADA during the study.

Following the thorough evaluation of the data obtained in the DELIVER and REFINE studies, no excess immunological risk with Tysabri when administered via the SC route as compared to IV infusion administration was noted. However, data are acknowledged to be limited.

Anticipated risk/consequence of the missing information

Persistent positive ANA formation may be associated with decreased efficacy of Tysabri and may elicit the potential for an increased incidence of hypersensitivity reactions.

PART II, MODULE SVIII – SUMMARY OF SAFETY CONCERNS

The Tysabri safety specification includes the following important identified risks, important potential risks and areas of missing information (Table 15).

Table 15: Summary of safety concerns

Important identified risks	• Progressive multifocal leukoencephalopathy (PML) • Serious herpes infections
Important potential risks	• Malignancies
Missing information	• PML risk following switch from disease modifying therapies with immunosuppressant effect • Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III: 1 Routine pharmacovigilance activities

Biogen employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP.

Routine Biogen pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to assess the ongoing safety profile of natalizumab throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent data appropriately. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to adverse reactions reporting and signal detection activities, the following routine pharmacovigilance activities are also employed in order to provide further characterisation data for specific safety concerns:

- **Specific adverse reaction follow-up questionnaires for PML, Serious herpes infections and Malignancies:** Data collection tools (DCTs) are used to collect information on reports of suspected PML, Serious herpes infections and Malignancies, which aim to collect detailed information relating to events of interest in a standardized fashion, to enable timely and robust collection of data, and thereby optimising risk evaluation. For confirmed cases of PML follow-up is conducted using DCTs at 3, 6, 12 and 24 months post-diagnosis of PML to collect clinical information including outcome for all cases. These DCTs are provided in Annex 4.

III. 2 Additional pharmacovigilance activities

Data from 3 studies are anticipated to aid the further characterization of the safety concerns described in Section II:7.3. These studies are summarized below:

- **Study name and title, including study design and population:** Study IMA-06-02 – Tysabri Observational Programme (TOP) – An observational study using real world data to assess long-term safety in patients with RRMS.
  - ***Rationale and Study Objectives:*** To assess the long-term safety, and impact on disease activity and progression, of Tysabri in patients with RRMS in a clinical practice setting. This study aims to address the safety concerns of PML, Serious herpes infection and Malignancies.
  - ***Milestones:***
    - *Final report: Q1 2025*
- **Study name and title, including study design and population:** Study 101MS411 – An observational cohort study utilising data from the US natalizumab TOUCH prescribing program and select EU MS Registries.

  - ***Rationale and Study Objectives:*** To estimate the risk of PML and other serious opportunistic infections among patients switching to Tysabri from newer DMTs (including fingolimod, DMF, teriflunomide) and from established DMTs (IFN beta and GA). This study aims to address the safety concern of PML risk in patients switching from DMTs with immunosuppressant effect.
  - **Milestones**:
    - *An annual review of data is conducted and an annual interim report is submitted*
    - *Final report*: Q1 2025

- **Study name and title, including study design and population:** Study 101MS412 – An Observational Study Utilising Data from EU National MS Registries to Estimate the Incidence of Anti-Natalizumab Antibody Among Patients Who Receive Subcutaneous Administration of Natalizumab for Treatment of RRMS.
  - ***Rationale and Study Objectives:*** This PASS is conducted to investigate the immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis), which is currently missing information.
  - The primary objective is to estimate the incidence of ANAs in the cohort of natalizumab-naïve and MS mAb-naïve patients who start receiving natalizumab SC injections. The secondary objectives are: to estimate the proportion of patients detected with ANAs when switched from natalizumab IV to natalizumab SC, to evaluate SAEs, including injection reactions and hypersensitivity reactions, by ANA status; to assess the proportion of patients who had MS relapse, by ANA status.
  - ***Milestones:***
    - *Final report Q4 2026*

III. 3 Summary table of additional pharmacovigilance activities

A summary of the studies included in the pharmacovigilance plan are summarised in Table 16.

Table 16: Ongoing and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Study IMA-06-02 Tysabri Observational Programme This is an observational study that will use real world data to assess the long-term safety of natalizumab • **Status:** Ongoing	*Study Objectives:* To assess the long-term safety and impact on disease activity and progression of Tysabri (natalizumab) in patients with RRMS in a clinical practice setting	• PML • Serious herpes infection • Malignancies	Final report	Q1 2025
Study 101MS411 **An observational cohort study utilising data from the US natalizumab TOUCH prescribing program and select EU MS Registries** This study uses multiple registries to assess the risk of PML and OI patients switching from established DMTs • **Status:** Ongoing	*Primary Objective:* To estimate the risk of PML among patients on Tysabri switching from the newer DMTs (including fingolimod, DMF, teriflunomide) and from established DMTs (IFN beta and GA) To estimate the incidence of serious adverse events of other serious opportunistic infections among patients who switch to Tysabri from newer DMTs (including fingolimod, DMF and teriflunomide) and the established DMTs (IFN beta and GA)	• Risk of PML and other serious opportunistic infections in patients switching from DMTs with immunosuppressant effect	Annual interim report	October
			Final report	Q1 2025

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study 101MS412 **An Observational Study Utilising Data from EU National MS Registries to Estimate the Incidence of Anti-Natalizumab Antibody Among Patients Who Receive Subcutaneous Administration of Natalizumab for Treatment of RRMS** • **Status:** Ongoing	*Primary Objective:* • To estimate the incidence of ANAs in natalizumab- and mAb-naïve patients who start receiving natalizumab SC injections *Secondary objectives:* • • To estimate the proportion of patients detected with ANAs when switched from natalizumab IV to natalizumab SC • To evaluate SAEs, including injection reactions and hypersensitivity reactions, by ANA status • To assess the proportion of patients who had MS relapse, by ANA status.	• Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	Final report	Q4 2026

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable - there are no imposed post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V: 1 Routine risk minimisation measures

Routine risk minimisation measures are in place in order to ensure the maintenance of a favourable risk-benefit balance to patients administered Tysabri.

In the post-marketing setting, routine risk minimisation measures are the SmPC and Patient Leaflet, which are the primary tools to communicate information about the benefits and risks associated with the use of Tysabri. These documents provide information to the prescriber and to the patient about the identified safety concerns and relevant potential safety concerns, and how these concerns should be managed in certain circumstances.

A description of the routine risk minimisation measures per safety concern are discussed in Table 17 below.

Table 17: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
PML	***Routine risk communication:*** • PML is listed as an adverse drug reaction in SmPC Section 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*). • Detail stating that no clinical data are available on either the safety or efficacy of this extended interval dosing with the SC route of administration are included in Section 4.4 (*Warnings and precautions for use*) and Section 5.1 *(Pharmacodynamic properties).* ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A contraindication for use in patients with pre-existing PML is included in SmPC Section 4.3 (*Contraindications*) and PL Section 2 (*What you need to know before you use TYSABRI*). • Information regarding the clinical presentation of PML and risk factors for its development are included in SmPC Section 4.4 (*Warnings and precautions for use*) and PL Section 2 (*What you need to know before you use TYSABRI*). • Recommendations regarding the detection and management of PML are included in SmPC Section 4.4 (*Warnings and precautions for use*). ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.

Safety concern	Routine risk minimisation activities
Serious herpes Infections	***Routine risk communication:*** • Herpes infections is discussed under SmPC Section 4.8 (*Undesirable effects*), and PL Section 4 (*Possible side effects*) description of selected adverse events. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A contraindication for use in patients with increased risk for opportunistic infections is included in SmPC Section 4.3 (*Contraindications*) and PL Section 2 (*What you need to know before you use TYSABRI*). • Information on the increased risk and clinical presentation of serious herpes infections are included in SmPC Section 4.4 (*Warnings and precautions for use*) and PL Section 2 (*What you need to know before you use TYSABRI*). • Recommendations on the detection and management of serious herpes infections are included in SmPC Section 4.4 (*Warnings and precautions for use*). ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.
Important Potential Risks	
Malignancies	***Routine risk communication:*** • SmPC Section 4.8 (*Undesirable effects*) provides information that no differences in incidence rates or the nature of malignancies between Tysabri and placebo-treated patients have been observed over 2 years of treatment; however, observation over longer treatment periods is required in order to further characterize the risk. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A contraindication for use in patients with known active malignancies (except for patients with cutaneous basal cell carcinoma) is included in SmPC Section 4.3 (*Contraindications*) and PL Section 2 (*What you need to know before you use TYSABRI*). ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.
Missing Information	
PML risk in patients switching from DMTs with immuno-suppressant effect	***Routine risk communication:*** • Not applicable.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Information regarding the uncertainty of increased PML risk in patients switching from DMTs with immunosuppressant effects to Tysabri, in addition to recommendations on increased monitoring and guidance on laboratory tests and washout periods prior to starting Tysabri is provided in SmPC Section 4.4 (*Warnings and precautions for use).* ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.
Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	***Routine risk communication:*** • Not applicable. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Information on immunogenicity potential of subcutaneously administered Tysabri is included in SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2. in addition to recommendations on increased monitoring and guidance on laboratory tests and washout periods prior to starting Tysabri in SmPC Section 4.4 (*Warnings and precautions for use).* ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.

V: 2 Additional Risk Minimisation Measures

Additional risk minimisation measures (in the form of educations tools) are currently in place for the important identified risk of PML. These are described in detail below.

V: 2.1 Progressive multifocal leukoencephalopathy

V: 2.1.1 Educational tools targeting healthcare professionals

Specialist physicians initiating and supervising Tysabri therapy will be educated on the important identified risk of PML via a 'Physician Information and Management Guideline' and via the distribution of a Direct Healthcare Professional Communication (DHPC) if/when new information becomes available. This educational tool applies equally to the IV and SC route of administration.

HCPs performing the administration of Tysabri SC OCS will be educated on the important identified risk of PML via the Pre-Administration Checklist and HCP Informational Supplement.

Objectives

The Physician Information and Management Guideline informs physicians of the current benefit/risk profile of Tysabri, the potential and risk factors for the development of PML, its diagnosis and treatment, and the identification and management of possible sequelae (e.g., IRIS).

The Pre-Administration Checklist and HCP Informational Supplement inform HCPs administering Tysabri OCS (e.g., at home) on the signs and symptoms of PML and that escalation to the supervising physician is required if signs, symptoms, or new risk factors for PML are suspected.

Rationale for the additional risk minimisation activity

The Physician Information and Management Guideline focuses on providing detailed information on PML, which currently remains the most important adverse reaction affecting patients treated with Tysabri and provides practical advice to physicians that is not available through the SmPC.

The PreAdministration Checklist aids HCPs in identifying signs and symptoms of PML, to ensure prompt escalation of patients to the specialized physician supervising the patient's Tysabri therapy if signs, symptoms, or new risk factors for PML are suspected. The HCP Informational Supplement informs on PML risk factors and diagnosis, to allow for better understanding and usability of the Checklist by HCPs.

Target audience and planned distribution path

The Physician Information and Management Guideline has been developed for physicians initiating and supervising treatment with Tysabri, and for radiologists involved in the differential diagnosis of PML.

The guidelines (and any relevant DHPC) will be provided to specialised physicians initiating and supervising Tysabri therapy, and in addition, a MRI learning module on the differentiation of MS relapse from PML will also be available.

The Pre-Administration Checklist and HCP Informational Supplement have been developed for HCPs administering Tysabri SC OCS. It is recommended that physicians initiating and supervising treatment with Tysabri should share the Pre-Administration Checklist and HCP Informational Supplement with HCPs administering Tysabri SC OCS. In each Member State, distribution modalities will be agreed upon with the National Competent Authority.

Plans to evaluate the effectiveness of the interventions and criteria for success

The effectiveness of the Physician Information and Management Guideline, as well as the OCS Administration Checklist and HCP Informational Supplement will be assessed via the review of reports of PML received (i.e., routine pharmacovigilance activities) and will focus on a review of the PML incidence, timing, % of fatalities, and the characteristics of the patients prescribed Tysabri treatment in the postmarketing setting, in order to ensure adherence to the guidelines.

Results of these assessments will be presented in PSURs. The Physician Information and Management Guideline, as well as the Pre-Administration Checklist and HCP Informational Supplement, will be judged a success if PML cases are noted to be diagnosed in a timely fashion and result in favourable patient outcomes, and if it is determined that patients prescribed Tysabri treatment are being selected in line with the licensed indication.

As PML is very rare in Tysabri-treated patients (see Part II SVII), outcome indicators are deemed appropriate for the evaluation of the effectiveness of the additional risk minimisation measures. Reviews of these data to date have indicated that PML appears to be diagnosed early and the survival rate for Tysabri-related PML has remained high, with the characteristics of the majority of patients being prescribed treatment corresponding to licensed indication, indicating that Tysabri is prescribed to appropriate patients.

V: 2.1.2 Educational tools targeting patients and/or carers

Patients will be educated on the important identified risk of PML via a 'Patient alert card', a 'Tysabri treatment initiation form', a 'Tysabri treatment continuation form' and a 'Tysabri discontinuation form'. Patients self-administering at home and caregivers administering at home will be additionally educated via the Pre-Administration Checklist.

Objectives

The educational tools are intended to educate patients and caregivers to ensure they are fully aware of the risk of PML whilst receiving Tysabri treatment (and for up to 6 months afterwards), and exercise vigilance regarding its development. The Pre-Administration Checklist is intended to provide guidance to patients when self-administering Tysabri SC at home and to caregivers administering Tysabri SC, to make them aware of the signs and symptoms of PML.

Rationale for the additional risk minimisation activity

The Tysabri treatment initiation form provides detailed information to patients on the risk of PML, which currently remains the most important adverse reaction affecting those treated with Tysabri. The form is used to ensure patients are fully informed of the risk of PML and consent to treatment prior to starting Tysabri.

The Tysabri treatment continuation form provides additional information to patients on the increased risk of PML development after 24 months of Tysabri treatment, to further promote patient understanding of the risk of treatment continuation and to ensure they consent to this risk.

The Tysabri treatment discontinuation form provides information to patients on when MRI imaging may be warranted, informs patients that PML has been reported up to 6 months after stopping Tysabri, reminds patients of PML symptoms, reporting side effects and to keep alert card with them after discontinuation.

The patient alert card focuses on providing targeted information on the risk of PML (which is not available through the PL) to educate both patients and their caregivers on the need for vigilance regarding this risk by providing information on early signs and symptoms, latency, and reinforcement of the importance of seeking Healthcare Professional (HCP) advice in a timely manner.

These measures, which taken together, aim to increase awareness of the risk of PML, thus promoting patient safety.

Target audience and planned distribution path

The patient alert card, Tysabri treatment initiation form, continuation form and discontinuation form are intended for use by patients and/or caregivers. The Pre-Administration Checklist is intended for patients self-administering and caregivers administering Tysabri SC at home.

These will be distributed by the patient's HCP at the time of treatment initiation, and after 24 months of Tysabri treatment, and at discontinuation.

Plans to evaluate the effectiveness of the interventions and criteria for success

The effectiveness of these patient/ caregiver educational materials (measured by their distribution and use) has been previously assessed by means of responses to a survey of patient organizations conducted by the Committee for Medicinal Products for Human Use (CHMP). Patient organizations reported that the educational materials were being distributed to patients and they considered them a useful tool for informing patients about the risk of PML. It was therefore concluded that this additional risk minimisation measure appears to be an effective method of informing patients about the possible symptoms of PML. Plans to evaluate the effectiveness of the Pre-Administration Checklist and criteria for success are described in Part V: 2.1.1.

V: 3 Summary table of risk minimisation measures

Table 18: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Progressive multifocal leukoencephalopathy (PML)	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4. • Legal status: Restricted medical prescription ***Additional risk minimisation measures:*** • Educational tools for HCPs (Physician Information and Management Guideline, Pre-Administration checklist and HCP Informational Supplement) • Educational tools for patients/ caregivers (Patient alert card, Tysabri treatment initiation form, Tysabri treatment continuation form and Tysabri discontinuation form, Pre-Administration Checklist for patients self-administering and caregivers administering Tysabri SC)	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • Specific adverse reaction follow-up questionnaire ***Additional pharmacovigilance activities:*** • Study IMA-06-02 • Study 101MS411
Serious herpes infections	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4 and 4.8; and PL Sections 2 and 4. • Legal status: Restricted medical prescription.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • None	***Additional pharmacovigilance activities:*** • Study IMA-06-02
Important potential risks		
Malignancies	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3 and 4.8; and PL Section 2. • Legal status: Restricted medical prescription. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • Specific adverse reaction follow-up questionnaire ***Additional pharmacovigilance activities:*** • Study IMA-06-02
Missing information		
PML risk in patients switching from DMTs with immuno-suppressant effect	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4. • Legal status: Restricted medical prescription. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • Study 101MS411
Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 • Legal status: Restricted medical prescription. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • Study 101MS412

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Tysabri (natalizumab)

This is a summary of the risk management plan (RMP) for Tysabri. The RMP details important risks of Tysabri, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of Tysabri.

The Tysabri Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Tysabri should be used.

This summary of the RMP for Tysabri should be read in the context of all available relevant information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current described safety concerns will be included in updates of the RMP for Tysabri.

VI: 1 The medicine and what it is used for

Tysabri is authorised for use as a single disease modifying therapy (DMT) in adult patients with highly active relapsing remitting multiple sclerosis (RRMS) and rapidly evolving severe RRMS (see SmPC for the full indication). It contains natalizumab as the active substance, and it is given by either intravenous infusion or subcutaneous injection.

Further information about the evaluation of the benefits of Tysabri can be found in the EPAR for Tysabri, including in its plain-language summary, available on the EMA (European Medical Agency) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/tysabri

VI: 2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tysabri, together with measures to minimise such risks and the proposed studies for learning more about Tysabri's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals, respectively;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly; and
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Tysabri, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessments so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tysabri is not yet available, it is listed under 'missing information' below.

VI: 2.1 List of important risks and missing information

Important risks of Tysabri are risks that need special risk management activities to further investigate or minimise the risk so that the medicinal product can be safely administered. Important risks can be categorised as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tysabri. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that needs to be collected (e.g. on the long- term use of the medicine):

List of important risks and areas of missing information	
Important identified risks	• Progressive Multifocal Leukoencephalopathy (PML) • Serious herpes infections
Important potential risks	• Malignancies
Areas of missing information	• PML risk following switch from disease modifying therapies with immunosuppressant effect • Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions including anaphylaxis)

VI: 2.2 Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risks	
Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	It is noted that all data available to characterise PML risk are from the IV route of administration. Considering the similar pharmacodynamic profiles, the same PML risk and relevant risk factors are also assumed for the different routes of administration (eg, SC). PML was reported in two patients in pre-authorization multiple sclerosis (MS) trials after about 2 years of combination treatment with

Important Identified Risks	
	natalizumab and beta- IFN 1a (AVONEX®). A third case was reported in a patient from the Crohn's disease clinical trials, who had terminated use of immunosuppressants 2 to 3 months prior to starting natalizumab monotherapy. In the post-marketing setting, Biogen utilizes a framework that uses standardized criteria and case definitions to differentiate and classify reported cases of PML by levels of diagnostic certainty. This objective adjudication process was developed with external PML expert input and has been used to evaluate PML case reports for natalizumab for several years. PML case definitions (which categorize cases into Level 1 to Level 5) allow classification of cases based on various levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out (Level 5), includes a category for cases with insufficient data despite exhaustive due diligence (Level 4), as well as categories for high and low suspect cases (Levels 2 and 3, respectively). Following this adjudication process, confirmed PML cases (Level 1) have been identified in association with natalizumab use. Consequently, PML was added as a listed adverse drug reaction (ADR) in Section 4.8 (Undesirable effects) of the natalizumab SmPC, and wording relating to the detection and management of PML was implemented in Section 4.4 (Special warnings and precautions for use).
Risk factors and risk groups	PML can only occur in the presence of a John Cunningham virus (JCV) infection, with studies indicating that approximately 60-70% of MS patients were seropositive when screened for anti-JCV antibody. • The following risk factors are associated with an increased risk of PML in natalizumab-treated patients: The presence of anti-JCV antibodies • Treatment duration; especially beyond 2 years • Immunosuppressant prior to receiving Tysabri Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of natalizumab therapy and have received prior immunosuppressant therapy) have a significantly higher risk of PML. In anti-JCV antibody positive Tysabri treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e., the risk is greater in those with a high antibody index compared to those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with Tysabri for longer than two years. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result.

Important Identified Risks	
	Patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results. Using the three risk factors (JCV antibody status, prior immunosuppressant use and duration of Tysabri therapy), and patients with high anti-JCV antibody index who have received more than 2 years of Tysabri therapy and without prior history of immunosuppressant therapy, subgroups of patients with distinctly lower and higher risk for PML can be identified. Consequently, an algorithm containing these risk factors and the associated PML risk has been developed to allow physicians to assess the risk of patients for developing PML. This algorithm is contained in an additional risk minimisation guideline entitled 'Physician Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI Therapy' The risk of PML persists for up to 6 months following discontinuation of Tysabri.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • Educational tools for healthcare professionals (Physician Information and Management Guideline, Pre-Administration Checklist and Informational Supplement for healthcare professionals administering Tysabri SC outside a clinical setting, e.g., at home) • Educational tools for patients/caregivers (Patient alert card, Tysabri treatment initiation form, Tysabri treatment continuation form and Tysabri discontinuation form, Pre-Administration Checklist for patients self-administering and caregivers administering Tysabri SC)
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study IMA-06-02 • Study 101MS411 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.
Serious Herpes Infections	
Evidence for linking the risk to the medicine	In clinical trials, herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab.

Important Identified Risks	
	In post-marketing experience, rare cases of acute retinal necrosis (ARN) have been observed in patients receiving natalizumab, with some of these cases having occurred in patients with central nervous system herpes infections (e.g. herpes meningitis and encephalitis).
Risk factors and risk groups	No specific risk groups have been identified.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4 and 4.8, and PL Sections 2 and 4. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study IMA-06-02 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.

Important Potential Risk(s)	
Malignancies	
Evidence for linking the risk to the medicine	This risk is based on the class of product and based on scientific literature. No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded.
Risk factors and risk groups	None known for natalizumab. Based on the available epidemiological data and the review of malignancy cases, there is no evidence to suggest an increased risk for malignancy associated with long-term natalizumab therapy.
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3 and 4.8, and PL Section 2. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None

Important Potential Risk(s)	
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study IMA-06-02 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.

Missing Information	
PML risk in patients switching from DMTs with immuno-suppressant effect	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4. • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 101MS411 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan.
Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 • Legal status: Restricted medical prescription - Tysabri is prescribed and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI. ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 101MS412 See Section VI:2.3.2 of this summary for an overview of the post-authorisation development plan

VI: 2.3 Post-authorisation development plan

VI: 2.3.1 Studies that are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for Tysabri.

VI: 2.3.2 Other studies in post-authorisation development plan

Other studies in the post authorisation development plan are as follows:

- **Study IMA-06-02 - Tysabri Observational Programme – An observational study using real world data to assess long-term safety in patients with RRMS.**

  Purpose of the study: To assess the long-term safety, and impact on disease activity and progression, of Tysabri (natalizumab) in patients with RRMS in a clinical practice setting. This study aims to address the safety concerns of PML, Serious herpes infection and Malignancies.

- **Study 101MS411 – An observational cohort study utilising data from the United States natalizumab TOUCH prescribing program and select European Union MS Registries.**

  Purpose of the study: To estimate the risk of PML and other serious opportunistic infections among patients switching to Tysabri from the newer DMTs (including fingolimod, dimethyl fumarate, teriflunomide) and from established DMTs (IFN beta and glatiramer acetate). This study aims to address the safety concern of PML risk in patients switching from DMTs with immunosuppressant effect.

- **Study 101MS412 – An Observational Study Utilising Data from EU National MS Registries to Estimate the Incidence of Anti-Natalizumab Antibody Among Patients Who Receive Subcutaneous Administration of Natalizumab for Treatment of RRMS**

  Purpose of the study: The primary objective is to estimate the incidence of ANAs in patients who start receiving natalizumab SC injections and have never received natalizumab or other monoclonal antibodies. This study aims to evaluate the immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis).

ANNEX 4 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Adverse event follow up forms will be distributed for potential events of PML, serious herpes infections and malignancies (see Part III [*Pharmacovigilance Plan*] of the EU RMP for details).

The follow up forms for distribution are provided in this Annex below:

- Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool
- Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 3 and 6.
- Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 12 and 24.
- Serious herpes infections Data Collection Tool
- Malignancies Data Collection Tool

Biogen Unique Case ID#:

I. Patient Information

Patient Initials: _____ DOB: _____ (DD/MMM/YYYY) Gender: _____

Height: _____ Weight: _____ BMI: _____

II. Primary Neurologist:

Name: _____ Email: _____

Address: _____

Phone: _____ Fax: _____

III. Treating Physician (if different from primary neurologist):

Name: _____ Email: _____

Address: _____

Phone: _____ Fax: _____

IV. Primary Suspect Product

Select the product you believe to be the Primary Suspect Product:

☐ Tysabri ☐ Avonex ☐ Tecfidera ☐ Other:

☐ Fampyra/Ampyra ☐ Plegridy ☐ Vumerity ☐ dimethyl fumarate (authorized generic) distributed by Teva

Is this patient receiving Tysabri at an extended interval dosing (e.g. > 4 weeks)?

☐ **Yes** ☐ **No**

Provide additional details on the dosing and frequency of the Primary Suspect Product, including information on the use of multiple regimens:

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Route	Frequency of Dosing	Number of Administered Doses (Tysabri)	Lot/ Batch #

In your assessment, is the suspected PML related to the Primary Suspect Product?

☐ **Yes** ☐ **No**

Biogen Unique Case ID#:

V. Secondary Suspect Product (if applicable)

Select the product you believe to be the Secondary Suspect Product:

☐ Tysabri ☐ Avonex ☐ Tecfidera ☐ Other:

☐ Fampyra/Ampyra ☐ Plegridy ☐ Vumerity ☐ dimethyl fumarate (authorized generic) distributed by Teva

Provide additional details on the dosing and frequency of the Secondary Suspect Product, including information on the use of multiple regimens:

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Route	Frequency	Lot/ Batch #

In your assessment, is the suspected PML related to the Secondary Suspect Product? ☐ Yes ☐ No

Since discontinuation of Biogen suspect product, is the patient being treated with any other MS therapy? ☐ Yes ☐ No If yes, specify:

VI. Multiple Sclerosis History

1) **MS diagnosis date:** _____ (DD/MMM/YYYY)

2) **Provide the MS therapies used prior to Primary Suspect Product:**

Medication	Dose	Route	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

3) Has the patient received prior immunosuppressant therapy, radiation therapy, antineoplastic or immunomodulatory therapy for a condition other than MS?

☐ Yes ☐ No

If yes, list the drug and include the indication:

4) Is this patient immunocompromised from any other cause?

☐ Yes ☐ No

If yes, provide diagnosis:

5) Has the patient ever been or currently is enrolled in a Biogen Clinical Trial?

☐ Yes ☐ No

If yes, specify the trial name/number: Provide the patient's study ID:

VII. PML Suspicion

1) Indicate the reason(s) the patient is being evaluated for PML:

- Patient presented with clinical signs and symptoms? ☐ Yes ☐ No (Asymptomatic)
- Patient presented with radiological findings consistent with PML? ☐ Yes ☐ No
- Reason for MRI: (Check all that apply)

  ☐ MS standard of care ☐ PML surveillance ☐ Patient request ☐ Other:

2) List earliest presenting <u>signs and symptoms</u> that led to the evaluation for possible PML (even if identified in retrospect):

Symptoms	Date (DD/MMM/YYYY)

Biogen Unique Case ID#:

3) **Provide copies of MRI reports for 6 months prior to PML suspicion. If not possible, provide detailed MRI results including lesion characteristics and location.**

   a. MRI at the time of the suspected PML diagnosis:

   Date of MRI: _____ (DD/MMM/YYYY)

   Detailed description:

   b. MRI prior to suspected PML diagnosis

   Date of MRI: _____ (DD/MMM/YYYY)

   Detailed description:

4) **Provide copies of CSF JCV DNA reports, if not possible provide details of lumbar puncture (LP) and CSF sample collection (provide all tests, even if multiple assays are performed on a single puncture):**

	Test 1	Test 2	Test 3
Date of LP (DD/MMM/YYYY)			
LP performed Pre-PLEX (if applicable)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
CSF JCV DNA Result	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate
Quantitative (copies/mL)			
Laboratory Name and Limit of Detection			

5) **Has a CSF analysis been performed? (cell count, protein, glucose, albumin, various viral PCR testing, etc.)**

   ☐ Yes ☐ No Date of Test: _____ (DD/MMM/YYYY)

   Provide cell count: _____

Biogen Unique Case ID#:

6) **Provide details of all serum anti-JCV antibody testing**:

(Provide copies of the anti-JCV antibody test results)

Date of Test: (DD/MMM/YYYY)	Result of Test: (positive, negative, pending)	Index Value Available:	Index Value:	Laboratory Name:
	☐ **Positive** ☐ **Negative** ☐ **Pending**	☐ Yes ☐ No		☐ Focus/Quest ☐ Unilabs ☐ Other
	☐ **Positive** ☐ **Negative** ☐ **Pending**	☐ Yes ☐ No		☐ Focus/Quest ☐ Unilabs ☐ Other
	☐ **Positive** ☐ **Negative** ☐ **Pending**	☐ Yes ☐ No		☐ Focus/Quest ☐ Unilabs ☐ Other
	☐ **Positive** ☐ **Negative** ☐ **Pending**	☐ Yes ☐ No		☐ Focus/Quest ☐ Unilabs ☐ Other

7) **Was a brain biopsy performed?** ☐ Yes ☐ No

Date of Test: _____ (DD/MMM/YYYY)

(If yes, provide a copy of the brain biopsy report.)

8) **HIV status:** ☐ Positive ☐ Negative ☐ Unknown

Date of Test: _____ (DD/MMM/YYYY)

9) **Was patient lymphopenic within 12 months prior to PML suspicion?** ☐ Yes ☐ No

Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CD8, CD4/CD8 ratio, etc.)	
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐

VIII. Current Treatment

Biogen Unique Case ID#:

1) Has the patient received steroids within the past 3 months? ☐ Yes ☐ No

Drug	Dose	Route	Frequency	Start date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Reason for steroids

2) PML Treatment: (check all that apply)

Medication	Dose	Route	Frequency	Start date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
☐ Mefloquine					
☐ Cidofovir					
☐ Mirtazapine					
☐ Other:					
☐ Other:					

Biogen Unique Case ID#:

3) PLEX / IA:

Plasma Exchange (PLEX): ☐ Yes ☐ No Immunoadsorption (IA): ☐ Yes ☐ No

Session	Date (DD/MMM/YYYY)	Volume
1		
2		
3		
4		
5		

IX. Patient's Location

Patient's current location: (check appropriate box)

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation Facility

☐ N/A (Patient is deceased)

If patient is deceased, provide the following information:

Date of Death: (DD/MMM/YYYY)

Reported Cause of Death:

Was an autopsy performed? ☐ Yes ☐ No *(If yes, provide a copy of the autopsy report)*

In your assessment, was the patient's death related to the Primary Suspect Product?

☐ Yes ☐ No

If applicable, in your assessment, was the patient's death related to the Secondary Suspect Product? ☐ Yes ☐ No

Biogen Unique Case ID#:

X. Functional Scores

Provide the patient's functional status scores

On Primary Suspect Product prior to PML

EDSS: _____ Date: _____ (DD/MMM/YYYY)

Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

At the time of PML suspicion:

EDSS: _____ Date: _____ (DD/MMM/YYYY)

Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Biogen Unique Case ID#:

Karnofsky Performance Status Scale Definitions/Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

XI. Rule Out PML

1) **Based on your evaluation, was PML ruled out?** ☐ Yes ☐ No ☐ Still under investigation
2) **If PML was ruled out, provide the <u>final</u> diagnosis (if available):**
3) **Was the final diagnosis related to the Primary Suspect Product?** ☐ Yes ☐ No
   a. Was the final diagnosis related to the Secondary Suspect Product? (if applicable)
      ☐ Yes ☐ No
   b. Provide the outcome for the final diagnosis:
      ☐ Fatal ☐ Recovered ☐ Recovered with sequelae ☐ Not recovered ☐ Unknown
4) **What MS therapy is planned or is the patient currently on?**

Biogen Unique Case ID#:

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

(When signing electronically, check "Lock Document After Signing" in the Sign Document window).

Biogen Unique Case ID#:

I. Patient Demographics

Patient Initials: _____ DOB: _____ (DD/MMM/YYYY)

II. Is the Patient alive? ☐ Yes ☐ No

If yes, provide the patient's current location (check appropriate box):

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation Facility

If no, provide the following information:

Date of Death: _____ (DD/MMM/YYYY)

Reported Cause of Death: _____

Was an autopsy performed? ☐ Yes ☐ No
(If yes, provide a copy of the autopsy report)

III. In your assessment, was the patient's death related to one of the following products?

☐ Yes ☐ No

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex ☐ dimethyl fumarate (authorized generic) distributed by Teva

IV. Functional status post-PML diagnosis: (see tables below)

EDSS: _____ Date: _____ (DD/MMM/YYYY)

Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Karnofsky Performance Status Scale Definitions/Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not Imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

V. Test results post-PML diagnosis: *(provide a copy of test results)*

Provide copies of MRI reports, including most recent MRI report. If not possible, provide detailed MRI results including lesion characteristics and location:

Date of MRI: _____ (DD/MMM/YYYY)

Detailed description: _____

Provide copies of CSF JCV DNA reports. If not possible, provide details of lumbar puncture (LP) and CSF sample collection (provide all tests, even if multiple assays are performed on a single puncture).

	Test 1	Test 2	Test 3
Date of LP (DD/MMM/YYYY)			
LP performed Pre-PLEX (if applicable)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
CSF JCV DNA Result	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate
Quantitative (copies/mL)			
Laboratory Name and Limit of Detection			

Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CD8, CD4/CD8 ratio, etc.)	
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐

VI. Is your patient currently on another therapy for Multiple Sclerosis? ☐ Yes ☐ No

If yes, what is the therapy?

Include start date and dosing regimen:

Provide patient's EDSS at time of new DMT onset:

VII. PML Treatment:

Plasma Exchange (PLEX): ☐ Yes ☐ No Immunoadsorption (IA): ☐ Yes ☐ No

Session	Date (DD/MMM/YYYY)	Volume
1		
2		
3		
4		
5		

Medication	Dose	Route	Frequency	Start date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
☐ Mefloquine					
☐ Cidofovir					
☐ Mirtazapine					
☐ Other:					
☐ Other:					

VIII. PML Outcome:

a. What is the outcome of the patient's PML?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Fatal

Provide the date of the assessed outcome: _____ (DD/MMM/YYYY)

IX. Was the patient diagnosed with PML-IRIS?

☐ Yes; onset date (DD/MMM/YYYY): _____ ☐ No

a. Any new or worsening symptoms? ☐ Yes ☐ No

If yes, specify the symptoms:

Onset date of IRIS symptoms:

b. Any contrast enhancements or MRI at time of PML-IRIS? ☐ Yes ☐ No

c. Any mass effect or edema on MRI? ☐ Yes ☐ No

X. PML-IRIS Treatment:

a. Did the patient receive corticosteroids pre-PML-IRIS onset? ☐ Yes ☐ No

b. Did the patient receive corticosteroids post-PML-IRIS onset? ☐ Yes ☐ No

Biogen Unique Case ID#:

Specify all treatments the patient received for PML-IRIS: (*including corticosteroid regimens*):

Medication	Dose	Route	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Specify if treatment is pre- or post-PML-IRIS

XI. PML-IRIS Outcome:

a. What is the outcome of the patient's PML-IRIS?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Fatal

Provide the date of the assessed outcome of PML-IRIS: _____ (DD/MMM/YYYY)

b. What is the causality of the PML-IRIS to the following Biogen products?

☐ Related ☐ Not Related ☐ Unknown

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex ☐ dimethyl fumarate (authorized generic) distributed by Teva

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

(When signing electronically, check "Lock Document After Signing" in the Sign Document window).

Biogen Unique Case ID#:

I. Patient Information

Patient Initials: _____ DOB: _____ (DD/MMM/YYYY)

II. Is the Patient alive? ☐ Yes ☐ No

If yes, provide the patient's current location (check appropriate box):

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation

Facility

If no, provide the following information:

Date of Death: _____ (DD/MMM/YYYY)

Reported Cause of Death: _____

Was an autopsy performed? ☐ Yes ☐ No
(If yes, provide a copy of the autopsy report)

III. In your assessment, was the patient's death related to one of the following products?

☐ Yes ☐ No

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex ☐ dimethyl fumarate (authorized generic) distributed by Teva

IV. Functional Status post-PML Diagnosis (see tables below):

EDSS: _____ Date: _____ (DD/MMM/YYYY)

Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Karnofsky Performance Status Scale Definitions/Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not Imminent.
	20	Very sick; hospital admission necessary; active supportive treatment Necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Biogen Unique Case ID#:

V. Test results post-PML diagnosis: *(provide a copy of test results)*

Provide copies of MRI reports, including most recent MRI report. If not possible, provide detailed MRI results including lesion characteristics and location:

Date of MRI: _____ (DD/MMM/YYYY)

Detailed description: _____

Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CD8, CD4/CD8 ratio, etc.)	
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐

VI. Is your patient currently on another therapy for Multiple Sclerosis? ☐ Yes ☐ No

If yes, what is the therapy?

Include start date and dosing regimen:

Provide patient's EDSS at time of new DMT onset:

VII. PML Outcome:

b. What is the outcome of the patient's PML?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Fatal

Provide the date of the assessed outcome: _____ (DD/MMM/YYYY)

Biogen Unique Case ID#:

VIII. PML-IRIS Outcome:

c. What is the outcome of the patient's PML-IRIS?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Fatal

Provide the date of the assessed outcome of PML-IRIS: _____ (DD/MMM/YYYY)

d. What is the causality of the PML-IRIS to the following Biogen products?

☐ Related	☐ Not Related	☐ Unknown	
☐ Tysabri	☐ Tecfidera	☐ Vumerity	
☐ Fampyra/Ampyra	☐ Plegridy	☐ Avonex	☐ dimethyl fumarate (authorized generic) distributed by Teva

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

(When signing electronically, check "Lock Document After Signing" in the Sign Document window).

Tysabri Herpes Meningitis/Encephalitis

To provide consistency in our due diligence of Tysabri Herpes Meningitis/Encephalitis reports, please ask the follow-up questions below.

1. Provide the status of MS disease activity prior to starting Tysabri.
2. Does patient have a prior history of herpes meningitis/encephalitis and/or aseptic meningitis?
3. Provide any other medical history or risk factors relevant to herpes meningitis/encephalitis.
4. Provide any clinical findings, including signs and symptoms.
5. Provide results from the physical examination.
6. Has the patient been tested for anti-natalizumab antibodies? If yes, then provide the test results (positive, negative, pending) and corresponding test dates. If the initial test was positive, was a confirmatory testing of anti-natalizumab antibodies performed? Provide the date and test results.
7. Provide details of Tysabri therapy (start and stop date, dose, frequency and route of administration, batch/lot #, number of infusions/injections). If the route of administration was switched from intravenous infusion to subcutaneous injection or vice versa, then provide the dates.
8. Provide any concomitant medications the patient is taking, including prescription medications, OTC, dietary supplements, vitamins, and herbs.
9. List all medications the patient has taken in the past 2 years, particularly any recent disease modifying treatments for MS, corticosteroid treatment, immunomodulators, or immunosuppressants (e.g., mitoxatrone, methotrexate, etc.).
10. Was a brain biopsy performed? If yes, then provide the date and test results.
11. Was the type of herpes virus that caused meningitis/encephalitis identified? If yes, then specify the type (e.g., varicella zoster virus, herpes simplex type 1 virus, or herpes simplex type 2 virus).
12. Provide the below laboratory results for the patient. Include reference ranges, baseline levels, and levels for the treatment and management of the event.
    a. CSF (e.g., protein, WCC, oligoclonal banding, culture, serology)
    b. PCR
    c. Any other tests related to the diagnosis or management of meningitis/encephalitis.
13. Provide results from all imaging studies (e.g., MRI, electroencephalogram (EEG), computed tomography (CT) Study, etc.).
14. If the patient was hospitalized, then provide admission dates and discharge report.
15. Provide the treatment given for herpes meningitis/encephalitis.
16. Provide outcome for herpes meningitis/encephalitis and date of resolution if applicable.
    a. If the patient recovered with sequelae, then describe the sequelae.

Tysabri General Malignancies

To provide consistency in our due diligence of Tysabri General Malignancy reports, please ask the follow-up questions below.

1. Specify the patient's type, stage, and grade of cancer and anatomic location.
2. Provide all signs and symptoms related to the malignancy.
3. Provide any medical history (including prior history of cancer) and social risk factors the patient had for cancer (e.g., family history of malignancies, radiation exposure, smoking, diabetes mellitus, etc.).
4. List the medications the patient has taken in the past 2 years.
5. Provide any concomitant medications the patient is taking, including prescription medications, OTC, dietary supplements, vitamins, and herbs.
6. Provide any concomitant or previous immunomodulators, immunosuppressants, or corticosteroids.
7. If a tissue biopsy was performed, provide the findings and the date it was performed.
8. Provide results from all pathology or cytology studies.
9. Provide results from all imaging studies.
10. Provide results from physical examination.
11. If the patient was hospitalized, provide hospitalization diagnosis, dates of hospitalization, and discharge report.
12. Provide any treatments the patient received for the event.
13. Provide outcome for event (recovered, not yet recovered, recovered with sequelae, unknown, death) and date of resolution if applicable.
    a. If the patient recovered with sequelae, describe the sequelae.
    b. If the outcome was death, provide a copy of death certificate and autopsy results.
14. Was Tysabri discontinued because of this event? If so, specify the date and reason.
    a. Was Tysabri later resumed? If so, specify the date and dosing regimen.
15. Provide details of Tysabri therapy (start and end date, dose, frequency, route of administration, batch/lot # and number of infusions/injections). If the route of administration was switched from intravenous infusion to subcutaneous injection or vice versa, then provide the dates.

Tysabri Breast Cancer

To provide consistency in our due diligence of Tysabri Breast Cancer reports, please ask the follow-up questions below.

1. Specify the patient's type, stage, and grade of breast cancer.
2. Specify the anatomic location (left breast, right breast, bilateral).
3. Provide any medical history (including prior history of breast cancer) and risk factors the patient had for breast cancer (e.g., family history, hormone replacement therapy, Breast Cancer (BRCA) gene mutations, history of proliferative benign breast disease or breast carcinoma, etc.).
4. Provide any social risk factors for breast cancer (e.g., smoking, alcohol consumption).
5. List the medications the patient has taken in the past 2 years.
6. Provide any concomitant medications the patient is taking, including prescription medications, Over the Counter (OTC), dietary supplements, vitamins, and herbs.
7. Provide any concomitant or previous immunomodulators, immunosuppressants, or corticosteroids.
8. Provide results from all imaging studies including mammogram, ultrasound, or Magnetic Resonance Imaging (MRI).
9. Provide results from pathology/cytology. If a tissue biopsy was performed, provide the findings.
10. Was the patient tested for estrogen receptor, progesterone receptor, or Human Epidermal Growth Factor Receptor-2 (HER-2)/neu protein? If so, then provide test results.
11. Provide results from the physical examination.
12. If the patient was hospitalized, then provide hospitalization diagnosis, dates of hospitalization, and discharge report.
13. Provide any treatments the patient received for the event.
14. Provide outcome for event (recovered, not yet recovered, recovered with sequelae, unknown, death) and date of resolution if applicable.
    a. If the patient recovered with sequelae, describe the sequelae.
    b. If the outcome was death, provide a copy of death certificate and autopsy results.
15. Was Tysabri discontinued because of this event? If so, then specify the date and reason.
    a. Was Tysabri later resumed? If so, then specify the date and dosing regimen.
16. Provide details of Tysabri therapy (start and end date, dose, frequency, route of administration, batch/lot # and number of infusions / injections). If the route of administration was switched from intravenous infusion to subcutaneous injection or vice versa, then provide the dates.

Tysabri Leukemia

To provide consistency in our due diligence of Tysabri Leukemia reports, please ask the follow-up questions below.

1. Specify the classification and staging.
2. Provide all signs and symptoms at presentation (include onset dates).
3. Provide any social or medical risk factors (e.g., smoking, chemical or radiation exposure, etc.).
4. Provide any concomitant medications the patient is taking, including prescription medications, OTC, dietary supplements, vitamins, and herbs.
5. Provide laboratory results (e.g., red blood cell (RBC), white blood cell (WBC), Hct, Hgb, Platelets, and WBC differential), including dates of testing, reference range, and units.
6. Provide results from bone marrow biopsy.
7. Did the event prompt an emergency room visit or hospitalization?
    a. If the patient was hospitalized, then provide hospitalization diagnosis, dates of hospitalization, and discharge report.
8. Provide any treatments the patient received for the event.
9. Provide outcome for event (recovered, not yet recovered, recovered with sequelae, unknown, death) and date of resolution if applicable.
    a. If the patient recovered with sequelae, then describe the sequelae.
    b. If the outcome was death, then provide a copy of death certificate and autopsy results.
10. Was Tysabri discontinued because of this event? If so, then specify the date and reason.
    a. Was Tysabri later resumed? If so, then specify the date and dosing regimen.
11. Provide details of Tysabri therapy (start and end date, dose, frequency, route of administration, batch/lot # and number of infusions/injections). If the route of administration was switched from intravenous infusion to subcutaneous injection or vice versa, then provide the dates.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Based on how patients treated with Tysabri are currently monitored at national level, the MAH shall discuss and agree with the National Competent Authorities measures to enhance further this monitoring (e.g. registries, post-marketing surveillance studies) as appropriate. The MAH shall implement agreed measures for monitoring within a time frame agreed with the National Competent Authorities.

The educational programme is aimed at educating healthcare professionals (HCPs) and patients/carers of the potential and risk factors for the development of PML, its diagnosis and treatment, and the identification and management of possible sequelae.

The MAH shall ensure that in each Member State where Tysabri is marketed, all healthcare professionals and patients/carers who are expected to prescribe/use Tysabri have access to/are provided with the educational materials listed below. Prior to implementation, the MAH must agree on the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

- Educational materials for HCPs:
    - Summary of Product Characteristics
    - Physician Information and Management Guidelines
    - For HCPs administering Tysabri SC Outside a Clinical Setting (OCS):
        - Pre-Administration Checklist
        - HCP Informational Supplement
- Patient information pack:
    - Package Leaflet
    - Patient Alert Card
    - Treatment initiation and treatment continuation forms
    - Treatment discontinuation form
    - For patients and caregivers administering Tysabri SC: Pre-Administration Checklist

These educational materials shall contain the following key elements:

Physician Information and Management Guidelines:

- Background information on the increased risk of atypical/opportunistic infections, in particular PML, which may occur with Tysabri therapy, including a detailed discussion of data (including **epidemiology, aetiology, and pathology**) pertaining to the development of PML in Tysabri-treated patients.
- Information relating to the **identification of risk factors** for Tysabri-associated PML, including details of the PML risk estimates algorithm summarising PML risk by risk factor

(anti-John Cunningham virus [JCV] antibody status, prior IS use, and duration of treatment [by year of treatment]), and stratification of this risk by index value when applicable.

- **Information on extending the dosing interval for PML risk mitigation**, including a reminder of the approved dosing schedule. The decrease in PML risk is based on data from IV route of administration. No clinical data are available on either the safety or efficacy of dosing every 6 weeks with SC route of administration.
- Inclusion of **monitoring guidance** for MRI and anti-JCV antibody based on PML risk, including recommended timing, protocols, and interpretation of results.
- Details regarding the **diagnosis of PML**, including principles, clinical assessment (including MRI and laboratory testing), and differentiation between PML and MS.
- **Management** recommendations in the event of cases of suspected PML, including considerations on the the effectiveness of PLEX treatment and the management of associated IRIS.
- Detail on the **prognosis** on PML, including information on improved outcomes observed in asymptomatic PML cases.
- A reminder that irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with Tysabri and for 6 months following **discontinuation of therapy**.
- A statement that all data available to characterise PML risk are from the IV route of administration. Considering the similar PD profiles, the same PML risk and relevant risk factors are assumed for different routes of administration.
- A reminder on the need to discuss the benefit-risk profile of Tysabri treatment with the patient, and the requirement to provide the patient information pack.
- Reminder that it is the responsibility of the treating specialised physician to determine the patient's suitability for Tysabri SC administration OCS at regular intervals, and to ensure appropriate monitoring for PML (including risk factors and MRI screening).
- A statement that the administration of Tysabri SC OCS does not replace the need for regular contact with and clinical monitoring by the patient's treating specialised physician.

Pre-Administration Checklist:

- The Pre-Administration Checklist is designed to aid the administering HCPs and administering patients/caregivers in identifying risk factors for and early signs and symptoms of PML.
- The Pre-Administration Checklist is to be used by both, HCPs administering Tysabri SC OCS and by patients and caregivers administering Tysabri SC, and needs to be reviewed prior to each Tysabri SC administration.
- Guidance based on patient/caregiver checklist responses for escalation to the supervising specialised physician, whose responsibility it remains to determine next steps regarding the appropriateness and timing of Tysabri administration, if signs, symptoms, or new risk factors for PML are suspected.

- A statement that the checklist is not intended to be a substitute for consultation with the patient's treating specialised physician.

HCP Informational Supplement

- Background information on PML, to allow for better HCP understanding and usability of the Pre-Administration Checklist.
- Information relating to the **identification of risk factors** for Tysabri-associated PML, including details of the PML risk estimates algorithm summarising PML risk by risk factor (anti-John Cunningham virus [JCV] antibody status, prior IS use, and duration of treatment [by year of treatment]), and stratification of this risk by index value when applicable.
- A reminder that irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with Tysabri and for 6 months following **discontinuation of therapy**.
- Details regarding clinical assessment in PML, including clinical features that may help differentiate MS lesions from PML.
- A statement that all data available to characterise PML risk are from the IV route of administration. Considering the similar PD profiles, the same PML risk and relevant risk factors are assumed for different routes of administration.
- Reminder that the patient must receive the Patient Alert Card and that the card can be requested from the local Biogen affiliate.
- Reminder that it is the responsibility of the treating specialised physician to determine the patient's suitability for Tysabri SC administration OCS at regular intervals, and to ensure appropriate monitoring for PML (including risk factors and MRI screening).
- A statement that the administration of Tysabri SC OCS does not replace the need for regular contact with and clinical monitoring by the patient's treating specialised physician.

Patient alert card:

- Reminder to patients to show the card to any doctor and/or caregiver involved with their treatment, and to keep the card with them for 6 months after the last dose of Tysabri treatment.
- Reminder to patients to read the package leaflet carefully before starting Tysabri, and not to start Tysabri if there is a serious problem with their immune system.
- Reminder to patients no to take any other long-term medicines for MS while receiving Tysabri.
- A description of PML, potential symptoms and management of PML.
- A reminder of where to report side effects.
- Details of the patient, treating doctor and date Tysabri was started.
- Reminder to patients self-administering and caregivers administering Tysabri SC to review the Pre-Administration Checklist prior to each administration of Tysabri SC. If any

symptoms of PML are noted, Tysabri SC may not be administered, and the prescriber needs to be informed immediately.

Treatment initiation and treatment continuation forms:

- Information on PML and IRIS, including the risk of developing PML during Tysabri treatment stratified by prior treatment with immunosuppressants and JCV infection.
- Confirmation that the doctor has discussed the risks of PML and the risk of IRIS if treatment is discontinued following suspicion of PML, and confirmation of patient understanding of the risks of PML and that they have received a copy of the treatment initiation form and a patient alert card.
- Patient details and prescriber name.
- The treatment continuation form should contain the elements of the treatment initiation form and, in addition, a statement that the risks of PML increase with duration of treatment and that treatment beyond 24 months carries additional risk.

Treatment discontinuation form

- Information for the patient that PML has been reported up to 6 months after stopping Tysabri, and to therefore keep the patient alert card with them after treatment discontinuation.
- Reminder of PML symptoms, and when MRI imaging may be warranted.
- Reporting of side effects.