26 May 2016
EMA/579064/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Tysabri

International non-proprietary name: natalizumab

Procedure No. EMEA/H/C/000603/II/0077

Marketing authorisation holder (MAH): Biogen Idec Ltd

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

α4β1	alpha-4 beta-1
AE	adverse event
ARR	annualised relapse rate
BBB	blood-brain barrier
CI	confidence Interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
DCC	Data Compilation Centre
DMF	dimethyl fumarate
DMT	Disease modifying therapy
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EID	Extended Interval Dosing
EU	European Union
GA	Glatiramer acetate
evvGCP	Good clinical practice
IFN-β	interferon beta
IRIS	Immune Reconstitution Inflammatory Syndrome
IS	immunosuppressants
JCV	JC virus (human polyomavirus)
MAH	Marketing authorisation holder
MRI	magnetic resonance imaging
MS	Multiple sclerosis
PIP	paediatric investigation plan
PML	progressive multifocal leukoencephalopathy
PT	preferred term
RMP	Risk management plan
RRMS	Relapsing-remitting Multiple Sclerosis
RSI	Request for supplementary information

SABR	Safety and Benefit-Risk Management
SAE	Serious Adverse Event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
TOP	Tysabri Observational Program

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Biogen Idec Ltd submitted to the European Medicines Agency on 11 March 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include new indication for Tysabri
As a consequence, sections 4.1 and 4.4 of the SmPC are updated in order to provide physicians with more options for treating RRMS patients with high disease activity who fail an initial disease modifying therapy (DMT). Consequential changes to sections 4.2, 4.3, 5.1 and Package Leaflet in Sections 2 and 3 are also proposed.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0252/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0252/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Dates
Submission date	11 March 2015
Start of procedure:	28 March 2015
CHMP Rapporteur Assessment Report	26 May 2015
CHMP Co-Rapporteur Assessment Report	26 May 2015
PRAC Rapporteur Assessment Report	26 May 2015
PRAC Outcome	11 June 2015
CHMP members comments	15 June 2015
Updated CHMP Rapporteur Assessment Report	18 June 2015
Request for supplementary information (RSI)	25 June 2015
CHMP Rapporteur Assessment Report	26 October 2015
PRAC Rapporteur Assessment Report	26 October 2015
PRAC members comments	28 October 2015
Updated PRAC Rapporteur Assessment Report	12 November 2015
PRAC Outcome	6 November 2015
CHMP members comments	09 November 2015
Updated CHMP Rapporteur Assessment Report	12 November 2015
Request for supplementary information (RSI)	19 November 2015
Clarification Meeting with PEI, AIFA and EMA	18 January 2016
CHMP Rapporteur Assessment Report	1 March 2016
PRAC Rapporteur Assessment Report	3 March 2016
PRAC members comments	09 March 2016
Updated PRAC Rapporteur Assessment Report	10 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	21 March 2016
Updated CHMP Rapporteur Assessment Report	N/A
Request for supplementary information (RSI)	1 April 2016
Joint Rapporteur’s assessment report circulated on:	11 May 2015
Opinion	26 May 2016

2. Scientific discussion

2.1. Introduction

Tysabri is a selective adhesion molecule inhibitor. It specifically exerts its immunologic effects by targeting the α4β1 integrin receptor, which has a key role in the migration of leucocytes, most notably lymphocytes, from the peripheral blood into inflamed tissue. In multiple sclerosis (MS), the rationale for natalizumab therapy is to taper off the transmigration of mononuclear leukocytes from the bloodstream across the endothelium into inflamed parenchymal tissue, included the central nervous system (CNS) parenchyma, by specifically targeting α4β1, or very-late-activation antigen 4 (VLA-4).

Tysabri is currently indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- *Adult patients aged 18 years and over with high disease activity despite treatment with a beta interferon or glatiramer acetate.*

These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon or glatiramer acetate. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

- *Adult patients aged 18 years and over 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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.*

The recommended dose of Tysabri is 300 mg administered by intravenous infusion once every 4 weeks.

At the time of the initial marketing authorization application, the efficacy of Tysabri in patients with RRMS has been established in two pivotal controlled studies, one (AFFIRM) conducted in monotherapy in patients naïve to previous disease modifying treatments (patients were excluded if they had a history of ≥ 6 months on interferon or other prior immunomodulatory or immunosuppressant therapy) and the other (SENTINEL) conducted as add-on to Avonex, (patients had to be on Avonex treatment for at least one year and had to show active disease despite this active treatment). SENTINEL was stopped approximately one month early, on February 2008, because of two reports of PML.

In both studies, Tysabri was associated with a significant reduction in the rate of clinical relapse in sustained progression of disability and in other MRI measures of MS disease activity. The reduction in the relapse rate compared to placebo at one year was 68% in monotherapy and 53% as add on to Avonex. The decrease in the risk of disability progression, when compared to placebo over a 2-year period was 42% in monotherapy and 24% as add on to Avonex.

In EU, natalizumab is under additional monitoring because reports of serious adverse event represented by progressive multifocal leukoencephalopathy (PML), occurring on patients diagnosed with MS and under natalizumab treatment, increased with post-marketing experience and lengthening of patients' exposure to Tysabri. A formal request of reviewing the benefit/risk profile of Tysabri was issued by the CHMP on 22 October 2009 and the European Commission has consequently requested CHMP opinion in order to ensure

the safe use of Tysabri according to a procedure under Article 20 of Regulation (EC) No 726/2004. By the end of this procedure on 20 January 2010, the CHMP concluded that the benefit still outweighed the risks related to Tysabri treatment, but the MAH was committed to further activities for risk minimization.

In November 2012, the application for the extension of indication in RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure was endorsed by the CHMP. The other extension of indication requested in November 2012 -to Relapsing Remitting Multiple Sclerosis (RRMS) patients without high disease activity and negative for anti-JCV Antibodies - was withdrawn by the MAH in May 2013 on the basis that additional data were required and these were considered still provisional.

At the time of initial marketing authorization of Tysabri the only first-line therapies approved for the treatment of patients with relapsing MS were IFN-β and GA. Until a few years ago, patients with inadequate or insufficient response to IFN-β and GA were switched to natalizumab or fingolimod (Gilenya), which is an oral therapy administered once daily.

Newer MS drugs, dimethyl fumarate (Tecfidera), a twice daily oral capsule, teriflunomide (Aubagio), a once daily oral tablet, and alemtuzumab (Lemtrada), administered by intravenous infusions, received positive opinions by the CHMP recommending the granting of the Marketing Authorisation for their use in RRMS population. The European Commission Decisions on the Marketing Authorisation were issued in August and September 2013 for Aubagio and Lemtrada, and in January 2014 for Tecfidera.

The purpose of this variation is to extend the approved indication for Tysabri, currently restricted to non-responders to IFN-β or GA, to include patients who are non-responders to other first-line disease-modifying treatments. The application is based on an interim clinical study report with data from the Tysabri Observational Program (TOP, study IMA-06-02).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The efficacy of Tysabri in patients with RRMS has been established in 2 controlled studies, namely, Studies C-1801 and C-1802 [Polman 2006; Rudick 2006]. In both studies, Tysabri was associated with a significant reduction in sustained progression of disability; the rate of clinical relapse; and other measures of MS disease activity, such as reduction in the accumulation of new or enlarging T2 hyperintense lesions, gadolinium-enhancing lesions, and T1 hypointense lesions.

Tysabri is currently indicated as second-line therapy in patients with highly active relapsing remitting multiple sclerosis (RRMS) and high disease activity or those who have failed to respond to an adequate course of beta-interferon or glatiramer acetate (GA). At the time of the initial marketing authorisation for Tysabri, the only other treatment options for patients with RRMS were beta-interferons and GA. However, more recently an increasing number of alternative DMTs have been approved in the European Union (EU) for patients with RRMS e.g. fingolimod, dimethyl fumarate (DMF) and teriflunomide. However, the current

wording of the Tysabri indication statement only allows patients who continue to have high disease activity despite treatment with a beta-interferon or GA to switch to Tysabri.

GCP

The MAH has provided a statement that the observational study TOP is being conducted in accordance with the International Conference on Harmonisation guidelines, Good Clinical Practice guidelines, local regulations, and recommendations contained in the Declaration of Helsinki.

Table 1 Tabular overview of the clinical study

Study ID	study centres/ location	Design	Study posology	Study objective	Patient numbers	Duration	Gender M/F Median Age	Dg and Incl. criteria	Primary endpoint
IMA- 06-02	391 study sites in Europe, Australia, Argentina, Canada	Multinational multicentre observational study of efficacy and safety of Tysabri	300 mg/4 wks	Evaluation of long-term safety + impact on disease activity and progression of Tysabri as single disease-modifying agent in RRMS patients in a clinical practice sett	Analyses total 5623 Discontinued 2104 withdrawn 1196	Ongoing Each patient will be followed for 10 years	Female/ male ratio: 2,57 to 1,0 Median age: 37 (range 12 to 70)	Patients with RRMS, naïve to Tysabri at initiation of Tysabri treatment, met criteria defined in indication statement, at least 1 relapse in previous year, anti-natalizumab Ab negative, no history of PML or infection	Long-term safety (incidence and pattern of SAEs) in patients receiving Tysabri

2.3.2. Pharmacokinetics

No new PK data have been submitted.

2.3.3. Pharmacodynamics

No new PD data have been submitted.

2.4. Clinical efficacy

2.4.1. Main study

Study title: Tysabri® Observational Program (TOP)

TOP is an ongoing multinational, multicentre, epidemiological observational study of patients receiving Tysabri, with each patient to be followed for approximately 10 years. This study is designed to address the long-term safety profile and the long-term effect on disease activity and disability progression of Tysabri with marketed use and to provide supportive evidence, in the absence of formal switching studies, for the effectiveness of Tysabri for patients that have previously failed GA, beta-interferon and fingolimod. In TOP, efficacy and safety data were collected at 6-month intervals to coincide with regular clinic visits and routine clinical practice.

The submitted documents cover the analyses of data on 5623 MS patients from 391 study sites based on a data cut-off of 01 May 2014. The highest proportion of patients was from Germany (30.3%). The median age of the study population was 37 years and the ratio of female to male patients was 2.57 to 1.0. Similar demographics were seen in subgroups of patients whose last therapy before Tysabri infusion was glatiramer acetate, beta-interferon, or fingolimod.

Study participants

The study enrolled patients with RRMS, who were naïve to Tysabri at the initiation of Tysabri treatment and who met the criteria defined in the indication statement for prescription in their respective countries.

Principles of enrolment into TOP were as follows:

- Must have given written informed consent and provided all authorisations required by local law.
- Decision to treat with Tysabri must have preceded enrolment.
- Must have had no more than 3 Tysabri infusions prior to enrolment.

Patient characteristics and contraindications to treatment with Tysabri in accordance with prescribing information were as follows:

- Documented diagnosis of RRMS.
- Must have had at least 1 relapse in the previous year and must have satisfied the locally approved therapeutic indications for Tysabri.
- Males or females whose age was within the Tysabri indication statement.
- Must not have had a history of positive anti-natalizumab antibodies.
- Must not have had a history of PML or other opportunistic infections, or an increased risk for such infections.
- Must not have received concomitant immunomodulatory or immunosuppressive therapy during therapy with Tysabri.
- Must not have been immunocompromised at the time of enrolment.
- Must not have been suffering from known active malignancies (patients with cutaneous basal cell carcinoma that has been completely excised prior to study entry remain eligible).
- Must not have shown a known hypersensitivity to Tysabri or to any of the excipients.
- Female patients must have been postmenopausal for at least 1 year, surgically sterile (does not include tubal ligation), or willing to practice effective contraception (as defined by the treating physician) while receiving Tysabri.

- Women must not have been breastfeeding or pregnant.

Treatments

Patients were treated with Tysabri according to the prescribing information.

Objectives

The objectives of TOP are to evaluate the long-term safety and impact on disease activity and progression of Tysabri as a single disease-modifying agent in patients with RRMS in a clinical practice setting. The safety of Tysabri is being assessed by collecting data on the incidence of non-MS-related serious adverse events (SAEs), including all serious infections, regardless of causality. The effect of Tysabri on disability progression and disease activity is being assessed by using the Expanded Disability Status Scale (EDSS) and evaluating the frequency of clinical relapses.

Outcomes/endpoints

Primary Endpoint

The primary endpoint is long-term safety (incidence and pattern of SAEs) in patients receiving Tysabri.

Secondary Endpoints

- MS disease activity as determined by the occurrence of clinical relapses (annualised relapse rate [ARR], distribution of the total number of relapses up to 10 years, time to first relapse, proportions of patients with and without relapse).
- Disability progression as determined by EDSS (based on neurological examination, "physical EDSS").
- Evaluation of baseline disease characteristics as prognostic indicators for disease activity and disability progression over time. Such baseline disease characteristics include the following:
    - EDSS
    - disease duration at Baseline
    - number of relapses during 1 and 2 years before Baseline
    - previous use of DMTs
    - age, gender, and any other characteristics available for the total population or sufficiently large subgroups to be defined by the Study Steering Committee as putative prognostic indicators to be studied
- Evaluation of short-term (1 year) disease outcomes as prognostic indicators for disease activity and disability progression over time. Such short-term outcomes include the following:
    - EDSS progression during the first 12 months
    - occurrence of relapses during the first 12 months
    - others to be defined by the Study Steering Committee as putative prognostic indicators to be studied

Additional Endpoint

An additional endpoint for this study was the evaluation of anti-JC virus (JCV) antibody prevalence in patients with MS for the duration of the study.

Sample size

Sample size of the TOP study is not based on statistical considerations. The actual sample size is based on the data cut-off date of 01 May 2014.

Statistical methods

All patients enrolled in TOP receiving at least 1 dose of Tysabri were included in the evaluation of safety and efficacy.

Data were summarised by statistical characteristics (continuous data: # of observations, mean, standard deviation, median and range; categorical data: absolute and relative frequencies).

Patients' baseline information was summarised and included demographics (e.g., age and gender), disease characteristics (EDSS, anti-JCV antibody status, number of relapses, and MS duration), and medical history (immunomodulator or immunosuppressant use and duration of use). Number of Tysabri infusions received was also summarised. Safety was assessed by incidence of patients experiencing at least 1 SAE. Patterns of SAEs over time were investigated. MS disease activity was assessed by:

- ARR
- distribution of the total number of relapses up to 10 years
- time to first relapse
- proportions of patients with relapse

ARR including its 95% CI was estimated using a Poisson model with a robust covariance matrix. This analysis was repeated for different time intervals. In addition ARR in various subgroups was calculated. The time to first relapse was evaluated using a Kaplan-Meier analysis, with the estimated cumulative risk of relapse reported at each time point of interest.

EDSS was used to describe disease progression. Post-baseline longitudinal EDSS scores were summarised for all patients and subgroups of patients with baseline and post-baseline data. Time to sustained progression and time to sustained improvement were both analysed using Kaplan-Meier analysis. Sustained progression was defined as an increase in EDSS, sustained for at least 24 weeks, of at least 0.5 points from a baseline EDSS score $\geqslant$6.0, at least 1.0 points from a baseline EDSS score of 1.0 to <6.0, or at least 1.5 points from a baseline EDSS score of 0. Sustained improvement was defined as at least a 1-point decrease in EDSS sustained for at least 24 weeks for patients with baseline EDSS scores $\geqslant$2.

The prevalence of anti-JCV antibodies in patients with MS was estimated as the number of patients with anti-JCV antibodies detected by the total number of patients with reported results. Once a patient tested positive for anti-JCV antibodies, she/he was considered positive for the remainder of the study.

An interim analysis was performed when the following milestones were achieved:

-The first 500 patients completed 1 year of observation.

-The first 1000 patients completed 1 year of observation.

Data analyses were performed on a biannual basis thereafter. The results for this clinical study report were based on a data cutoff date of 01 May 2014.

Results

- **Participant flow**

Total number of subjects included: 5623

- ➔ 5076 patients with 1 prior DMT (90.3%)
- ➔ 2359 patients with ≥ 2 DMTs (45.2%)
- ➔ 547 patients naïve to DMTs (9.7%)

Number of subjects dosed with Tysabri: 5623

Number of subjects who did not receive Tysabri every month: 2211/5623 (39.3%)

Number of subjects who discontinued Tysabri: 2104/5623 (37.4%)

- ➔ 1246 patients stayed on study,
- ➔ 855 withdrew from TOP,
- ➔ and 3 discontinued Tysabri after withdrew from TOP

The most common reasons for discontinuation of Tysabri included positive anti-JCV antibody status (14.1%), patient decision (7.7%), medication change (7.0%), insufficient efficacy (6.0%), physician decision (4.6%), and Tysabri treatment duration concern (4.2%).

Number of subjects who withdrew from TOP: 1196/5623 (21.3%)

- ➔ 858 discontinued Tysabri,
- ➔ 338 continued Tysabri

Patient decision (4.8%) was the most common reason for withdrawal from TOP.

- **Recruitment**

The first patient was treated on January 19, 2007. Cut-off date for interim analysis was May 1, 2014

20 December 2013. There were 391 study sites.

- **Baseline data**

Eligible patients had a documented diagnosis of RRMS, with at least 1 relapse in the previous year, and were naïve to natalizumab at the initiation of natalizumab treatment (must not have had >3 natalizumab infusions prior to enrolment). They must have met the locally approved therapeutic indications for natalizumab and have made the decision to be treated with natalizumab prior to enrolment.

Of the total patient population (n = 5623), prior to entry into this study, 547 patients (9.7%) were naïve to DMTs, 5076 patients (90.3%) had received ⩾1 DMTs, and 2539 patients (45.2%) had received ⩾2 DMTs.

Of the 5076 patients who received prior DMT(s), as last medication prior to Tysabri infusion, 3210 patients (57%) received IFN-β, 1354 patients (24%) received glatiramer acetate, 130 patients (2.3%) received fingolimod, 215 patients (3.8%) received "traditional" immunosuppressants (mitoxantrone,

azathioprine, cyclophosphamide, cyclosporine, mycophenolate, tacrolimus, rituximab, methotrexate, cladribine), 6 patients (0.1%) received teriflunomide and 5 patients (0.1%) received dimethyl fumarate.

As for ever received MS therapies prior to first Tysabri infusion, 4390 patients (78%) ever received IFN-β, 1959 patients (35%) ever received glatiramer acetate, 152 patients (3%) ever received fingolimod, 777 patients (14%) ever received "traditional" immunosuppressants. In addition, a small number of patients ever used teriflunomide or dimethyl fumarate prior to Tysabri (13 and 8 patients, respectively). Please also refer to Table 3.

Duration of prior immunomodulator or immunosuppressant use

Table 2 Medical History of Patients Included in TOP: Duration of Immunomodulator or Immunosuppressant use (Patients who ever used the Specific Medication)

	Total[a]			
Specific Medications	n*	Mean (SD)	Median	Min, Max
Interferon beta 1-a (Avonex)	1787	38.0 (36.80)	25.0	0.7, 201.1
Interferon beta 1-b (Betaferon/Betaseron/Extavia)	1642	41.8 (41.37)	27.2	0.3, 218.5
Interferon beta 1-a (Rebif)	2001	37.6 (36.04)	26.1	0.6, 209.9
Glatiramer acetate (Copaxone)	1959	29.9 (31.56)	17.5	0.0, 212.0
Fingolimod (Gilenya)	152	11.4 (15.17)	7.7	0.0, 120.7
Teriflunomide (Aubagio)	13	19.2 (20.08)	7.6	2.2, 50.0
Tecfidera	8	13.5 (8.65)	14.7	2.1, 25.0
Immunosuppressants (IS)	777	35.8 (41.04)	22.9	0.0, 281.6
Mitoxantrone (Novantrone)	266	13.9 (13.08)	9.9	0.0, 78.5
Azathioprine (Imuran)	438	47.2 (47.06)	33.7	0.0, 276.1
Cyclophosphamide (Cytoxan)	118	9.7 (16.08)	5.5	0.0, 130.5
Cyclosporin (Sandimmune)	4	72.0 (41.66)	75.6	19.6, 117.4
Mycophenolate (Mofetil)	9	17.6 (11.35)	13.1	1.1, 36.0
Tacrolimus (Prograf)	6	29.8 (27.88)	24.5	3.3, 77.3
Rituximab (Rituxan)	2	6.6 (0.03)	6.6	6.6, 6.6
Methotrexate (Trexall)	65	31.2 (30.95)	20.7	0.0, 117.4
Cladribine	2	49.5 (50.00)	49.5	14.1, 84.9
Other	472	62.9 (54.09)	47.8	1.1, 345.7

Included patients: 1) Consent provided; 2) Criteria met; 3) <=3 doses of Tysabri at enrollment.
[a]A 28-day month was used in this summary.
* Patients with known start and stop dates.

Table 3 Medical History of Patients Included in TOP: Duration of Immunomodulator or Immunosuppressant use (Patients who used the Specific Medication as Medication last used before first Tysabri Infusion)

	Total[a]			
Specific Medications	n*	Mean (SD)	Median	Min, Max
Interferon beta 1-a (Avonex)	979	41.5 (39.84)	26.1	1.0, 201.1
Interferon beta 1-b (Betaferon/Betaseron/Extavia)	939	44.3 (43.69)	28.8	1.0, 218.5
Interferon beta 1-a (Rebif)	1292	38.0 (36.52)	26.1	1.0, 209.9
Glatiramer acetate (Copaxone)	1354	30.2 (32.40)	17.4	0.0, 212.0
Fingolimod (Gilenya)	130	11.0 (14.95)	7.1	0.0, 120.7
Teriflunomide (Aubagio)	6	29.8 (19.07)	33.7	6.6, 50.0
Tecfidera	5	13.1 (8.04)	14.2	4.4, 22.9
Immunosuppressants (IS)	215	25.9 (32.77)	16.4	0.0, 209.9
Mitoxantrone (Novantrone)	77	14.4 (11.48)	13.1	0.0, 54.4
Azathioprine (Imuran)	90	38.9 (42.71)	28.8	0.0, 209.9
Cyclophosphamide (Cytoxan)	24	9.6 (12.46)	3.8	0.0, 49.0
Mycophenolate (Mofetil)	4	19.1 (15.20)	19.6	1.1, 36.0
Tacrolimus (Prograf)	3	31.9 (39.74)	15.3	3.3, 77.3
Rituximab (Rituxan)	2	6.6 (0.03)	6.6	6.6, 6.6
Methotrexate (Trexall)	13	34.0 (32.80)	26.1	1.1, 94.5
Cladribine	2	49.5 (50.00)	49.5	14.1, 84.9
Other	307	67.8 (55.06)	56.6	1.1, 345.7

Included patients: 1) Consent provided; 2) Criteria met; 3) <=3 doses of Tysabri at enrollment.
[a]A 28-day month was used in this summary.
* Patients with known start and stop dates.

Table 4 Summary of DMT Use Duration (years) Prior to Tysabri Infusion

	Statistics
Descriptive (yrs.)	
n	5623
Mean (SD)	4.0 (3.75)
Median	3.0
Min, Max	0.0, 26.5
MS Duration Cut - n (%) (yrs.)	
No DMT	547/5623 (9.7%)
<=1 year	762/5623 (13.6%)
>1 - 2 years	838/5623 (14.9%)
>2 - 4 years	1157/5623 (20.6%)
>4 - 6 years	825/5623 (14.7%)
>6 - 10 years	1015/5623 (18.1%)
>10 years	479/5623 (8.5%)
Total	5623/5623 (100%)

Included patients: 1) Consent provided; 2) Criteria met; 3) <=3 doses of Tysabri at enrollment.

Sequence of treatments and duration of exposure (Patients ⩾ 2 prior DMT)

Of the 2539 patients that had received ⩾2 DMTs prior to treatment with Tysabri in TOP, the most common treatment sequences were an initial treatment with interferon beta (1-a or 1-b) followed by treatment with glatiramer acetate (N=535, 21% of patients). The three most common treatment sequences within this group were: (1) initial treatment with interferon beta 1-a (Rebif) followed by treatment with glatiramer acetate (Copaxone) (N=214); (2) initial treatment with interferon beta 1-b (Betaferon or Betaseron or Extavia) followed by treatment with Copaxone (N=164); (3) initial treatment with interferon beta 1-a (Avonex) followed by treatment with Copaxone (N=157). Other common sequences included switching between two different betainterferons before treatment with Tysabri, such as initial treatment with Avonex followed by treatment with Rebif (N=156), and switching from glatiramer acetate to beta-interferon, prior to Tysabri treatment (N=191). Though less common, it is also noteworthy, that 65 patients switched from either beta-interferon or glatiramer acetate to fingolimod before treatment with Tysabri.

Although the most common treatment sequences prior to Tysabri treatment comprise an initial treatment with interferon followed by treatment with glatiramer acetate, there are many different prior treatment sequences for patients entering TOP. In some cases, patients received up to 6 or 7 DMT switches before entering TOP where they subsequently received Tysabri. It is important to note that the number of patients represented by each of these multi-DMT treatment sequences is small and thereby precludes derivation of meaningful trends in benefit/risk. In fact, there are 293 patients who have unique treatment sequences in TOP.

Update TOP efficacy data (up to 01 May 2015)

As of 01 May 2015, only a small number of patients enrolled in the TOP study had switched from dimethyl fumarate (DMF) or teriflunomide to Tysabri (5 and 7 patients, respectively). The small size of these subgroups combined with the limited length of exposure preclude meaningful efficacy analysis.

The pretreatment ARR of 1.98 (95% CI: 1.93, 2.03) in patients whose last therapy was GA decreased to 0.24 (95% CI: 0.22, 0.27) while on Tysabri therapy. In patients whose last therapy was beta interferon, the pretreatment ARR of 1.98 (95% CI: 1.94, 2.01) decreased to 0.21 (95% CI: 0.19, 0.22) while on Tysabri therapy.

Data is accumulating in TOP for patients who have switched from fingolimod to Tysabri. As of May 2015, there is adequate fingolimod to Tysabri switch data (1-3 years Tysabri treatment) related to ARR, relapse number and sustained EDSS progression or improvement, discussed forthwith and Figure 1 show a summary of ARR and relapse count in patients who received fingolimod as last therapy prior to switching

to Tysabri (n=147). For prior fingolimod patients, the mean ARR at baseline (1 year prior to the first dose of Tysabri) was 2.05; it decreased to 0.41, 0.3 and 0.37 during the first, second and third years of Tysabri treatment, respectively. During the fourth year of treatment, there was an increase in ARR to a mean 0.77, though the sample size during Year 4 was considerably smaller (N=18), and precludes meaningful interpretation.

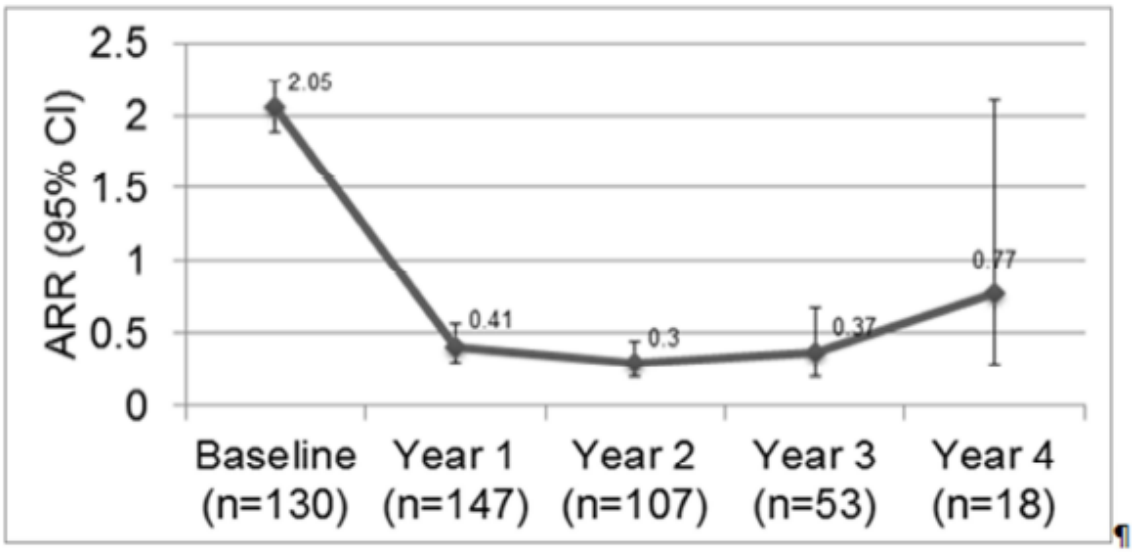


Figure 1 ARR by Tysabri Treatment Duration in Patients with Fingolimod as Last Prior Therapy

During the first year of Tysabri treatment, 80.3% (57/71) of patients who received fingolimod as last therapy prior to switching to Tysabri were relapse-free. During the second year on Tysabri, 85.9% (61/71) of patients were reported to be relapse-free and during the third year on Tysabri, 77.3% (17/22) of patient were reported to be relapse-free. As of May 2015, the number of patients with >3 years of follow up is too small to conduct a meaningful analysis.

The probability of confirmed EDSS worsening for patients who were on fingolimod and switch to Tysabri at year 1, 2 and 3 of treatment were 4.17%, 11.74% and 15.01% respectively. The probability of confirmed EDSS improvement for patients who were on fingolimod and switch to Tysabri at year 1, 2 and 3 of treatment were 13.02%, 18.89% and 20.92% respectively. Therefore, the probability of sustained EDSS improvement on Tysabri outweighs the probability of EDSS worsening for patients in TOP who received fingolimod as last therapy prior to switching to Tysabri.

Table 5 Baseline data

	Total (5623)	**Glatiramer acetate (Copaxone)**	**Interferon**	**Fingolimod (Gilenya)**
Number of patients included in TOP with last therapy of		1352	3186	130
Gender	Male: 1577 (28.0%) Female: 4046 (72.0%)	Male: 362 (28.0%) Female: 990 (73.2%)	Male: 887 (27.8%) Female: 2299 (72.2%)	Male: 36 (27.7%) Female: 94 (72.3%)
Age at First Dose	Male: 12–70 years (Median: 37.0) Female: 13-68 years (Median: 37.0)	Male: 16–66 years (Median: 38.0) Female: 17-65 years (Median: 37.0)	Male: 12–70 years (Median: 36.0) Female: 13-68 years (Median: 37.0)	Male: 20–60 years (Median: 42.0) Female: 18-61 years (Median: 38.0)
EDSS Baseline	N = 5587 (36 unknown) Median: 3.5 Min, Max: 0.0 – 9.5	N = 1343 (9 unknown) Median: 3.5 Min, Max: 0.0 – 8.5	N = 3167 (19 unknown) Median: 3.5 Min, Max: 0.0 – 8.0	N = 130 Median: 3.5 Min, Max: 0.0 – 7.0
Duration of MS Symptoms at time of first dose	N = 5605 (18 unknown) Median: 7.1 Min, Max: 0.0 – 43.9 years	N = 1351 (1 unknown) Median: 7.7 Min, Max: 0.2 – 37.2 years	N = 3178 (8 unknown) Median: 7.3 Min, Max: 0.2 – 42.2 years	N = 129 (1 unknown) Median: 8.1 Min, Max: 0.8 – 31.9 years
Number of relapses before Tysabri	<u>Year 1 prior:</u> N=5621 (2 unknown) Median: 2.0 Min, Max 0.0-10 <u>Year 2 prior</u>: N=5620 Median: 1.0 Min, Max 0.0-11 <u>2 Years prior</u> N=5620 Median: 3.0 Min, Max 0.0-14	<u>Year 1 prior:</u> N=1352 Median: 2.0 Min, Max 0.0-7 <u>Year 2 prior</u>: N=1352 Median: 1.0 Min, Max 0.0-11 <u>2 Years prior</u> N=1352 Median: 3.0 Min, Max 0.0-12	<u>Year 1 prior:</u> N=3185 Median: 2.0 Min, Max 0.0-10 <u>Year 2 prior</u>: N=3185 Median: 1.0 Min, Max 0.0-7 <u>2 Years prior</u> N=3185 Median: 3.0 Min, Max 0.0-14	<u>Year 1 prior:</u> N=130 Median: 2.0 Min, Max 0.0-6 <u>Year 2 prior</u>: N=130 Median: 1.0 Min, Max 0.0-5 <u>2 Years prior</u> N=130 Median: 3.0 Min, Max 1.0-8
Immunomodulator or Immunosuppressant use prior to Tysabri	Yes: 5075/5623 (90.3%) No: 547/5623 (9.7%)			
Patients with history of malignancy	Yes: 35/5623 (0.6%) No: 5588/5623 (99.4%)			

Number of Tysabri doses at the end of current reporting period	Median: 27.0 Min, Max: 1.0-90.0	N=1352 Median: 27.0 Min, Max: 1.0-90.0	N=3186 Median: 28.0 Min, Max: 1.0-88.0	N=130 Median: 13.0 Min, Max: 1.0-59.0
JCV Antibody status at enrolment	Tested: 3397/5623 (60.4%) Positive: 1663/3397 (49.0%) Negative: 1734/3397 (51.0%)			
DMT use duration (years) prior Tysabri	Median: 3.0 Min, Max: 0.0 – 26.5			

- **Numbers analysed**

5623 subjects were included in the efficacy evaluation. All of these subjects had received at least one dose of Tysabri.

To estimate the extent to which extended interval dosing (EID) might be present in TOP, the MAH examined the treatment exposure in the subgroup who indicated not receiving Tysabri every month for the past 6 months as compared to the subgroup that indicated receiving monthly infusions. The exposure characteristics of the subgroup identified as receiving Tysabri every month and subgroup that did not receive Tysabri every month were highly similar, having mean (median) exposures of 29.8 (27.0) and 29.4 (27.0) infusions over total treatment durations of 29.4 (26.2) and 31.1 (28.5) months, respectively. Moreover, the total person-years of exposure in the group that did not receive Tysabri every month divided by the overall total person-years of exposure is 0.390, which closely matches the proportion of subjects in this subgroup. Thus, subjects in the subgroup that did not receive Tysabri every month, as a whole, received a similar exposure to the subgroup of patients identified as receiving Tysabri every month. These data demonstrate most of the patients in this subgroup were not consistently receiving Tysabri with EID (Table 6). In fact, current data suggests that only a small percentage of patients receive an EID regimen.

Table 6 Exposure to TYSABRI as of the end of the Current Reporting Period by Tysabri Received

Exposure to TYSABRI [1]	Received Tysabri Every Month (N=3412) n (%)	Didn't Receive Tysabri Every Month (N=2211) n (%)	Total (N=5632) n (%)
Descriptive Statistics			
n	3412	2211	5623
Mean (SD)	29.8 (19.50)	29.4 (17.69)	29.6 (18.81)
Median	27.0	27.0	27.0
Min, Max	1.0, 88.0	1.0, 90.0	1.0, 90.0
Tysabri Dose Count			
1-6 dose	358/3412 (10.5%)	228/2211 (10.3%)	586/5623 (10.4%)
7-12 doses	363/3412 (10.6%)	222/2211 (10.0%)	585/5623 (10.4%)
13-18 doses	387/3412 (11.3%)	196/2211 (8.9%)	583/5623 (10.4%)
19-24 doses	421/3412 (12.3%)	271/2211 (12.3%)	692/5623 (12.3%)
25-30 doses	412/3412 (12.1%)	350/2211 (15.8%)	762/5623 (13.6%)
31-36 doses	283/3412 (8.3%)	246/2211 (11.1%)	529/5623 (9.4%)
37-42 doses	291/3412 (8.5%)	179/2211 (8.1%)	470/5623 (8.4%)
43-48 doses	241/3412 (7.1%)	183/2211 (8.3%)	424/5623 (7.5%)
49-54 doses	216/3412 (6.3%)	130/2211 (5.9%)	346/5623 (6.2%)
55-60 doses	192/3412 (5.6%)	83/2211 (3.8%)	275/5623 (4.9%)
61-66 doses	92/3412 (2.7%)	50/2211 (2.3%)	142/5623 (2.5%)
67-72 doses	69/3412 (2.0%)	46/2211 (2.1%)	115/5623 (2.0%)
73-78 doses	56/3412 (1.6%)	19/2211 (0.9%)	75/5623 (1.3%)
79-84 doses	26/3412 (0.8%)	7/2211 (0.3%)	33/5623 (0.6%)
85-90 doses	5/3412 (0.1%)	1/2211 (0.0%)	6/5623 (0.1%)
Total Person-Years of TYSABRI Exposure (based on number of doses received) [2]	7650.63	4887.02	12537.7

Included patients: 1) Consent provided; 2) Criteria met; 3) <=3 doses of Tysabri at enrollment.
[1] Exposure to TYSABRI was based on time from first dose to date of discontinuation/withdrawal/last visit, assuming doses every 28 days, and including TYSABRI infusions received prior to TOP enrollment. Missed doses were subtracted out.
[2] Person-year was calculated as (Total number of days exposed to Tysabri)/365.25; Total person-years is the sum of person-year over all patients.

A new CRF was implemented in November 2014 to collect information on dosing schedule (q4 weekly, q6 weekly, q8 weekly or other) and infusion dates. Since introduction of this new CRF and as of May 2015, additional data on dosing regimen and infusion dates are available for 2198 of 5770 (38.1%) patients. Of these 2198 patients, 96.8% (2127) were reported as being on a Tysabri dosing regimen of q4w while 1.0% (23), 0.3% (7) and 1.9% (41) were reported to be on a Tysabri dosing regimen of q6w, q8w, or other regimen, respectively. Collectively, these data indicate that only 3.2% (71) of patients in TOP are receiving dosing other than q4w.

Only 71 patients have contributed confirmed EID data as indicated in the new CRF and the available data for these patients is limited to 7 months (from November 2014 to May 2015). In the 71 confirmed EID patients in TOP, over this limited observation period, there have been no cases of PML and 5 patients (7%) have experienced a relapse.

TOP data on EID (in relation to Abstract presented at the American Academy of Neurology in Washington (Herbert et al, 2015),The MAH claimed that there were insufficient data in either source to allow for any conclusions on the potential for EID to mitigate PML risk while maintaining the efficacy profile of Tysabri. Herbert and colleagues conducted a retrospective analysis of 886 patients from 10 large MS Centers across the US who received standard dose (defined as q4w± 2days with < 2 consecutive missed monthly infusions) or EID of Tysabri. EID was defined as an interval ranging from 4 weeks and 3 days (q4w3d or 31 days) to 8 weeks and 5 days (q8w5d or 61 days) for ⩾ 3 consecutive doses. There were no significant differences in annual relapse rate, proportion of patients with MRI activity, and NEDA (no evidence of disease activity) between the standard dose (SD) and EID groups. No major unexpected adverse effects and no cases of PML were reported in the EID cohort as compared to 2 cases of PML in the standard dosing cohort. The authors concluded "1) extending the Tysabri dosing schedule to q5-8 weeks does not appear to affect the excellent efficacy profile of drug as seen by the comparison to the standard dose cohort, and 2) although the PML trend is favorable, it has not yet achieved statistical significance. If the

zero-PML trend continues to significance, it would support the concept of a dosing 'safety zone' which is protective of MS relapse but is also non-permissive of JC Virus activation." There are, however, several limitations in the design of this study that prevent the results from informing on the hypothesis that EID can achieve comparable efficacy while reducing PML risk.

- **Outcomes and estimation**

The main objectives of this study were to determine the long-term safety and impact on disease activity and progression of Tysabri as a single disease-modifying agent in patients with RRMS in a clinical practice setting. Safety was evaluated by incidence and pattern of SAEs. For further information please refer to Section 2.5 Clinical Safety of this AR. Efficacy evaluation is documented below.

Annualised Relapse Rate (ARR)

There was a significant reduction in ARR for patients starting on natalizumab therapy. The overall ARR decreased from 1.99 (95% confidence interval [CI]: 1.96, 2.01) in the pretreatment year to 0.22 (95% CI: 0.21, 0.24) while on natalizumab therapy ($p < 0.0001$) and remained stable over 5 years (Figure 2).

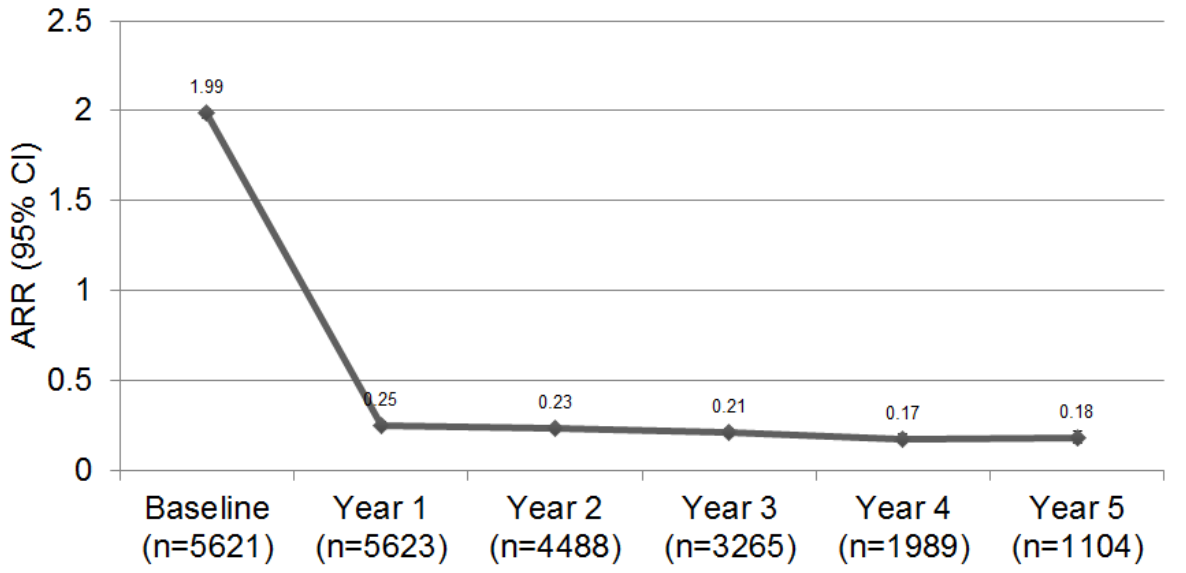


Figure 2 ARR by Natalizumab Treatment Duration (Total Population)

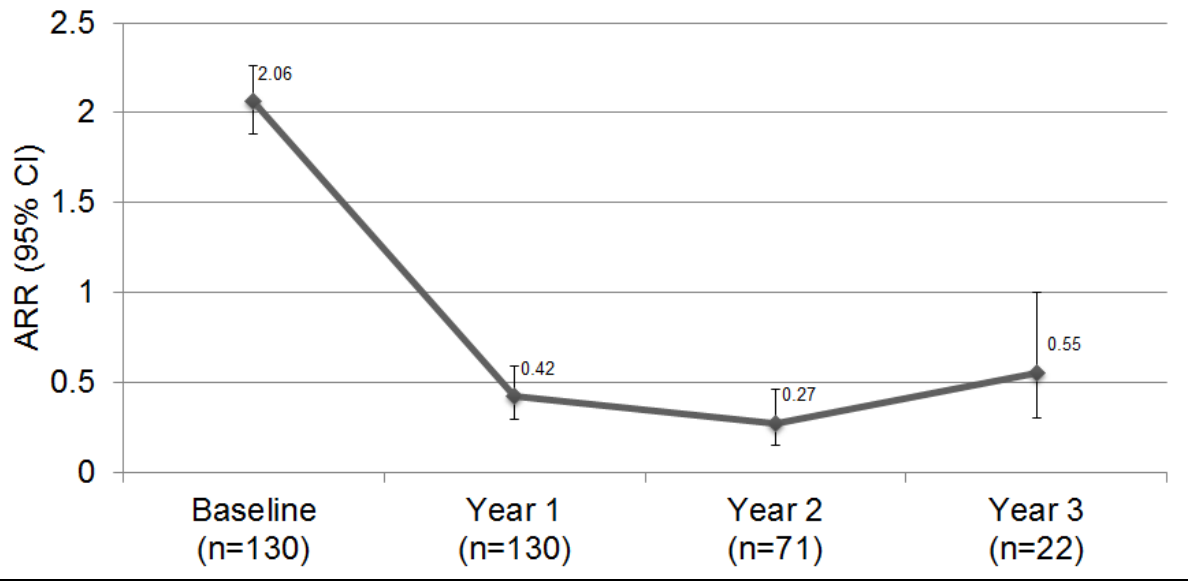
ARR = annualised relapse rate; CI = confidence interval; TOP = Tysabri Observational Program.

A significant reduction in ARR with natalizumab occurred **regardless of the number of prior DMTs** used, with greater reductions seen in patients who were either DMT naïve or had taken only 1 DMT prior to dosing with natalizumab. The pretreatment ARR of 2.07 (95% CI: 1.99, 2.16) in DMT-naïve patients decreased to 0.18 (95% CI: 0.14, 0.22) while on natalizumab therapy ($p < 0.0001$). In patients who had taken 1 DMT, the pretreatment ARR of 2.00 (95% CI: 1.96, 2.04) decreased to 0.19 (95% CI: 0.17, 0.20) while on natalizumab therapy ($p < 0.0001$). In patients who had taken >1 DMT, the pretreatment ARR of 1.95 (95% CI: 1.92, 1.99) decreased to 0.27 (95% CI: 0.25, 0.29) while on natalizumab therapy ($p < 0.0001$).

A significant reduction in ARR with natalizumab occurred **regardless of the last therapy** received prior to dosing with natalizumab ($p < 0.0001$). The pretreatment ARR of 1.98 (95% CI: 1.93, 2.03) in patients whose last therapy was GA decreased to 0.24 (95% CI: 0.22, 0.27) while on natalizumab therapy. In patients whose last therapy was beta interferon, the pretreatment ARR of 1.98 (95% CI: 1.94, 2.01)

decreased to 0.21 (95% CI: 0.19, 0.22) while on natalizumab therapy. In patients whose last therapy was fingolimod, the pretreatment ARR of 2.06 (95% CI: 1.88, 2.26) decreased to 0.38 (95% CI: 0.28, 0.52) while on natalizumab therapy. As with the total population, the reduction in ARR remained stable over 5 years for the subgroups of patients whose last therapy prior to dosing with natalizumab was GA or beta interferon. For patients whose last therapy prior to dosing with natalizumab was fingolimod, the reduction in ARR remained stable over 3 years (given later market entry) (**Figure 3**), with more variability observed than in the other subgroups due to the small sample size (n⩽130). Data for the fingolimod subgroup after the 3 year period are less meaningful due to the smaller sample size (n⩽4).

Figure 3: ARR by Natalizumab Treatment Duration in Patients With Fingolimod as Last Prior Therapy



ARR = annualised relapse rate; CI = confidence interval; TOP = Tysabri Observational Program.

In the overall study population, the reduction in ARR after natalizumab treatment was significant regardless of baseline EDSS score, with slightly greater reductions seen in patients with lower baseline EDSS scores. In patients with an EDSS score of <3, the pretreatment ARR decreased from 2.00 (95% CI: 1.96, 2.05) to 0.18 (95% CI: 0.17, 0.20) while on natalizumab therapy (p<0.0001). In patients with a baseline EDSS score of ⩾3, the pretreatment ARR decreased from 1.97 (95% CI: 1.94, 2.01) to 0.25 (95% CI: 0.23, 0.27) while on natalizumab therapy (p < 0.0001).

For the group of patients who received interferon as the last therapy before switching to Tysabri (N=695), the mean ARR during the baseline period was 1.99. After initiation of Tysabri, the ARR dropped dramatically and remained constant at 0.19 over the first 3 years of treatment with Tysabri, then dropped slightly to 0.15 in the fourth year (month 36 to 48).

For the group of patients who received Copaxone as the last therapy before switching to Tysabri (N=252), the mean ARR during the baseline period was 2.09. After initiation of Tysabri, the ARR dropped significantly after the first 12 months of treatment to 0.22, and remained low over 4 years of treatment, ranging from 0.19 to 0.25.

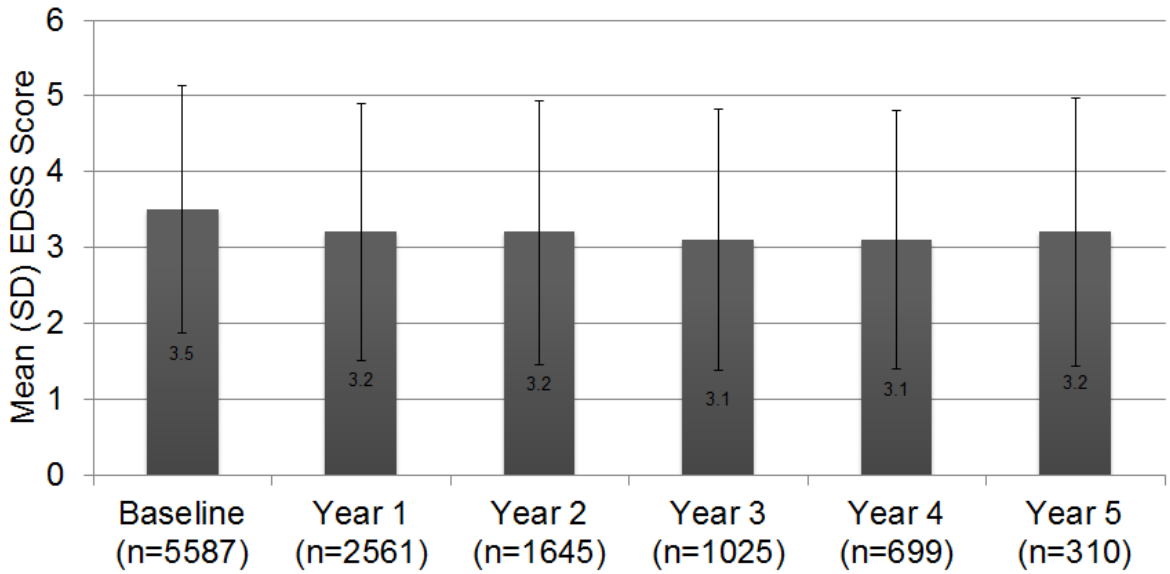
For the group of patients who received fingolimod as the last therapy before switching to Tysabri (N=71), the mean ARR during the baseline period was 2.27. After 12 months of treatment with Tysabri the ARR dropped to 0.23. The available data is limited to 12 months of fingolimod exposure prior to Tysabri. For

Given the limitations of sample size and subject-years followed, the interpretation of these findings is limited.

EDSS

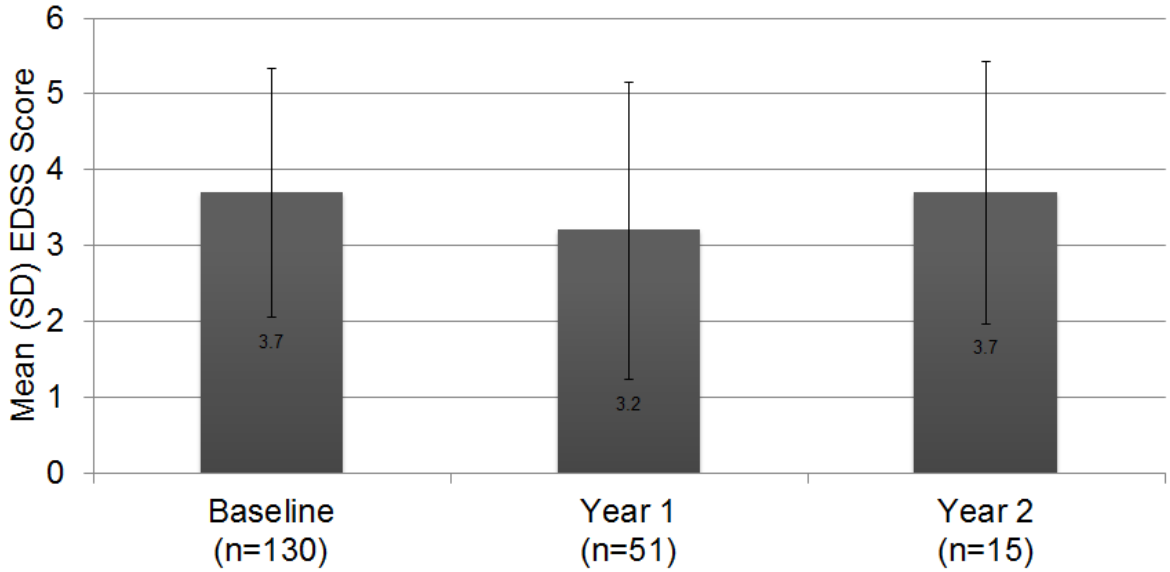
Mean EDSS scores were similar from Baseline (3.5) to Year 5 (3.2) in patients treated with natalizumab. Similar results were seen for the subgroups of patients whose last therapy prior to dosing with natalizumab was GA or beta interferon. For the fingolimod subgroup, mean EDSS scores were also similar from Baseline to Year 2 (**Figure 4**). Data for the fingolimod subgroup after the 2 year period are less meaningful due to the smaller sample size (n≤4).

Figure 4: Mean EDSS Scores Over Time by Natalizumab Treatment Duration (Total Population)



For the fingolimod subgroup, mean EDSS scores were also similar from Baseline to Year 2 (see **Figure 5**). Data for the fingolimod subgroup after the 2 year period are less meaningful due to the smaller sample size (n≤4).

Figure 5: Mean EDSS Scores by Natalizumab Treatment Duration in Patients With Fingolimod as Last Prior Therapy



EDSS = Expanded Disability Status Scale; SD = standard deviation; TOP = Tysabri Observational Program.

Time to Sustained EDSS Progression and Improvement

The time to sustained progression and time to sustained improvement based on EDSS scores were analyzed using Kaplan-Meier analysis. The cumulative probabilities of sustained progression or improvement were estimated for multiple time points. At all time points, the cumulative probability of sustained improvement was higher than the cumulative probability of sustained progression (30.34% and 19.70%, respectively, at 5.5 years).

Similarly, the cumulative probability of sustained improvement was higher than the cumulative probability of sustained progression at all time points for the subgroups of patients whose last therapy prior to dosing with natalizumab was GA, beta interferon, or fingolimod. For the GA subgroup, the cumulative probabilities of sustained improvement or progression at 5.5 years were 31.43% and 15.87%, respectively. For the beta interferon subgroup, the cumulative probabilities of sustained improvement or progression at 5.5 years were 29.43% and 21.44%, respectively. For the fingolimod subgroup, the cumulative probabilities of sustained improvement or progression at 24 months were 23.02% and 5.53%, respectively.

- **Summary of main study**

The following tables summarize the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 Summary of Efficacy for TOP

Title: Tysabri® Observational Program (TOP)		
Study identifier	IMA-06-02	
Design	Multinational multicentre observational study of efficacy and safety of Tysabri	
	Duration of main phase:	Ongoing, 10 years
Hypothesis	Exploratory: to determine whether it is safe and efficacious to switch therapy from other DMTs to Tysabri	

Treatments groups	Tysabri treatment		Tysabri as per local prescription, N=5623
Endpoints and definitions	Primary endpoint	Incidence and pattern of SAEs	Long-term safety in patients receiving Tysabri
	Secondary endpoints	ARR, EDSS,	The effect of Tysabri on disability progression and disease activity
	Additional endpoint	Anti-JCV antibody	Evaluation of anti-JC virus (JCV) antibody prevalence in patients with MS for the duration of the study
Database lock	cutoff date of May 1, 2014 (interim analysis)		

Results and Analysis

Analysis description	**Primary Analysis (Safety)**			
Analysis population and time point description	Safety population Up to 5 years following start of Tysabri			
Descriptive statistics and estimate variability	Treatment group	Tysabri		
	Number of subject	5263		
	Frequency of patients with at least 1 SAE	9.8%		
	<variability statistic>	Not available		
Effect estimate per comparison	Not applicable (no comparator)			
Analysis description	**Secondary analysis (Efficacy)**			
Analysis population and time point description	All patients documented up to 5 years following start of Tysabri			
Descriptive statistics and estimate variability	Treatment group	Tysabri		
	Number of subject	5621		
	Baseline ARR	1.99		
	95% CI	(1.96, 2.01)		
	Number of subjects	5623		
	Post baseline ARR	0.22		
	95%-CI	(0.21, 0.24)		
Effect estimate per comparison	Change in ARR	Post vs. pre		
		Ratio	0.11	
		P-value	< 0.0001	

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study IMA-06-02 (TOP) is an observational study of patients with relapsing remitting multiple sclerosis (RRMS) receiving natalizumab as a single disease-modifying agent in a clinical practice setting, with patients followed for approximately 10 years. This study was designed to evaluate the long-term safety profile of natalizumab and the long-term effect of natalizumab on disease activity and disability progression in clinical practice for patients have previously failed GA, beta-interferon and fingolimod. Eligible patients had a documented diagnosis of RRMS, with at least 1 relapse in the previous year, and were naïve to natalizumab at the initiation of natalizumab treatment (must not have had >3 natalizumab infusions prior to enrolment).

5623 MS patients from 391 study sites were analysed based on a data cut-off of 01 May 2014. The highest proportion of patients was from Germany (30.3%). The median age of the study population was 37 years and the ratio of female to male patients was 2.57 to 1.0. Similar demographics were seen in subgroups of patients whose last therapy before Tysabri infusion was glatiramer acetate, beta-interferon, or fingolimod.

Of the total patient population (n = 5623), prior to entry into this study, 547 patients (9.7%) were naïve to DMTs, 5076 patients (90.3%) had received $\geqslant$1 DMTs, and 2539 patients (45.2%) had received $\geqslant$2 DMTs.

Of the 5076 patients who received prior DMT(s), 3210 patients (57.1%) received beta interferon as their last therapy before dosing with natalizumab, 1354 patients (24.1%) received GA as their last therapy before dosing with natalizumab, and 130 patients (2.3%) received fingolimod as their last therapy before dosing with natalizumab.

The patients dosed in this study received a mean (standard deviation [SD]) of 29.6 (18.81) natalizumab infusions and a median of 27 natalizumab infusions (range: 1 to 90). Similar natalizumab exposure was seen in the subgroups of patients whose last therapy before natalizumab was GA or beta interferon. Fewer natalizumab infusions were seen in the fingolimod subgroup, with a mean (SD) of 14.2 (10.29) natalizumab infusions and a median of 13 natalizumab infusions (range: 1 to 59). Natalizumab exposure in the fingolimod subgroup was lower since its approval in Europe was more recent (i.e., 2011) than the other DMTs.

The primary endpoint of the study was long-term safety (incidence and pattern of SAEs) in patients receiving Tysabri. The chosen efficacy endpoints included clinical relapse rate (ARR), degree of disability (EDSS) and evaluation of baseline disease characteristics as prognostic indicators for disease activity and disability progression over time. An additional endpoint for this study was the evaluation of anti-JC virus (JCV) antibody prevalence in patients with MS for the duration of the study. The chosen endpoints are considered appropriate.

Efficacy data and additional analyses

As RRMS is characterized by unpredictable relapses the evaluation of ARR is deemed meaningful. The data from TOP showed a reduction in annualised relapse rate (ARR) from baseline at every time point tested. The pretreatment ARR (95% Confidence Interval (CI) decreased from 1.99 (1.96, 2.01) to 0.22 (0.21, 0.24) on Tysabri therapy ($p<0.0001$) and remained stable over time. The effect size for the subgroup of patients whose last therapy was fingolimod is similar to the effect sizes for the subgroups of

patients whose last therapy was GA or beta-interferon (which serve as internal controls).

For all subgroups, treatment with Tysabri significantly decreased the ARR ($p < 0.0001$). The pre-treatment ARR (95% CI) of 1.98 (1.93, 2.03) in patients whose last therapy was GA, decreased to 0.24 (0.22, 0.27) during Tysabri therapy. In patients whose last therapy was all commercially available beta-interferon, the pre-treatment ARR (95% CI) of 1.98 (1.94, 2.01) decreased to 0.21 (0.19, 0.22) during Tysabri therapy. In patients whose last therapy was fingolimod, the pre-treatment ARR of 2.06 (1.88, 2.26) decreased to 0.38 (0.28, 0.52) during Tysabri therapy.

In the total TOP population, the reduction in ARR remained stable over 5 years for the subgroup of patients whose last therapy prior to Tysabri infusion was GA or beta-interferon. For patients whose last therapy prior to Tysabri infusion was fingolimod, the reduction in ARR remained stable over 2 years (given later market entry). Data for the fingolimod subgroup after the 2 year period are less meaningful due to the smaller sample size (n=22 at 3 years; n$\leqslant$4 after 3 years).

EDSS evolution was used to assess disease progression. Sustained progression was defined as an increase in EDSS, sustained for at least 24 weeks, of at least 0.5 points from a baseline EDSS score $\geqslant$6.0, at least 1.0 points from a baseline EDSS score of 1.0 to <6.0, or at least 1.5 points from a baseline EDSS score of 0. Sustained improvement was defined as at least a 1-point decrease in EDSS sustained for at least 24 weeks for patients with baseline EDSS scores $\geqslant$2.

Mean EDSS scores were similar from Baseline (3.5) to Year 5 (3.2) in patients treated with Tysabri. Similar results were seen for the subgroups of patients whose last therapy prior to dosing with natalizumab was GA or beta interferon. For the fingolimod subgroup, less meaningful conclusions may be drawn due to the limited sample size ad due to the shorter Tysabri exposure (n=51 at year 1, n=15 at year 2 and n $\leqslant$4 after the 2 year period). From the limited data available, mean EDSS scores were similar from Baseline to Year 2. The time to sustained progression and time to sustained improvement based on EDSS scores were evaluated using Kaplan-Meier analysis. For the overall study population the cumulative probability of sustained EDSS improvement was evaluated and observed to be higher than the cumulative probability of sustained EDSS progression, (30.34% and 19.70%, respectively) at 5.5 years.

Similarly, the cumulative probability of sustained EDSS improvement was higher than the cumulative probability of sustained EDSS progression at all timepoints for the subgroup of TOP patients whose last therapy prior to Tysabri infusion was GA, beta-interferon, or fingolimod. For the fingolimod subgroup, the cumulative probability of sustained improvement at 24 months was 23.02%, and the cumulative probability of sustained progression at 24 months was 5.53. For the GA subgroup, the cumulative probability of sustained improvement at 5.5 years was 31.43%, and the cumulative probability of sustained progression at 5.5 years was 15.87%. For the beta-interferon subgroup, the cumulative probability of sustained improvement at 5.5 years was 29.43%, and the cumulative probability of sustained progression at 5.5 years was 21.44%. Due to the open label nature of the TOP study and due to the very high dropout rate, no conclusion may be drawn on an endpoint such as time to sustained improvement on EDSS.

The aim of the TOP interim analyses performed by the MAH was to demonstrate that, in a clinical practice setting, the type of prior treatment does not impact the safety or efficacy profile in patients with RRMS who are subsequently treated with natalizumab. However the majority of patients treated with natalizumab in the TOP study did not receive new DMTs prior to Tysabri treatment and were mainly (81%) treated with either beta interferon (n= 3210, 57%) or glatiramer acetate (GA) (n= 1354, 24%) as last treatment prior to starting Tysabri. Fingolimod was administered, as last treatment prior to starting Tysabri, to only 130 patients, while very few patients received teriflunomide or dimethyl fumarate prior to Tysabri (6 and 5 patients, respectively). Furthermore, the subgroup of patients who received fingolimod as last therapy before natalizumab was exposed to a lower number of Tysabri infusions (mean 14.29) compared to the subgroups of patients whose last therapy before natalizumab was GA or beta interferon

(mean respectively 29 and 31 natalizumab infusions). Results from the TOP study may thus provide only limited evidence of similar efficacy of Tysabri when administered after fingolimod. In addition, both the length of exposure to different DMTs prior to Tysabri as well as the sequence of treatments in patients (45%) who have assumed ⩾2 prior DMTs prior to the first Tysabri infusion are currently not specified. Similarly, frequency and reasons for Tysabri discontinuation and withdrawal from TOP study according to different MS drugs used prior to switching to Tysabri have not been stated and discussed. An update of the TOP efficacy data in the year after the cut-off date should be provided on the subgroup of patients who previously received a DMT different from GA or IFN beta.

Having highlighted the several limitations of the data derived from the TOP study, it is noted that overall efficacy data from the interim analysis presented in support of the present variation confirm the known efficacy profile of Tysabri and do not appear to raise new efficacy concerns.

Of note:

- Fingolimod is indicated for the same state of disease as Tysabri (highly active RRMS)
- The current indication for fingolimod is identical to the proposed new Tysabri indication (at least one disease modifying therapy (DMT)).
- Data for the fingolimod cohort are limited (N=130)
- No data are available for patients switching from prior DMF or teriflunomide therapy to Tysabri
- DMTs have different mechanisms of action compared to Tysabri. Efficacy of Tysabri could therefore be possible in patients who failed prior DMT therapy.

The MAH argued that according to the current indication of Tysabri patients in need for treatment of their highly active RRMS treated with other DMTs than GA and beta-interferon would need to be switched to beta-interferon or GA before being considered for treatment with Tysabri. For patients with moderate RRMS who started treatment with teriflunomide or DMF and subsequently experienced a worsening of their MS this would result in a prolongation of insufficient (mild to moderate) treatment although these patients were in need of a treatment for highly active disease to reduce the risk of exacerbations (relapses) and to slow the accumulation of disability.

In principle, this argumentation can be followed and while it is clear that the efficacy data from the TOP study are not adequate to clearly prove that the efficacy of Tysabri is not influenced by the type of DMT administered in the first line setting, there is however no reason to think that Tysabri would not be efficacious after failing of different first-line DMTs. The CHMP was of the view that there was a reasonable scientific plausibility that even if treatment with teriflunomide and/or dimethyl fumarate failed due to lack of efficacy, the treatment with fingolimod would be effective. Given the current situation and the available therapeutic options in clinical practice, the CHMP considered that it would be unreasonable to expect separate data to be provided in patients treated with each of the marketed drugs.

However, the main concern with Tysabri use after new DMTs, all endowed with immunosuppressive properties, is the increased risk of PML. A recent abstract presented at the American Academy of Neurology in Washington (Herbert et al, 2015) discussed preliminary data coming from a multicentre retrospective study of extended dosing of natalizumab in 886 patients, suggesting that increasing Tysabri dosing interval may be a strategy for mitigating risk of PML while maintaining efficacy. In this regard, it is of note that 2,211 out of 5,623 patients (39.3%) in the TOP study did not receive Tysabri every month. Further data have been requested on this subgroup of patients, with regard to dosing schedule, efficacy and safety, in order to understand if Tysabri safety profile could be favourable affected by changing in the schedule and if further studies addressing the issue should be required post-approval.

The MAH stated that the current request of extension of indication is not advocating earlier treatment of patients with Tysabri than indicated in the current approved label, and this was agreed by CHMP.

2.4.3. Conclusions on the clinical efficacy

A reduction of the ARR was found following treatment with Tysabri after failure of at least one DMT for patients who failed prior therapy with GA and beta-interferon. Switching to Tysabri resulted in a reduction in ARR compared to the pre-treatment ARR. A similar trend could be seen in patients with prior fingolimod therapy even though numbers are limited.

A further efficacy parameter in TOP was EDSS to evaluate disease progression. Mean EDSS scores were similar from Baseline (3.5) to Year 5 (3.2) in patients treated with Tysabri. For the overall study population the cumulative probability of sustained EDSS improvement was evaluated and observed to be higher than the cumulative probability of sustained EDSS progression, (30.34% and 19.70%, respectively) at 5.5 years. The EDSS scale has been questioned in the past for its ability to detect clinically meaningful improvement in disability. Sustained EDSS as potential indicator of neurological improvement has been evaluated, although further research is needed to validate its use as an MS clinical outcome (Phillips et al, 2011). Due to the open label nature of the TOP study and due to the very high dropout rate, no conclusion may be drawn on a untested endpoint such as time to sustained improvement on EDSS.

Taking into account that fingolimod and Tysabri are both indicated for highly active forms of RRMS and a switch from fingolimod to Tysabri showed a positive trend towards efficacy it could be assumed that patients with prior teriflunomide and DMF therapy would benefit from a switch to Tysabri especially as these DMTs are indicated for less severe forms of RRMS. However, the TOP study did not provide any efficacy data for patients switching from prior teriflunomide and DMF therapy to Tysabri and in the absence of a control group the observed treatment effects are prone to bias and have to be interpreted with caution.

The MAHs proposal to extend the indication for Tysabri is comprehensible considering the introduction of new therapeutic options in the MS treatment over the past years and the corresponding changes to current MS treatment guidelines.

Tysabri is one of the most efficacious DMTs currently available in patients with RRMS. From a biological perspective, there is no reason why Tysabri efficacy should be different according to the type of first line DMT. Overall the data presented support the MAH's view that beneficial effect of Tysabri is observed irrespective of initial first line treatment, even though it must be emphasized that only limited data are available (in terms of number of patients and time of exposure) for patients switching from fingolimod to Tysabri.

2.5. Clinical safety

Introduction

The safety profile of Tysabri has been evaluated extensively in clinical trials, post-marketing observational studies and postmarketing passive surveillance. In placebo-controlled trials in 1,617 MS patients treated with natalizumab for up to 2 years (placebo: 1,135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse reactions (placebo: 39.6%). The highest incidence of adverse reactions identified from placebo-controlled trials in multiple sclerosis patients with natalizumab given at the recommended dose, are reported as dizziness, nausea, urticaria

and rigors associated with infusions.

The major safety concern remains the risk of developing PML (and IRIS). As a safety precaution physicians must discuss the benefits and risks of Tysabri therapy with the patient and provide them with a Patient Alert Card.

Prior immunosuppressants use was originally identified as a risk factor for PML development based on data from the global TYGRIS study, which showed that Tysabri-treated patients with prior immunosuppressants use have a 4-fold greater risk of PML than patients with no prior immunosuppressants use. Because prior immunosuppressants status was not available for all Tysabri-treated patients in the post-marketing setting, data on prior immunosuppressants use in the TYGRIS study was utilized with the assumption that it would be representative of the overall Tysabri-treated population. Further characterization of prior immunosuppressants use on the risk of PML events following Tysabri administration obtained from a combined clinical study dataset from STRATA, TOP, and TYGRIS studies failed to identify any pattern or trend with regard to PML risk associated with type and duration of immunosuppressants treatment, or length of washout period. It is thus not possible at present to assume that a long washout period may decrease the risk of PML associated with prior use of immunosuppressants. In parallel to this assessment, at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004, a procedure was started to assess if, in view of existing evidence, there was a need to update the product information and/or the risk management plan, or to take any other regulatory measure for Tysabri in relation to PML risk. As scientific evidence on PML is rapidly growing, there was a need to assess whether, in view of current knowledge, the risk of PML is adequately described and risk minimisation measures were optimal. The procedure was finalized in February 2016 and the Committees concluded that:

- PML which is clinically asymptomatic at diagnosis represents more frequently localised disease in MRI, with a higher survival rate and better clinical outcome as compared to symptomatic PML. Early diagnosis of PML appears to be associated with improved outcomes.
- As a consequence, it was recommended that more frequent MRI screening for PML (e.g. every 3-6 months) using an abbreviated MRI protocol should be considered in patients at higher risk of development of PML.
- In patients who have not received prior immunosuppressant therapy and are anti-JCV antibody positive, the level of anti-JCV antibody response (index) is associated with risk of developing PML. Current evidence suggests that risk increases with increasing antibody index but there is no clear cut off value. In patients treated for longer than 2 years, the risk of PML is low at index values of 0.9 or less, and increases substantially at values above 1.5.
- It was recommended that patients with low anti-JCV antibody index who have not received prior immunosuppressant therapy should be retested every six months once they reach the 2-year treatment point.
- It was considered necessary to update the existing educational material, particularly in relation to the risk estimates for development of PML in Tysabri-treated patients.

Other important identified risks with natalizumab are:

- <u>Opportunistic infections</u>

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of cryptosporidium diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some

of which were fatal. 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, there have been reports of serious cases, including one fatal case of herpes encephalitis.

- Immunogenicity

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of TYSABRI and an increased incidence of hypersensitivity reactions. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing.

- Hepatic events

Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post marketing phase.

An important potential risk with the use of Tysabri is malignancies (see relevant sections of the SmPC and of the RMP).

In a different ongoing procedure the MAH submitted data from the Pregnancy Registry (101MS401) which is a category 3 MEA study listed in the Risk Management Plan. In this procedure the MAH was requested to update Section 4.6 of the SmPC with regards to available data from the pregnancy registry and the risk for transient effect on haematological parameters for newborns of mothers exposed to Tysabri during pregnancy.

Patient exposure

Table 8 Patient exposure

	Patients exposed	**Patients exposed to the proposed dose range**	**Patients with long term* safety data**
Placebo-controlled clinical trials **(information obtained from RMP)**	**1441**	**1271**	**Up to 6 months: 1158** **Up to 12 months:** **1117** **Up to 18 months:** **1088**
TOP study (post marketing)	**5623**		**≥ 6 months: 5299** **≥ 12 months: 4843**

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Adverse events

Adverse events associated with the use of Tysabri include fatigue, allergic reaction, hypersensitivity reactions, anxiety, pharyngitis, sinus congestion, and peripheral oedema. In this trial focus was put on the evaluation of the incidence and pattern of SAEs.

Serious adverse event/deaths/other significant events

In TOP the safety of Tysabri is being assessed by collecting data on the incidence of non-MS-related serious adverse events (SAEs), including all serious infections, regardless of causality.

Prescribers of Tysabri were aware of the possibility that PML and other opportunistic infections could occur during this therapy. Therefore, opportunistic infections were considered in their differential diagnosis of all infections and any new or worsening neurological symptoms that occurred in Tysabri-treated patients. For this purpose, Biogen Idec established Tysabri MS patient management algorithms ("Physician Information and Management Guidelines for MS Patients on Tysabri Therapy"). The clinician evaluated the patient to determine whether the symptoms were indicative of neurological dysfunction, and if so, whether these symptoms were typical of MS or possibly suggestive of PML or other opportunistic infections. If they were suggestive of PML, or if any doubt existed, further evaluation was considered, including an MRI scan (compared with MRI prior to therapy), cerebrospinal fluid testing for JCV DNA, and repeat neurological assessments. If new neurological symptoms suggestive of PML occurred, further Tysabri dosing was to be suspended until PML had been excluded. Once the clinician had excluded PML, dosing of Tysabri could resume.

Overall, 550 of 5623 patients (9.8%) experienced at least 1 SAE, and 197 patients (3.5%) experienced at least 1 SAE that was considered related to natalizumab. The system organ classes (SOCs) with the highest incidence of SAEs were infections and infestations (160 patients, 2.8%) and nervous system disorders (96 patients, 1.7%). No single SAE occurred in more than 0.5% of patients. The most common SAEs were progressive multifocal leukoencephalopathy (PML) (30 patients [26 confirmed and 4 suspected], 0.5%), hypersensitivity (26 patients, 0.5%), immune reconstitution inflammatory syndrome (IRIS) (20 patients, 0.4%), pneumonia (16 patients, 0.3%), spontaneous abortion (16 patients, 0.3%), herpes zoster (15 patients, 0.3%), multiple sclerosis (MS) relapse (15 patients, 0.3%), depression (14 patients, 0.2%), MS (11 patients, 0.2%), and epilepsy (11 patients, 0.2%). Nineteen of 20 patients with IRIS also had PML.

The SAE data for the GA and beta interferon subgroups were similar to the safety data observed for the total population. In the fingolimod subgroup, a lower incidence of SAEs was observed (7 of 130 patients, 5.4%) than in the total population (550 of 5623 patients, 9.8%). The SAEs reported by the 7 patients comprised 12 preferred terms (PTs). As in the total TOP population, the highest incidence of SAEs in the fingolimod subgroup was observed in the infections and infestations SOC, with 3 patients reporting SAEs within 5 PTs (cystitis, infectious enterocolitis, herpes zoster, septic encephalopathy, and urinary tract infection). In the nervous system disorders SOC, 3 patients reported SAEs within 3 PTs (dementia, MS relapse, and neuralgia). The following events were also reported in 1 patient each: gastritis, neutralising antibodies, intervertebral disc protrusion, and spontaneous abortion. No SAE was reported in more than 1 patient.

The overall PML incidence rate was 4.6/1000 (95% confidence interval: 3, 6.8) based on confirmed cases of PML. The median number of natalizumab infusions prior to the report of PML (both confirmed and suspected cases) was 36.5, with number of infusions ranging from 11 to 54. Twenty five of the 30 reported PML cases occurred in patients receiving natalizumab for more than 2 years. Anti-JC virus (JCV) antibody status was available for 10 of the patients with PML, and all 10 patients were anti-JCV antibody positive. Eight PML patients previously used immunosuppressants, 3 within the last 24 months before

receiving natalizumab.

Table 9 Medical History of Patients Included in TOP: History of Immunomodulator or Immunosuppressant Use and Treatment for Multiple Sclerosis Prior to First Tysabri Infusion (PML Patients)

	Total - n/N (%)		
Specific Medications	Ever Used	Used in the past 24 months [1]	Last medication prior to starting Tysabri [2]
Patients using one or more Interferon beta products	26/ 30 (86.7%)	22/ 30 (73.3%)	19/ 30 (63.3%)
Interferon beta 1-a (Avonex)	8/ 30 (26.7%)	3/ 30 (10.0%)	4/ 30 (13.3%)
Interferon beta 1-b (Betaferon/Betaseron/Extavia)	11/ 30 (36.7%)	9/ 30 (30.0%)	8/ 30 (26.7%)
Interferon beta 1-a (Rebif)	12/ 30 (40.0%)	10/ 30 (33.3%)	7/ 30 (23.3%)
Glatiramer acetate (Copaxone)	11/ 30 (36.7%)	10/ 30 (33.3%)	9/ 30 (30.0%)
Fingolimod (Gilenya)	1/ 30 (3.3%)	1/ 30 (3.3%)	0
Immunosuppressants (IS)	8/ 30 (26.7%)	3/ 30 (10.0%)	1/ 30 (3.3%)
Mitoxantrone (Novantrone)	4/ 30 (13.3%)	1/ 30 (3.3%)	0
Azathioprine (Imuran)	5/ 30 (16.7%)	2/ 30 (6.7%)	1/ 30 (3.3%)
Cyclophosphamide (Cytoxan)	2/ 30 (6.7%)	0	0
Cyclosporin (Sandimmune)	1/ 30 (3.3%)	0	0
Other	3/ 30 (10.0%)	3/ 30 (10.0%)	2/ 30 (6.7%)

Included patients: 1) Consent provided; 2) Criteria met; 3) <=3 doses of Tysabri at enrollment.
Includes patients with confirmed and pending progressive multifocal leukoencephalopathy.
[1] Stop date is within 24 months of the first Tysabri infusion.
[2] Last medication stopped before the first Tysabri infusion.

There were 60 patients (1.1%) diagnosed with a neoplasm, and 41 of these events in 39 patients (0.7%) were malignant. The most frequently reported malignancy was breast cancer (n = 11). Leukaemia was diagnosed in 5 patients: 2 patients with chronic lymphocytic leukaemia (CLL), 2 with chronic myeloid leukaemia, and 1 with acute promyelocytic leukaemia. Thyroid cancer, renal carcinoma (1 patient also had CLL and 1 patient also had colon cancer), and melanoma (1 in situ and 1 ocular) were each diagnosed in 3 patients. Lung carcinoma, cervical cancer (1 in situ), and colon cancer were each diagnosed in 2 patients. The other cancer diagnoses (carcinoma of ampulla of Vater, ovarian cancer, testicular cancer, rectal cancer, basal cell carcinoma, Waldenstrom macroglobulinemia, gliobastoma, oligodendroglioma, chordoma, and bladder cancer) each occurred in 1 patient. The distribution of the type of malignancies in natalizumab-treated TOP patients is similar to that observed in the general population [Ferlay 2013].

Seventeen deaths (0.3% of patients) occurred during the TOP study as of 01 May 2014. Six deaths were attributed to suicide; 2 deaths were attributed to pulmonary embolism; and 1 death each was attributed to colon cancer, lung cancer, IRIS following PML (patient had brain oedema), urosepsis (patient had ongoing PML), autonomic nervous system imbalance, respiratory failure (patient had ongoing PML), drowning, benzodiazepine overdose, and unknown cause. With the exception of PML-related deaths, the reported deaths in TOP appear to be consistent with the fatal events observed in the general MS population.

Table 10 Adverse events in the different subgroups according to previous treatment

SAE by SOC and	Total	Glatiramer	Interferon	Fingolimod

MedDRA	N=5623	**acetate (Copaxone)** N=1352	N=3186	**(Gilenya)** N=130
at least 1 SAE	550/5623 (9.8%)	139/1352 (10.3%)	314/3186 (9.9%)	7/130 (5.4%)
Infections and infestations	160/5623 (2.8%)	41/1352 (3.0%)	92/3186 (2.9%)	3/130 (2.3%)
Nervous system disorders	96/5623 (1.7%)	23/1352 (1.7%)	55/3186 (1.7%)	3/130 (2.3%)
Immune system disorders	60/5623 (1.1%)	12/1352 (0.9%)	40/3186 (1.3%)	n.a.
Neoplasm	55/5623 (1.0%)	16/1352 (1.2%)	27/3186 (0.8%)	n.a.
Injury, poisoning and procedural complications	50/5623 (0.9%)	11/1352 (0.8%)	29/3186 (0.9%)	n.a.
Psychiatric disorders	46/5623 (0.8%)	n.a.	23/3186 (0.7%)	n.a.
Gastrointestinal disorders	36/5623 (0.6%)	7/1352 (0.5%)	20/3186 (0.6%)	1/130 (0.8%)
Musculoskeletal and connective tissue disorders	34/5623 (0.6%)	6/1352 (0.4%)	22/3186 (0.7%)	1/130 (0.8%)
Pregnancy, puerperium and perinatal conditions	24/5623 (0.4%)	7/1352 (0.5%)	13/3186 (0.4%)	1/130 (0.8%)
General disorders and administration site conditions	19/5623 (0.3%)	5/1352 (0.4%)	11/3186 (0.3%)	n.a.
Vascular disorders	17/5623 (0.3%)	3/1352 (0.2%)	9/3186 (0.3%)	
Renal and urinary disorders	16/5623 (0.3%)	4/1352 (0.3%)	10/3186 (0.3%)	n.a.
Respiratory, thoracic and mediastinal disorders	16/5623 (0.3%)	4/1352 (0.3%)	n.a.	n.a.
Surgical and medical procedures	16/5623 (0.3%)	6/1352 (0.4%)	8/3186 (0.3%)	n.a.
Hepatobiliary disorders	15/5623 (0.3%)	10/1352 (0.7%)		n.a.
Cardiac disorders	14/5623 (0.2%)		8/3186 (0.3%)	n.a.
Reproductive system and breast disorders	13/5623 (0.3%)	2/1352 (0.1%)	6/3186 (0.2%)	n.a.
Blood and lymphatic system disorders	12/5623 (0.2%)	1/1352 (0.1%)	6/3186 (0.2%)	n.a.
Investigations	10/5623 (0.1%)	2/1352 (0.1%)	6/3186 (0.2%)	1/130 (0.8%)
Skin and subcutaneous tissue disorders	8/5623 (0.1%)	2/1352 (0.1%)	6/3186 (0.2%)	n.a.
Ear and labyrinth disorders	6/5623 (0.1%)	n.a.	4/3186 (0.1%)	n.a.
Eye disorders	4/5623 (0.1%)	n.a.	2/3186 (0.1%)	n.a.
Metabolism and nutrition disorders	4/5623 (0.1%)	n.a.	1/3186 (0.0%)	n.a.
Endocrine disorders	3/5623 (0.1%)	n.a.	3/3186 (0.1%)	n.a.
Congenital, familial and genetic disorders	2/5623 (0.0%)	n.a.	1/3186 (0.0%)	n.a.
Social	1/5623 (0.0%)	1/1352 (0.1%)	n.a.	n.a.

circumstances				

Updated Safety information: Patients switching from fingolimod to Tysabri (147 patients as of May 2015; previously 130 patients)

For the SOCs with the greatest number of events overall (e.g., 3 events each in infections and infestations, nervous system disorders), the SAE incidence rates for the subgroup of patients who previously received fingolimod are comparable to the prior GA and prior interferon subgroups. The incidence rates for SAEs in the SOC of Infections and Infestations in patients who previously received fingolimod, GA and interferon were 1.41, 1.32 and 1.19 per 100 patient years, respectively. The incidence rates for previous fingolimod, GA and interferon subgroups for the SOC of Nervous system disorders were 1.41, 0.84 and 0.67 per 100 patient years, respectively. For the remaining SOCs which contained only a single SAE, the incidence rates were somewhat less similar among subgroups who last used fingolimod, GA or interferon. While subject year adjusted incidence rates (instead of percentages) generally provides a reliable means for comparison of safety across studies of longer duration when the rates are stable, the SAE rates for patients last exposed to fingolimod are less stable due to the relatively small sample size (N=147) compared with the GA (N=1384) and interferon (N=3255) groups, and the small number (e.g., 3 or fewer) of events within each SOC for patients last exposed to fingolimod. For instance, the SOC of pregnancy, puerperium and perinatal conditions for patients who received prior fingolimod had a single event among 212 patient years which provides a less stable estimate of the incidence (e.g., each additional event results in a greater change in the rate), as compared to the prior interferon subgroup which had 19 events among 8889 patient years.

Table 11 Incidence of Serious Adverse Events (SAEs) By MedDRA System Organ Class and Preferred Term in Descending Frequency for Patients whose Last Therapy Prior to Natalizumab was Fingolimod

System Organ Class Preferred Term (MedDra)	N=147	Incidence Rate (per 100 Patient-Years)
Infections and infestations	3/ 212	1.41
Cystitis	1/ 212	0.47
Enterocolitis infectious	1/ 212	0.47
Herpes zoster	1/ 212	0.47
Septic encephalopathy	1/ 212	0.47
Urinary tract infection	1/ 212	0.47
Nervous system disorders	3/ 212	1.41
Dementia	1/ 212	0.47
Multiple sclerosis relapse	1/ 212	0.47
Neuralgia	1/ 212	0.47
Gastrointestinal disorders	1/ 212	0.47
Gastritis	1/ 212	0.47
Investigations	1/ 212	0.47
Neutralising antibodies	1/ 212	0.47
Musculoskeletal and connective tissue disorders	1/ 212	0.47
Intervertebral disc protrusion	1/ 212	0.47
Pregnancy, puerperium and perinatal conditions	1/ 212	0.47
Abortion spontaneous	1/ 212	0.47

Included patients: 1) Consent provided; 2) Criteria met; 3) <=3 doses of Natalizumab at enrollment.
Collection of SAEs begins at time of TOP enrollment.
For incidence calculation, a patient is counted once per system organ class or preferred term.
The SAEs beyond 6-month onset after the Natalizumab discontinuation are not included in the summary.

Updated Safety Information: Patients switching from teriflunomide (7 cases as of 01 May 2015, previously 6), and dimethyl fumarate (still 5 cases as before) to Tysabri.

For the 5 patients who switched to Tysabri from dimethyl fumarate, there were no SAEs reported. For the 7 patients who switched to Tysabri from teriflunomide, one SAE occurred (PT: sepsis and urinary tract infection). This single SAE with a PT of sepsis and urinary tract infection in the subgroup last exposed to teriflunomide (subject year exposure = 16 patient years) results in an incidence rate of 6.21 per 100 patient years for the infections and infestations SOC. Although this rate is greater than the incidence rate

for those previously exposed to the more established DMTs of GA and interferon (1.32 and 1.19 per 100 patient years, respectively), this likely reflects variation attributable to the relatively small sample size of those last exposed to teriflunomide. Therefore, the incidence rate does not appear meaningful.

The subgroup(s) of patients in TOP who last received treatment with teriflunomide included 7 patients with a mean and median exposure to teriflunomide of 26.1 (±19.87) months and 28.2 months, respectively (range 4.4 to 50 months). A subset of these 7 patients also received other therapies prior to teriflunomide (6 patients received IFN, 3 received GA).

The subgroup of patients enrolled in TOP who last received dimethyl fumarate prior to switching to Tysabri included 5 patients with mean and median exposure to dimethyl fumarate of 13.1 (±8.04) and 14.2 months, respectively (range 4.4 to 22.9 months). Of these 5 patients, a subset of these patients also previously received other therapies prior to dimethyl fumarate (4 patients received IFN, 2 patients received GA, 1 patient received fingolimod).

Exposure to NATALIZUMAB was based on time from first dose to date of discontinuation/withdrawal/last visit, assuming doses every 28 days, and including NATALIZUMAB infusions received prior to TOP enrollment. Missed doses were subtracted out. Exposure to Tysabri for patients whose last medication was teriflunomide had a mean and median of 30.6 and 26.0 respectively (range from 1.0 to 73.0 months) which is similar to Tysabri exposure for patients last exposed to dimethyl fumarate (mean and median of 31 and 36.0 respectively, range 9.0 to 52.0 months).

In summary, the small sample size for prior teriflunomide and dimethyl fumarate patient subgroups, most probably due to the recent approval of these DMTs and the closure date of enrollment for TOP, precludes meaningful analysis. Nonetheless, the data reflect useful experience to date for patients previously treated with these recently approved DMTs switching to Tysabri for efficacy reasons.

Additional safety data from ongoing studies

Spontaneously reported post marketing data collected outside the US are extremely limited as prior DMT use is not typically reported. Within the US, all patients receiving Tysabri are enrolled in the TOUCH Prescribing Program where the last MS therapy received prior to starting Tysabri is routinely collected. Therefore, the MAH has performed a review of the safety data in patients switching from other DMTs to Tysabri in TOUCH. Regarding TYGRIS (Tysabri Global Observational Program in Safety), the enrollment closed in 2009 prior to the marketing authorizations of fingolimod, dimethyl fumarate, teriflunomide and alemtuzumab and therefore all patients in TYGRIS who had prior DMT use before starting Tysabri had received interferon-beta and/or glatiramer acetate.

Review of Safety Data from MS Patients Ever Enrolled in TOUCH Stratified by Prior DMT used before starting Tysabri

The Tysabri global safety database was searched for HCP confirmed serious adverse events (SAEs) from MS patients ever enrolled in the TOUCH Prescribing Program as of 01 May 2015. The data were stratified based on the last DMT received by the patient before enrolling in TOUCH as provided on the TOUCH Enrollment Form. The TOUCH Enrollment Form has been updated over time to include patients switching from the newer approved DMTs; however, information on patients switching from alemtuzumab to Tysabri is not available yet as the Enrollment Form is currently in the process of being updated to include prior treatment with alemtuzumab. Given the mechanism of action of alemtuzumab and its prolonged impact on immune function, it is not anticipated that there will be many patients switching from that therapy to Tysabri unless the benefit clearly outweighs the risk for the patient. The current analysis from TOUCH will focus on safety data in patients switching from the following DMTs to Tysabri: fingolimod, dimethyl fumarate and teriflunomide. Comparison of the SAEs by MedDRA (version 18.0) System Organ

Classes (SOC) is shown in Table 12

Table 12 SAEs from MS patients ever enrolled in TOUCH as of 01 May 2015 stratified by prior DMT (fingolimod, dimethyl fumarate, teriflunomide).

	All TOUCH MS Patients		Switched from Fingolimod		Switched from Dimethyl fumarate		Switched from Teriflunomide	
Total Population (n)	73,968 (192,641 p-yrs)		1,710 (2,691 p-yrs)		1,783 (2,691 p-yrs)		274 (309 p-yrs)	
With at least 1 SAE	7,672 (3.98 per 100 p-yrs)		97 (3.60 per 100 p-yrs)		88 (3.27 per 100 p-yrs)		10 (3.23 per 100 p-yrs)	
SOC	# SAEs	# Patients (per 100 p-yrs)	# SAEs	# Patients (per 100 p-yrs)	# SAEs	# Patients (per 100 p-yrs)	# SAEs	# Patients (per 100 p-yrs)
Nervous system disorders	3174	2,438 (1.27)	39	31 (1.15)	39	28 (1.04)	4	4 (1.29)
Infections and infestations	3396	2,292 (1.19)	24	17 (0.63)	23	18 (0.67)	4	3 (0.97)
General disorders and administration site conditions	1310	1,164 (0.60)	19	15 (0.56)	10	10 (0.37)	3	3 (0.97)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	947	838 (0.44)	15	14 (0.52)	9	8 (0.3)	0	0 (0)
Injury, poisoning and procedural complications	1183	795 (0.41)	11	8 (0.30)	19	10 (0.37)	0	0 (0)
Respiratory, thoracic and mediastinal disorders	693	574 (0.3)	3	3 (0.11)	6	6 (0.22)	0	0 (0)
Gastrointestinal disorders	685	502 (0.26)	6	6 (0.22)	9	7 (0.26)	0	0 (0)
Surgical and medical procedures	536	494 (0.26)	7	6 (0.22)	13	10 (0.37)	3	2 (0.65)
Psychiatric disorders	589	485 (0.25)	9	8 (0.30)	8	7 (0.26)	2	1 (0.32)
Musculoskeletal and connective tissue disorders	550	450 (0.23)	8	7 (0.26)	3	3 (0.11)	0	0 (0)
Immune system disorders	421	408 (0.21)	3	3 (0.11)	5	5 (0.19)	0	0 (0)
Cardiac disorders	466	393 (0.20)	3	3 (0.11)	3	3 (0.11)	3	2 (0.65)
Vascular disorders	335	308 (0.16)	0	0 (0)	1	1 (0.04)	0	0 (0)
Renal and urinary disorders	328	289 (0.15)	5	4 (0.15)	1	1 (0.04)	0	0 (0)
Investigations	333	274 (0.14)	0	0 (0)	2	1 (0.04)	1	1 (0.32)
Metabolism and nutrition disorders	275	224 (0.12)	4	3 (0.11)	1	1 (0.04)	0	0 (0)
Pregnancy, puerperium and perinatal conditions	240	215 (0.11)	4	4 (0.15)	3	3 (0.11)	0	0 (0)
Skin and subcutaneous tissue disorders	191	169 (0.09)	4	3 (0.11)	0	0 (0)	0	0 (0)
Hepatobiliary disorders	183	160 (0.08)	1	1 (0.04)	3	3 (0.11)	0	0 (0)
Blood and lymphatic system disorders	175	148 (0.08)	2	2 (0.07)	2	2 (0.07)	0	0 (0)
Reproductive system and breast disorders	96	87 (0.05)	1	1 (0.04)	0	0 (0)	0	0 (0)
Eye disorders	69	63 (0.03)	0	0 (0)	0	0 (0)	0	0 (0)
Congenital, familial and genetic disorders	43	35 (0.02)	0	0 (0)	0	0 (0)	0	0 (0)
Ear and labyrinth disorders	24	22 (0.01)	1	1 (0.04)	0	0 (0)	0	0 (0)

	All TOUCH MS Patients		Switched from Fingolimod		Switched from Dimethyl fumarate		Switched from Teriflunomide	
Total Population (n)	73,968 (192,641 p-yrs)		1,710 (2,691 p-yrs)		1,783 (2,691 p-yrs)		274 (309 p-yrs)	
With at least 1 SAE	7,672 (3.98 per 100 p-yrs)		97 (3.60 per 100 p-yrs)		88 (3.27 per 100 p-yrs)		10 (3.23 per 100 p-yrs)	
SOC	# SAEs	# Patients (per 100 p-yrs)	# SAEs	# Patients (per 100 p-yrs)	# SAEs	# Patients (per 100 p-yrs)	# SAEs	# Patients (per 100 p-yrs)
Endocrine disorders	18	17 (0.01)	0	0 (0)	0	0 (0)	0	0 (0)
Social circumstances	13	12 (0.01)	0	0 (0)	0	0 (0)	0	0 (0)

SAEs in the overall TOUCH population

As of 01 May 2015, there were 73,968 MS patients (192,641 person-years) ever enrolled in the TOUCH program since it started in June 2006. Of these patients, 7,672 patients (3.98 per 100 person-years) experienced at least 1 SAE. The SOCs with the highest frequencies of SAEs were nervous system disorders (2,438 patients, 1.27 per 100 person-years), infections and infestations (2,292 patients, 1.19 per 100 person-years), and general disorders and administration site conditions (1,164 patients, 0.60 per 100 person-years).The most common SAEs reported in all TOUCH patients were multiple sclerosis relapse (1,092 patients, 0.57 per 100 person-years), urinary tract infection (567 patients, 0.29 per 100 person-years), and pneumonia (442 patients 0.23 per 100 person-years).

SAEs in Patients Who Switched from Fingolimod to Tysabri

As shown in Table 12, 1,710 patients (2,691 person-years) switched from fingolimod to Tysabri within TOUCH, and of those, 97 patients (3.60 per 100 person-years) experienced at least 1 SAE. Similar to that reported for the overall TOUCH population, the SOCs with the highest frequencies of SAEs in patients switching from fingolimod to Tysabri included nervous system disorders (31 patients, 1.15 per 100 person-years), infections and infestations (17 patients, 0.63 per 100 person-years), and general disorders and administration site conditions (15 patients, 0.56 per 100 person-years). The most frequently reported SAEs included multiple sclerosis relapse (16 patients, 0.59 per 100 person-years), multiple sclerosis (6 patients, 0.22 per 100 personyears), and death (5 patients, 0.19 per 100 person-years; listed as an event with cause of death unknown).

There was 1 confirmed case of progressive multifocal leukoencephalopathy (PML) reported in a patient who switched from fingolimod to Tysabri. To date there have only been 3 cases of confirmed PML with prior fingolimod exposure and of those, only 1 case was reported from the US (Case ID 2014BI037626). This patient had received prior immunosuppressant (mycophenolate concurrently with IFN-beta) before switching to fingolimod for approximately 2-3 years from 2011 to 2013. The patient was then switched to Tysabri in Feb 2013, which was administered concurrently with etanercept for 3 months, and then the patient received Tysabri monotherapy for the last dose received in Oct 2014.

SAEs in Patients Who Switched from Dimethyl Fumarate to Tysabri

There were 1,783 patients (2,691 person-years) who switched from dimethyl fumarate (DMF) to Tysabri within TOUCH (Table 12). Of these patients, 88 patients (3.27 per 100 person-years) experienced at least 1 SAE. The SOCs with the highest frequencies of SAEs were similar to that for the overall TOUCH population and included nervous system disorders (28 patients, 1.04 per 100 person-years), followed by infections and infestations (18 patients, 0.67 per 100 personyears), general disorders and administration site conditions, injury, poisoning and procedural complications and surgical and medical procedures (10 patients in each, 0.37 per 100 personyears).

The most frequently reported SAEs were multiple sclerosis relapse (11 patients, 0.41 per 100 person-

years), pneumonia (6 patients, 0.22 per 100 person-years), multiple sclerosis and urinary tract infection (5 patients in each, 0.19 person-years). No PML cases were reported for this subgroup.

SAEs in Patients Who Switched from Teriflunomide to Tysabri

Of the 274 patients (309 person-years) who switched from teriflunomide to Tysabri within TOUCH, 10 patients (3.23 per 100 person-years) had at least 1 SAE. The number of patients with reported SAEs who had switched from teriflunomide to Tysabri is very small; however the SOCs with the highest frequencies of SAEs were similar to that for the overall TOUCH population and included nervous system disorders (4 patients, 1.29 per 100 person-years), infections and infestations, and general disorders and administration site conditions (3 patients each, 0.97 per 100 person-years). The most frequently reported SAE (reported in more than 2 patients) was multiple sclerosis relapse (3 patients, 0.97 per 100 person-years). No PML cases were reported for this subgroup.

PML

As of 01 May 2015, there were 35 confirmed cases of PML reported from the TOP study. The baseline demographics and characteristic of these cases are summarized in the following Table 13.

Table 13 Baseline Demographics and Characteristics of Confirmed PML Patients from the TOP Study (N = 35)

Country of Origin	Germany: 13 Italy: 4 Belgium, Canada, Spain and the Netherlands : 3 each Czech Republic and France: 2 each Greece and Norway: 1 each
Age (Years)	Mean (SD): 43.0 (9.1) Median: 45.0 Minimum: 22; Maximum: 61
Gender	Male: 10/35 (28.6 %) Female: 25/35 (71.4 %)
MS Disease Duration (Years)	Mean (SD): 9.42 (6.1) Median: 8.4 Minimum: 0.8; Maximum: 24.2
Baseline EDSS	Mean (SD): 3.36 (1.51) Median: 3.0 Minimum: 1.0; Maximum: 6.5
Number of Tysabri doses received at the time of PML diagnosis (total months or total infusions)	Mean (SD): 36.2 Median: 39.0 Minimum: 12 ; Maximum: 62

Prior DMTs received by patients with confirmed PML in the TOP study

Of the 35 PML patients in the TOP study, 33 (94.3%) reported prior use of at least one DMT before initiating Tysabri. Of the 33 patients with prior DMT use, 11 patients had received ⩾ 2 DMTs (33.3%).

The most frequently used DMTs were interferon beta products in 29 patients. The duration of prior interferon beta therapy in PML patients varied widely with a median of at least 26.1 months.

There were 11 patients who received prior glatiramer acetate with a duration that ranged from 3.2 to 81.6 months and a mean and a median of 25.9 and 15.3 months, respectively. Of the 33 PML patients who received prior DMTs, none of them received fingolimod, dimethyl fumarate, teriflunomide or alemtuzumab at any time prior to initiating Tysabri.

Prior IS therapies received by patients with confirmed PML in the TOP study

In the initial variation submission, with a data cut of 01 May 2014, the MAH reported 30 cases of PML in the TOP study including 26 confirmed cases and 4 suspect cases. Prior IS use was reported in 8 of these 30 patients. However, 2 of these 8 patients were cases of suspect PML at the time of the submission. Since that time, PML was ruled out in one case on 03 Jun 2014 (based on negative CSF JCV DNA, MRI finding inconsistent with PML and an alternative diagnosis) and a second case was assessed as low suspect for PML (based on MRI findings suspicious for PML but CSF JCV DNA that tested negative). Therefore, these two cases were not included in the updated prior IS analysis that follows.

Based on the updated review as of 01 May 2015, of the 35 confirmed cases of PML in the TOP study, 6 (17.1%) received prior IS therapy. As shown in Table 14, the prior IS therapies included mitoxantrone in 4 patients, azathioprine in 3 patients and cyclophosphamide in 1 patient. Two patients received more than one IS therapy including 1 patient who received cyclophosphamide and azathioprine, and another patient who received mitoxantrone and azathioprine. One patient received 2 different treatment regimens of mitoxantrone (approximately 31.5 months apart).

Table 14 Type and Duration of IS use, and Washout Period prior to Tysabri in PML Patients from the TOP Study (N=6)

Prior IS	Number of PML patients	Duration of IS treatment (months)	Washout period from last dose of IS to 1st dose of Tysabri (months)
Mitoxantrone*	4/35 (11.4%)	Mean (SD): 30.0 (31.96) Median: 18.6 Minimum: 6.6; Maximum: 76.3	Mean (SD): 37.2 (16.86) Median: 32.3 Minimum: 23.4; Maximum: 60.6
Azathioprine	3/35 (8.6%)	Mean (SD): 35.9 (24.52) Median: 48.9 Minimum: 7.6; Maximum: 51.1	Mean (SD): 28.8 (34.5) Median 14.5 Minimum: 3.9; Maximum: 68.2
Cyclophosphamide	1/35 (2.9%)	<1 month	Mean (SD): 38.4 (N/A) Median: 38.4 Minimum: 38.4; Maximum: 38.4

**One of the 4 patients with prior mitoxantrone received 2 courses of therapy approximately 31.5 months apart. Durations of both therapies were taken into account for the calculation of mean and median duration. The last dose of the second mitoxantrone course was used for the calculation of the mean and median washout period.*
A 28-day month is used in this summary.

Duration and washout periods of prior treatment with mitoxantrone and azathioprine in these PML patients varied widely. Only 1 patient had received cyclophosphamide. No specific pattern or trend was identified in the small number of PML patients with regard to their prior IS use.

Other prior therapies received by patients with confirmed PML in the TOP study

Two of the 35 confirmed PML patients from the TOP study reported the chronic use of systemic corticosteroids prior to initiation of Tysabri, which was categorized as "other" therapies in the previous submission. Additionally, in the initial submission, a third patient (a suspect PML case) with chronic use of systemic corticosteroids prior to Tysabri was also included in the "other" category. This case is not included in the current analysis since PML was assessed as a low suspect based on MRI finding suspicious for PML but CSF JCV that tested negative.

Duration of Tysabri therapy at the time of PML diagnosis in patients with or without prior IS use

The mean and median durations of Tysabri received at the time of PML diagnosis in the 6 PML patients with prior IS use are compared with those in the 29 PML patients without prior IS use as shown in Table 15.

Table 15 Duration of Tysabri treatment in TOP PML patients with and without prior IS use (N = 35)

PML patients	Tysabri treatment duration at the time of PML diagnosis (months)
With prior IS use (N = 6)	Mean (SD): 29.8 (11.4) Median: 30.5 Minimum: 12; Maximum: 43
Without prior IS use (N = 29)	Mean (SD): 38.3 (13.7) Median: 40.0 Minimum: 11; Maximum: 62

The mean and median durations of Tysabri treatment at the time of PML diagnosis appear to be greater in patient without prior IS.

In the 2 PML patients with no prior IS use who had received chronic systemic corticosteroids before initiation of Tysabri, the durations of Tysabri treatment at the time of PML diagnosis were 44 and 24 months.

Prior DMT, IS or other therapies use in the non-PML population in the TOP study

As of 01 May 2015, there were 5735 non-PML patients in the TOP study. The majority of the patients (5543/5735, 96.7%) had received one of the interferon beta products prior to initiating Tysabri, which included Avonex in 1813/5735 patients (31.6%), Betaferon/Betaseron/Extavia in 1671/5735 patients (29.1%) and Rebif in 2059/5735 patients (35.9%). There were 2003/5735 (34.9%) patients who had received glatiramer acetate.

A small number of patients had received the newer DMTs, which included fingolimod, dimethyl fumarate and teriflunomide (Table 16). None of the patients had received alemtuzumab prior to Tysabri.

Table 16 Prior use of fingolimod, Dimethyl Fumarate or Teriflunomide in the non-PML Population from the TOP study (N=5735)

Prior DMT	Number of patients (%)	Duration of prior therapy (months)	Washout period prior to starting Tysabri (months)
Fingolimod	170/5735 (3.0%)	Mean (SD): 12.7 (18.85) Median: 8.2 Minimum: <0.1; Maximum: 160.9	Mean (SD): 6.3 (8.25) Median: 3.8 Minimum: < 0.1; Maximum: 76.7
Dimethyl fumarate	9/5735 (0.2%)	Mean (SD): 20.7 (23.08) Median: 15.3 Minimum: 2.1 ; Maximum: 78.3	Mean (SD): 25.7 (26.94) Median: 14.0 Minimum: 0.9 ; Maximum: 71.6
Teriflunomide	15/5735 (0.3%)	Mean (SD): 18.5 (19.04) Median: 7.6 Minimum: 2.2; Maximum: 50	Mean (SD): 19.6 (18.10) Median: 12.8 Minimum: 2.1 ; Maximum: 55.4

A 28-day month is used in this summary.

Of the non-PML patients who had received the newer DMTs prior to the initiation of Tysabri, the duration of the washout period of the therapies varied with a wide range. Since none of the PML patients had received these newer DMTs, no comparisons can be made with regards to the duration and washout periods between these 2 populations.

There were 805 non-PML patients who had received prior IS before starting Tysabri. These IS therapies

included mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate, cyclosporin, tacrolimus, rituximab and cladribine. The duration and washout period for these prior IS therapies in non-PML patients from TOP are summarized below.

Table 17 Duration and washout period for prior IS therapies in non-PML patients from TOP

Prior IS therapy	Number of patients on IS (%)	Duration of the therapy (month)	Washout period prior to Tysabri (month)
Azathioprine	462/5735 (8.1%)	Mean (SD): 48.4 (49.25) Median: 33.7 Minimum: <0.1; Maximum: 348	Mean (SD): 43.2 (50.67) Median: 21.7 Minimum: 0.6; Maximum: 311.2
Mitoxantrone	264/5735 (4.6%)	Mean (SD): 13.5 (12.59) Median: 9.8 Minimum: <0.1; Maximum: 78.5	Mean (SD): 46.4 (38.87) Median: 35.9 Minimum: 1.6 ; Maximum: 236.7
Cyclophosphamide	125/5735 (2.2%)	Mean (SD): 9.4 (15.71) Median: 5.4 Minimum: <0.1; Maximum: 130.5	Mean (SD): 43.1 (50.15) Median: 30.4 Minimum: 1.3 ; Maximum: 338.4
Methotrexate	68/5735 (1.2%)	Mean (SD): 30.9 (30.35) Median: 21.2 Minimum: <0.1; Maximum: 117.4	Mean (SD): 38.8 (47.18) Median: 18.7 Minimum: 1.9; Maximum: 78.2
Mycophenolate	9/5735 (0.2%)	Mean (SD): 17.6 (11.35) Median: 13.1 Minimum: 1.1; Maximum: 36.0	Mean (SD): 16.8 (12.05) Median: 16.3 Minimum: 4.3; Maximum: 44.2
Cyclosporin	4/5735 (0.1%)	Mean (SD): 72.0 (41.66) Median: 75.66 Minimum: 19.6 Maximum: 117.4	Mean (SD): 53.8 (62.55) Median: 34 Minimum: 7.3; Maximum: 140.0
Tacrolimus	6/5735 (0.1%)	Mean (SD): 29.8 (27.88) Median: 24.5 Minimum: 3.3; Maximum: 77.3	Mean (SD): 40.9 (32.02) Median: 44.5 Minimum: 1.9; Maximum: 202.2
Rituximab	2/5735 (0.03%)	Mean (SD): 6.6 (0.03) Median: 6.6 Minimum: 6.6; Maximum: 6.6	Mean (SD): 52.5 (13.18) Median: 52.5 Minimum: 43.2 ; Maximum: 61.8
Cladribine	2/5735 (0.03%)	Mean (SD): 49.5 (50.00) Median: 495 Minimum: 14.1; Maximum: 84.9	Mean (SD): 5.1 (3.03) Median: 5.1 Minimum: 2.9; Maximum: 7.2

A 28-day month is used in this summary.

Among the IS used by the non-PML patients, azathioprine was the most commonly used. Duration of the IS therapies and washout periods varied with a wide range.

As shown in Table 17 that compares the type and duration of prior IS between PML and non-PML patients, there were 3 IS including azathioprine, mitoxantrone and cyclophosphamide that had been received by both PML and non-PML patients. With azathioprine, the proportion of non-PML patients who had received the therapy was similar to that of PML patients (8.1% versus 8.6%). With mitoxantrone, the proportion of patients who had received the therapy appeared to be higher (11.4%) in PML than in non-PML patients (4.6%). However, given the small number of PML patients, whether mitoxantrone is associated with higher risk of PML cannot be concluded. The duration of the IS therapies varied in both non-PML and PML patients with a wide range. No specific pattern or trend was identified regarding the type or duration of prior IS therapy and the occurrence of PML.

The washout periods from the last dose of the 3 IS therapies to the start of Tysabri for the non-PML and

PML patients in TOP were also compared, and are shown below.

Table 18 Comparison of the washout periods of prior IS use in non-PML and PML patients in TOP

IS	*Washout period of prior IS therapy to the start of Tysabri (months)	
	Non-PML patients	PML patients
Mitoxantrone	Mean (SD): 46.4 (38.87) Median: 35.9 Minimum: 1.6; Maximum: 236.7	Mean (SD): 37.2 (16.9) Median: 32.3 Minimum: 23.4; Maximum: 60.6
Azathioprine	Mean (SD): 43.2 (50.67) Median: 21.7 Minimum: 0.6; Maximum: 311.2	Mean (SD): 28.9 (34.5) Median 14.5 Minimum: 3.9; Maximum: 68.3
Cyclophosphamide	Mean (SD): 43.1 (50.15) Median: 30.4 Minimum: 1.3; Maximum: 338.4	38.4 months

**Washout period is defined as the duration from the last dose of prior IS to the first dose of Tysabri. A 28-day month is used in this summary.*

The washout periods for the 3 prior IS therapies received by non-PML and PML patients in TOP varied with a wide range. No specific pattern or trend was observed.

Additionally, there were 299 non-PML patients (299/5735, 5.2%) in TOP who had received chronic systemic corticosteroids, 71 patients (71/5735, 1.2%) who had received prednisone, 111 patients (111/5735, 1.9%) who had received immunoglobulins, and 59 patients (59/5735, 1.0%) who had received "other" therapies prior to starting Tysabri as reported and specified by the investigators on the Case Report Form (CRF). These "other' therapies included DMTs other than various interferon beta products, glatiramer, fingolimod, teriflunomide and DMF; immunosuppressive/antineoplastic medications other than those specified in Table 7; and steroids/immunoglobulins other than those specified on the CRF.

Potential increased risk/cumulative effect for the development of PML in patients switching from fingolimod and dimethylfumarate

The MAH performed an analysis of all confirmed PML cases in Tysabri-treated patients as of 27 July 2015. There were a total of 580 confirmed Tysabri-treated PML patients; 476 patients had prior disease modifying therapy (DMT) status available before initiating Tysabri, of which 450 (95%) reported prior use of at least one DMT. Of the 450 PML cases who reported prior DMT use, 30 cases did not specify the type of DMT received. Of the 420 cases that provided the type of prior DMT received, all 420 cases reported prior interferon-beta (IFN-beta) and/or glatiramer acetate (GA), with 3 of these cases also reporting prior fingolimod use and no cases reporting prior use of DMF.

The fact that all 420 PML cases with available information reported prior use of IFN-beta and/or GA is not surprising given that these are first line agents for the treatment of MS commonly used over the last two decades. Although both medications have immunomodulatory mechanisms of action, there is no evidence that prior use of IFN-beta or GA before switching to Tysabri is associated with a higher risk of PML.

The prior MS therapies received by the 3 Tysabri-associated PML cases with prior fingolimod exposure (Case IDs 2014BI003698, 2014BI037626, and 2014BI124637) are shown below in Table 19.

Two of the 3 PML cases (Case IDs 2014BI003698 and 2014BI124637) initially received Tysabri and then switched to fingolimod, and subsequently switched back to Tysabri prior to PML onset.

Table 19 Prior MS Therapies and Dosing Dates for 3 Tysabri PML Cases with Prior Fingolimod

Case ID	Prior MS therapies	Dosing dates
2014BI003698	IFN-beta	Apr 2006 – Jun 2009
	GA	Aug 2009 – Aug 2009
	Tysabri	Sept 2009 – Nov 2011
	Fingolimod – only one dose administered	Feb 2012 – Feb 2012
	Tysabri	Feb 2012 – Dec 2013
2014BI037626	IFN-beta	Jan 2000 – Jan 2011
	Mycophenolate mofetil (concurrent with IFN-beta)	2006 – 2011
	Fingolimod	2011 – 2013
	Etanercept (concurrent with Tysabri)	Feb 2013 – May 2013
	Tysabri	Feb 2013 – Feb 2014
2014BI124637	GA	May 2008 – Jul 2008
	IFN-beta	Aug 2008 – Aug 2008
	Tysabri	Sept 2009 – unknown date
	Fingolimod	Oct 2012 – Dec 2012
	Tysabri	Unknown date – Oct 2014

Comparability of the US and EU populations

Following the request from the CHMP the MAH has also reviewed the Tysabri-treated patient populations in the US and the EU with regards to demographics, disease characteristics and frequency of known risk factors using data derived from post-marketing and observational studies. A comparison of the demographic characteristics of US and EU patient-subgroups included in STRATIFY-2 (all patients from US), TOP (all patients from EU), and TYGRIS (Tysabri Global Observational Program in Safety - including patients from EU and US) is shown in Table 20. The average age of Tysabri-treated patients in these studies is lower in the EU patient population compared to those in the US. The gender distribution in these studies appears comparable between EU and US patient populations, with some minor between-study variation. The MAH has previously shown that age and gender are not risk factors for PML using the proportional hazards model on Tysabri exposure time. Consequently, although there are demographic differences between Tysabri-treated patients in the EU and the US based on these postmarketing and observational studies, the MAH believed that these differences were sufficiently small to have no impact on any conclusions that may be drawn about the PML risk in patients switching from the newer DMTs using a US-only patient population.

Table 20 Demographic Characteristics in the US and EU Populations Based on STRATIFY-2 (US), TOP (EU), and TYGRIS (US vs EU)

	US		EU	
	STRATIFY-2	TYGRIS	TOP	TYGRIS
Number of natalizumab-exposed patients at time of data cut-off	24,402	2,207	5,691	4,167
Age at study entry (years)				
Mean	44.1	44.6	37.1	37.7
Median	44.0	45.0	37.0	38.0
Range	8-86	16-76	12-70	15-72
Gender (%)				
Male	26%	24%	28%	28%
Female	74%	76%	72%	72%

Disease characteristics

As the baseline disease characteristics (as measured by EDSS and ARR) data have not been collected within TOUCH, a direct comparison of these characteristics between the EU and the US patient population within the TYGRIS study or between the TOP (all patients from EU) and the STRATIFY-2 (all patients from US) studies is not possible. However, the MAH has evaluated whether differences in these baseline disease characteristics impact the overall risk of PML. An assessment of data available from EU patients in the TOP and TYGRIS studies (see Table 21) demonstrates that baseline EDSS score, and number of relapses in the year prior to starting Tysabri treatment, are comparable between the PML and non-PML Tysabri-treated patients. Regardless of PML status, patients in TOP and TYGRIS experienced a median of 2 relapses during the year prior to Tysabri initiation. Baseline EDSS was also similar among patients with and without PML (median 3.0 vs 3.5; respectively). Furthermore, there is currently no available literature to suggest that EDSS and ARR at baseline are risk factors for PML or confounders in the association between Tysabri exposure and PML.

The MAH believed that whilst a direct comparison of the baseline disease characteristics in the EU and US patient population is not possible, any variations that may exist between the two patient populations should not contribute to any differences in PML risk. Their proposal is to provide the necessary safety data using the TOUCH patient cohort.

Table 21 Baseline EDSS in TYGRIS and TOP studies

	TYGRIS EU Population		TOP (EU)	
	Patients without PML	PML cases	Patients without PML	PML cases
Number of Relapse During the Year Prior to Enrollment				
N	4127	40	5735	35
Mean	2.4 ± 1.4	2.4 ± 1.6	2.0 ± 1.0	2.4 ± 1.4
Median	2.0	2.0	2.0	2.0
% with ≥ 3 relapses	35.0%	36.6%	24.2%	31.4%
Baseline EDSS score				
N	Not available		5693	35
Mean			3.5 ± 1.6	3.4 ± 1.5
Median			3.5	3.0
% ≥ 4			43%	43%
% ≥ 5			22%	20%

PML Risk Factors in US and EU Tysabri Treated Populations

A review of the data from STRATIFY-2, TYGRIS and TOP of the three known risk factors for PML in Tysabri treated patients (positive anti-JCV antibody status, prior immunosuppressant use and duration of treatment) show that there is some between-study and between-geographic variation (see Table 22). In particular the proportion of prior IS use recorded within the TYGRIS study is lower in the US than in EU. This is likely to reflect medical practice in the EU where immunosuppressants were more widely used to treat MS prior to the approval of Tysabri, and is not seen to the same extent in the TOP patient cohort. The mean and median Tysabri exposure also shows between-study variation but the range within the EU patient populations overlaps with the US and is broadly consistent across the two geographies.

Table 22 PML Risk Factors in the US and EU Populations based on STRATIFY-2 (US), TOP (EU), and TYGRIS (US and EU)

	US		EU	
	STRATIFY-2	TYGRIS	TOP	TYGRIS
Number of natalizumab-exposed patients at time of data cut-off	24,402	2,207	5,691	4,167
Natalizumab Exposure (total number of infusions at time of data cut-off) Mean Median Range	45.7 44.0 1-129	37.2 37.0 1-74	32.4 29.0 1-96	41.8 46.0 1-81
Prior IS Use; n(%*) Yes No Unknown	2,776 (12%) 21,082 (88%) 544	309 (14%) 1,898 (86%) 0	797 (14%) 4,894 (86%) 0	989 (24%) 3174 (76%) 4
Anti-JCV Antibody Status; n(%*) Positive Negative Unknown	13,716 (56%) 10,657 (44%) 29	1114 (61%) 707 (39%) 386	2,183 (58%) 1,608 (42%) 1,900	1618 (64%) 908 (36%) 1641

*Excluding missing data

In summary, it is clear that the populations are not identical and some variations exist. However, the MAH considered that the small differences in demographics and disease characteristics are unlikely to impact or confound the estimated risk of PML in Tysabri-treated patients. On the other hand, differences between geographic regions in terms of the known risk factors of PML could be addressed by the stratified PML risk estimates. Stratifying adjusts the analysis to account for the known differences that impact the precision of the risk estimate and therefore allows valid conclusions to be drawn from the data that are applicable to all Tysabri-treated patients, irrespective of geographical location. For example, the risk estimates for anti-JCV antibody positive patients remain valid regardless of the seroprevalence rate in a given geographic region.

Similarly, the risk estimate for year 3 of Tysabri treatment remains valid regardless the proportion of patients treated for 3 years or more in a given geographic region. The proposed stratification by risk factors is shown in Table 23 below. This stratification of the analysis will present the PML risk estimates, determined using the life table method, by yearly exposure interval for each prior DMT, for anti-JCV antibody positive patients without prior IS exposure.

The time to PML following initiation of Tysabri treatment can also be assessed using Kaplan Meier curves for each prior DMT among anti-JCV antibody positive patients without prior IS exposure.

Table 23 PML Risk Estimates per 1000 Patients (with 955 CIs)in anti-JCV Antibody Positive Patients by Year of natalizumab Exposure using Life Table Method

Natalizumab exposure	Anti-JCV Antibody Positive			
	Treatment Prior to Switch without prior use of IS*			
	IFN-β, GA	Fingolimod	DMF	Teriflunomide
1-12 Months				
13-24 Months				
25-36 Months				
37-48 Months				
49-60 Months				
61-72 Months				

*Based on TOUCH data.

Central nervous system herpes simplex Type I and II and herpes zoster

Cumulatively, as of 31 May 2015, a total of 4 cases of CNS herpes infections have been reported in TOP. From these, 2 events were caused by herpes simplex virus and 2 by varicella zoster virus. In all 4 cases, patients presented with typical signs and symptoms such as acute onset of fever, headache and seizures. In all 4 cases, diagnosis was made by detecting the viral (VZV or HSV) DNA in the CSF; 2 cases also reported brain MRIs showing lesions consistent with herpes encephalitis. Treatment for the event of meningitis and outcome was not provided in one case (2014BI071512); in all other cases it was reported these patients recovered upon discontinuation of Tysabri and initiation of acyclovir/valacyclovir. There were three patients who received previous MS therapies. From these, one had previous exposure to interferon beta 1-a, other to mycophenolate mofetil, and other to systemic corticosteroids.

Table 24 Events Of CNS Herpes Infections by Preferred Term

Preferred Term	Number of Cases
Herpes simplex meningoencephalitis	1
Herpes simplex encephalitis	1
Meningitis Herpes	2
Total	4

CNS=Central nervous system

The incidence of herpes appears to be higher in the TOP population (13.27/100,000 patient-years) compared to the estimated incidence of HSV encephalitis worldwide (0.22 per 100,000 person years). Prior PSURs report rates were 4.9 – 5.22 per 100,000 patient-years. However, due to the limited set of data no definite conclusion can be drawn.

In the context of the evaluation of additional data submitted in a different procedure SmPC changes were endorsed to add CNS herpes simplex and herpes zoster to the list of adverse reactions.

Anemia/autoimmune haemolytic anemia

Cumulatively as of 31 May 2015, a total of 5 cases of anemia (3 non-hemolytic and 2 hemolytic) have been reported in TOP. Cases retrieved by the haematopoietic erythropenia SMQ identified cases of anemia that are likely due to decreased RBC (red blood cell) production while the SMQ of haemolytic disorders identified those cases with possible peripheral destruction of RBCs.

Table 25 Results from SMQ Search by Preferred Term

SMQ	Haematopoietic erythropenia	No. Events
PT	Anaemia	1
	Anaemia Macrocytic*	1
	Normochromic normocytic anaemia*	2
SMQ	Haemolytic disorders	No. Events
PT	Autoimmune haemolytic anaemia	2
Total		6

SMQ=Standardized MedDRA Query; PT= Preferred Term
*These events occurred in one patient

Of the 3 cases within the haematopoietic erythropenia SMQ, 1 case had limited information for a comprehensive assessment and 2 cases reported concurrent conditions likely responsible for the event of anemia. Exposure to other DMTs prior to Tysabri included interferon beta in 2 cases; another case reported prior immunoglobulin therapy. There were no reports of previous exposure to immunosuppressant therapies. Time between last DMT (interferons) to the first dose of Tysabri was 1 and 4 months.

With regard to the 2 cases identified within the SMQ of haemolytic disorders, one case presented with hemolysis but without anemia. There were no laboratory results provided for markers of hemolysis (e.g. bilirubin and LDH) with the exception of haptoglobin, which was slightly decreased. The diagnosis of autoimmunity in this case was made based on a slightly positive direct coombs. Follow up CBC and direct coombs results were from tests performed a year after the diagnosis, and at that time, these were all negative; the event of anemia was considered resolved.

Despite the higher rate of amenic events in TOP it has to be considered that the incidence rate of hemolytic anemia in the overall MS population (10.06 per 100,000 person-years) is also higher compared to non-MS patients (5.45 per 100,000 person-years, gender-adjusted: 1.85 per 100,000 person-years). Moreover, the incidence rates of anemia and haemolytic anemia seem to be comparable to recent PSUR data.

Temporal pattern of cases of anaphylaxis/anaphylactic shock and pneumonia

17 SAEs based on the specified anaphylaxis search criteria were identified in 13 patients in the TOP study as of 31 May 2015. Upon medical review of the individual reports, 3 SAEs from 2 patients were excluded from the analysis. The remaining 14 SAEs identified in 11 patients had Preferred Terms (PT) that are summarized in Table 26. These events included anaphylactic reaction reported in 3 patients, anaphylactic

shock reported in 4 patients, anaphylactoid reaction reported in 3 patients, and 4 other events of chest discomfort, dyspnea, erythema and angioedema each reported in 1 patient.

Table 26 Summary of the SAEs of Anaphylactic Reactions by Preferred Terms

Preferred Term	Number of Event
Anaphylactic shock	4
Anaphylactic reaction	3
Anaphylactoid reaction	3
Chest discomfort	1
Dyspnoea	1
Erythema	1
Angioedema	1

Last DMT received prior to switching to Tysabri included interferon-beta in 7 patients: (Betaferon/Betaseron/Extavia in 4 patients, Avonex in 2 patients, and Rebif in 1 patient) and glatiramer acetate in 2 patients. Additionally, the use of an IS (mitoxantrone) prior to switching to Tysabri was reported in 1 patient and the use of chronic systemic corticosteroids prior to switching to Tysabri was reported in another patient.

For 7 of 11 patients, the anaphylactic reactions occurred within approximately 30 minutes after the start of the Tysabri infusion; in 4 of 11 patients, the specific time of the anaphylactic reaction and the relationship to the Tysabri infusion was not provided. All 11 patients recovered from the event.

The incidence rate for anaphylactic reactions in TOP was estimated to be 0.2% (11 out of 5,770 patients) and is comparable to incidence rates in Tysabri clinical trials.

Pneumonia

33 SAEs based on the specified lower respiratory tract infection search criteria were identified in 32 patients in the TOP study as of 31 May 2015. Upon medical review of the individual reports, 8 SAEs in which there was no confirmed diagnosis of pneumonia were excluded from the analysis. The remaining 25 SAEs identified in 24 patients had Preferred Terms (PT) that are summarized in Table 27.

Table 27 Summary of the SAEs of Pneumonia by Preferred Terms

Preferred Term	Number of Event
Pneumonia	19
Atypical pneumonia	2
Bronchopneumonia	2
Pneumonia mycoplasmal	1
Lobar pneumonia	1

Baseline demographics and characteristics are available for 24 patients with pneumonia from the TOP study. The last DMT received prior to switching to Tysabri included interferon-beta in 16 patients: (Avonex in 3 patients, Rebif in 4 patients, Betaferon/Betaseron/Extavia in 9 patients), and glatiramer acetate in 4 patients. Additionally, the use of an IS (mitoxantrone) prior to switching to Tysabri was reported in 1 patient, and the use of immunoglobulins prior to switching to Tysabri was reported in another patient. In 2 patients, no prior DMT or IS therapy was reported.

Causality was assessed as "Related" in 9 cases, "Possible" in 3 cases, "Unrelated" in 11 cases, and not provided in 2 cases. Outcome was reported as "Recovered" in 20 cases, "Recovered with sequelae in 1 case, "Not recovered" in 3 cases, and "Fatal" in 1 case.

To further assess the association of lower respiratory tract infections (LRTI) in patients with MS and specifically in those treated with Tysabri, the MAH conducted an insurance claims study (Mini-Sentinel, modular program 3) using data from 01 Jan 2004 through 31 Dec 2012. The results are presented in Table 12 and report the incidence rate (and incidence rate ratio) for LRTI among the following groups: 1) All MS patients; 2) MS patients on any disease modifying therapy (DMT); 3) MS patients on DMTs other than Tysabri; 4) MS patients treated with Tysabri; 5) MS patients never treated with a DMT.

Table 28 Incidence Rate and Relative Incidence Rate of Lower Respiratory Tract Infection from Claims study

Incidence Rate and Relative Incidence Rate of Lower Respiratory Tract Infection (rates and CIs are per 100 person-years)						
Group	Numerator	Patient-years	Incidence Rate	Lower 95% CI	Upper 95% CI	Relative Incidence Rate (95% CI)
MS (all)	27,134	286674.7726	9.5	9.4	9.6	Reference
MS treated with any DMT	11,169	144509.1918	7.7	7.6	7.9	0.82 (0.80-0.83)
MS treated w/o natalizumab	9,970	130870.6	7.6	7.5	7.8	0.80 (0.79-0.82)
MS treated with Tysabri	1,223	13980.55068	8.7	8.3	9.2	0.92 (0.87-0.98)
MS untreated	9,348	88112.1589	10.6	10.4	10.8	1.12 (1.09-1.15)

Malignancies

A search of the global Tysabri safety database was performed on 31 May 2015 using the SMQ (Standardized MedDRA Query) of malignant tumors (MedDRA version 18.0). The search yielded a total of 39 cases with 41 events.

All 39 cases reported a primary site for the malignancy; in addition to this primary site, two cases (2012BI040805 and 2011BI000789) had associated metastatic events also coded within the case (1 metastatic event per case) accounting for the 41 total events. For the TOP malignancy incidence rates and analysis, only primary tumors were included leaving a total of 39 events. Among the reported malignancies in TOP, breast cancer was the most common, affecting 12 patients (all female). Leukemia was diagnosed in 5 patients: (acute promyelocytic leukemia (1 patient), chronic lymphocytic leukemia (2 patients) and chronic myeloid leukemia (2 patients). Thyroid cancer was also diagnosed in 5 patients; colon cancer in 4 patients; lung cancer, cervical cancer and melanoma were diagnosed in 2 patients each; these include one cervical and one melanoma cancer in situ. All other cancers (skin, brain, non-Hodgkin's lymphoma [NHL], bladder, kidney, and liver/biliary) occurred in one patient each.

Investigator causality was assessed as unrelated in 29 cases, unlikely related or possibly related in 2 cases each, and related in 5 cases; causality was not assessed in 1 case. The outcome was provided in 38 of the 39 cases. Of these, the outcome was not recovered/not resolved for 20 patients, recovered/resolved for 12 patients, recovered with sequelae in 4 patients, and fatal in 2 patients. See Appendix A for a summary of the case characteristics for the reported malignancies in TOP. The fatal malignancy cases are described in more detail later in this response.

In 9 cases, the Investigator reported that the patients did not have risk factors for the malignancy or a family history of malignancy, and in 24 cases, it was unknown if the patients had risk factors as no information was provided.

Prior treatment with DMTs (disease modifying therapies) before starting Tysabri included interferon beta

(19 patients) and glatiramer acetate (12 patients); some patients received more than one prior DMT. There were no reports of patients who received the newer DMTs (e.g. fingolimod, dimethylfumarate, teriflunomide) before Tysabri and then developed a malignancy. In addition, 1 patient had received CDP323 in a clinical trial; CDP323 is an oral α4-integrin inhibitor no longer in development. Other treatments received prior to starting Tysabri in these patients included immunoglobulins and chronic systemic steroids. There were no patients who reported receiving immunosuppressants (IS) as the last therapy before initiation of Tysabri; however, 5 cases did have a history of prior IS use. Of these, 4 cases reported the use of one IS therapy (cychophosphamide, azathioprine or mitoxantrone) while one case reported the use of three prior IS therapies (azathioprine, mycophenolate mofetil, and cyclophosphamide).

The 2 malignancy cases with a fatal outcome involved the following events: Colon cancer metastatic and lung neoplasm malignant .

There were two cases of melanoma reported in TOP. These cases corresponded to events of ocular melanoma and in situ melanoma. There were no cases reported of invasive skin melanoma. Onset of melanoma in these cases was after 14 and 35 infusions for each case, respectively.

There was one case of lymphoma reported in the TOP study.

There were five cases of leukemia reported in TOP. Two were reports of chronic lymphocytic leukemia (CLL), two were reports of chronic myeloid leukemia (CML), and one was a report of acute promyelocytic leukemia. Time to onset in these cases ranged from 9 to 31 infusions with a mean of 21.8 and a median of 21 infusions.

Cumulative incidence rates for malignancies in TOP stratified by gender were compared to the Surveillance, Epidemiology and End Results (SEER) incidence rates in the general population.

Pulmonary embolism, deep vein thrombosis

The MAH performed a medical review of the 8 SAEs of pulmonary embolism (PE) including the 2 fatal PE cases, and the 5 SAEs of deep vein thrombosis (DVT) reported from the TOP study. The MAH also performed a search of the Tysabri global safety database to identify any additional cases of PE and DVT from the TOP study captured under the MedDRA (version 18.0) SMQ of "Embolic and Thrombotic Events" as of 31 May 2015. The search identified 2 additional cases of PE, but no new cases of DVT. Narratives on the 2 fatal cases of PE, and available data for the SAEs of PE and DVT from the TOP study as of 31 May 2015 are provided below.

Pulmonary embolism

There were 10 patients with the reported event of PE. Baseline demographics and characteristics of the 10 patients with PEs are summarized in the Table 29 below.

Table 29 Baseline Demographics and Characteristics of the Patients with PEs (N = 10)

Country of Origin	Czech Republic: 3 Belgium: 3 Australia, Germany, Norway, and Spain: 1 for each
Age (Years)	Mean (SD): 43.4 (6.4) Median: 43.5 Minimum: 35; Maximum: 52
Gender	Male: 1/10 (10%) Female: 9/10 (90%)
MS Disease Duration (Years)	Mean (SD): 8.2 (7.1) Median: 6.0 Minimum: 1.3; Maximum: 24.5
Baseline EDSS	Mean (SD): 3.9 (1.56) Median: 4.0 Minimum: 1.5; Maximum: 6.0
Number of Tysabri doses at the time of the event	Mean (SD): 19.7 (14.9) Median: 15.5 Minimum: 2.0; Maximum: 53.0
Last DMT received prior to switching to Tysabri	Interferon-beta: 5/10 (50%) • Avonex: 2/10 (20%) • Rebif: 3/10 (20%) Glatiramer acetate: 3/10 (30%)
Prior IS use	Mitoxantrone: 1/10 (10%)

The Table 30 below provides the severity, comorbidities, concomitant medications, outcome, and Investigator causality for the 10 patients with PEs in the TOP study.

Table 30 Severity, comorbidities, concomitant medications, outcome and Investigator causality for cases of PE in the TOP study

Case ID	Comorbidities/ Medical history	Concomitant medications	Severity of the PE event	Outcome	Investigator Causality
2011BI043083	Not reported	Contraceptives (Unspecified)	Moderate	Recovered	Unrelated
2011BI044632	Crawitz tumor of right kidney (Grade III)	Not reported	Not reported	Fatal	Unrelated
2011BI044637	Pathological fracture of the right humerus with surgical repair; colon carcinoma with liver metastasis	Not reported	Not reported	Fatal	Unrelated
2012BI017603	Deep venous thrombosis	Gabapentin	Severe	Recovered	Unrelated
2012BI018836	Thrombophlebitis	Not reported	Not reported	Recovered	Unrelated
2015BI026632	Superficial vein thrombosis	Nomegestrol acetate	Severe	Recovered with sequelae	Unrelated
2015BI026738	Type I diabetes, hypertension, idiopathic DVT for 15 years in right lower extremity	Glucagon Insulin aspart Mirtazapine Venlafaxine Alfuzosin	Moderate	Recovered	Unrelated

As shown in the Table 30 above, risk factors for thromboembolic disease were present in all 10 patients with a PE. These risk factors included history or concurrent DVT (3 patients), superficial vein thrombosis or thrombophlebitis (3 patients), lower limb venous insufficiency (1 patient), history of malignancy (2 patients), bone fracture with surgical repair (1 patient), use of contraceptives (2 patients) and smoking history (1 patient). Severity of the PE was assessed by the Investigator as moderate in 5 patients, severe in 2 patients and not reported in 3 patients. Causality was assessed as unrelated by the Investigator in all cases. Six of the 10 patients with PEs recovered from the event, and 2 patients recovered with sequelae. There were 2 patients with a fatal outcome. Narratives of these 2 fatal PE cases are provided below.

First case

A 50-year-old female patient from the Czech Republic with relapsing remitting multiple sclerosis was enrolled in the TYSABRI Observational Program (IMA-06-02) and received 2 doses of Tysabri (300 mg IV QM) on 06 Apr 2011 and 09 May 2011. She experienced a PE and died on 14 Oct 2011 at home, approximately 5 months after her last dose of Tysabri. Per the autopsy report performed on an unspecified date, the cause of death was PE, which was assessed by the Investigator as unrelated to Tysabri treatment. The patient's expanded disability status scale (EDSS) and Karnofsky scores were not

reported. Medical history included Grawitz tumor of the right kidney (grade III) diagnosed on 25 Aug 2011, and a nephrectomy of the right kidney was performed on 12 Sep 2011. It was unknown if the patient had a history of cigarette smoking. No concomitant medications were reported. Prior therapies received before starting Tysabri included unspecified chronic systemic corticosteroids received from Nov 2008 to Mar 2011, glatiramer acetate received from Mar 2009 to Mar 2010 and interferon beta-1a (Rebif) from Mar 2010 to Mar 2011.

Second case

A 54-year-old female patient from the Czech Republic with relapsing remitting multiple sclerosis was enrolled in the TYSABRI Observational Program (IMA-06-02) and received 15 doses of Tysabri (300 mg IV QM) from 16 Oct 2009 to 21 Dec 2010. Five months after her last dose of Tysabri, she was hospitalized on 21 May 2011 due to a pathological fracture of the right humerus and had osteosynthesis performed on 22 May 2011. She experienced a PE and sudden death on 28 May 2011. No autopsy was reported. The Investigator assessed the event of PE as unrelated to Tysabri treatment.

The patient's EDSS and Karnofsky scores were not reported. Relevant medical history included colon carcinoma with liver metastasis diagnosed on16 Mar 2011(reported in Case ID 2011BI018797). It was unknown if the patient had a history of cigarette smoking. No concomitant medication was reported. Previous therapies received before starting Tysabri included chronic systemic corticosteroids from Jul 2009 to Sep 2009 for unknown indications.

Deep Vein Thrombosis

There were 5 patients with the reported event of DVT in the TOP study, including 1 case that also reported a PE (Case ID 2012BI017603). Baseline demographics and characteristics of the 5 patients with DVTs are summarized in the Table below.

Table 31 Baseline Demographics and Characteristics of the patients with DVTs (N = 5)

Country of Origin	Czech Republic: 2 Belgium: 1 Australia, Germany: 1 for each
Age (Years)	Mean (SD): 42.8 (11.76) Median: 45.0 Minimum: 23; Maximum: 53
Gender	Male: 1/5 (20%) Female: 4/5 (80%)
MS disease duration (Years)	Mean (SD): 5.7 (4.98) Median: 4.84 Minimum: 0.4; Maximum: 11
Baseline EDSS	Mean (SD): 5 (1.77) Median: 5.0 Minimum: 3.0; Maximum: 7.0
Number of Tysabri doses at the time of the event	Mean (SD): 24.6 (15.5) Median: 27 Minimum: 5.0; Maximum: 47.0
Last DMT received prior to switching to Tysabri	Glatiramer acetate: 2/5 (40%)

Table 32 provides the severity, co-morbidities, concomitant medications, outcome, and Investigator causality for the 5 patients with DVTs in the TOP study.

Table 32 Severity, co-morbidities, concomitant medications, outcome and Investigator causality for cases of DVT in the TOP study

Case ID	Comorbidities /Medical history	Concomitant medications	Severity of the DVT event	Outcome	Investigator Causality
2008BI023059	Not Reported	Combivir Kaletra intravenous immunoglobulin	Severe	Not recovered	Possible
2009BI026331	Prostate hypertrophy	Gabapentin Sirdalud Detrusiol tilicomp tamsulosin	Mild	Not recovered	Unrelated
2011BI048246	Not reported	Contraceptives (Unspecified)	Moderate	Recovered with sequelae	Unrelated
2012BI017603	PE	Gabapentin	Severe	Recovered	Unrelated
2013BI061059	Not Reported	Desvenlafaxine Tramadol Levlen ED Caltrate	Moderate	Recovered with sequelae	Unrelated

As shown in Table 32, risk factors for thromboembolic disease were present in 3 of the 5 patients with DVT. The risk factors included use of contraceptives (2 patients) and use of an anti-HIV drug (Kaletra) known to be associated with DVTs (Kaletra Prescribing Information, 2013). Severity of the DVT was assessed by the Investigator as severe in 2 patients, moderate in 2 and mild in 1. Outcome of the event at the time of the SAE report was "Recovered" in 1 patient, "Recovered with sequelae" in 2 patients, and "Not recovered" in 2 patients. The event was assessed as unrelated in 4 patients and as possibly related in 1 patient by the Investigator.

Laboratory findings

Anti-JC virus (JCV) antibody status was available for 10 of the patients with PML, and all 10 patients were anti-JCV antibody positive**.**

Safety in special populations

As the proposed extension of indication is only related to prior disease modifying therapies the target population remains the same with regards to age.

Elderly

Whilst the Clinical Trial safety database contains adequate patient numbers to assess any effect of gender or age up to 55 years on the safety profile, there are inadequate numbers of patients over this age to determine the safety profile in this older group of patients.

Pediatric population

Only a small number of adolescents and children have been studied. Therefore, safety in the paediatric population has not been established, although an open-label repeat-dose PK and safety study in paediatric patients aged 10 to less than 18 years old has been agreed with the Paediatric Committee at the EMA in relation to the paediatric investigation plan for natalizumab. The last patient completed this study in June 2014.

Pregnant or breast feeding women

Immunohistological studies indicate natalizumab binds to the placenta and foetal tissues, indicating a potential for teratogenic and/or abortifacient activity. A reproductive toxicology study evaluating the effects of natalizumab demonstrated no fetotoxicity or drug-related teratogenic effects.

The Tysabri pregnancy exposure registry initially enrolled 376 women with pregnancies exposed to Tysabri and outcome data from 355 completed pregnancies were obtained. There were 316 live births with birth defects being reported in 29 of these infants. An additional birth defect was detected in a pregnancy which ended in elective termination. The rate of major birth defects in infants born to subjects with MS or CD exposed to Tysabri in the Registry was 7.9% (95% CI: 5.2%, 11.4%). The birth defects were reviewed at the end of the study by an Advisory Committee of external experts in relevant specialities of teratology, epidemiology and maternal and foetal medicine. The Advisory Committee determined that 16 infants had defects which met criteria used by the Metropolitan Atlanta Congenital Defect Program (MACDP), the comparator for the study, and the Committee's definition of major defects. These 16 infants from 317 pregnancies (316 live births plus defect in one elective termination) reflect a birth defect rate of 5.05% (95% CI: 2.9%, 8.1%). While this rate is higher than that reported in the MACDP (2.67%), the Advisory Committee did not observe patterns of defects that were suggestive of an unusual distribution and found no specific signals of concern.

There were 32 spontaneous abortions reported in the pregnancy registry. The spontaneous abortion reporting rate among the 339 completed pregnancies enrolled into the registry prior to 22 weeks gestation was 9.4% (95% CI: 6.6%, 13.1%) which is comparable to background rates of 15%-17% reported in the general population in the literature. (Anokute 1987, Ventura 2009).

Among the 840 serious adverse events reported for female patients in the TOP study as of May 1, 2015, there were a total of 25 events in 22 patients coded to the MedDRA (version 18.0) Preferred Term (PT) of spontaneous abortion.

The 25 spontaneous abortions (SA) included 2 patients with multiple SA events (one patient with 2 reports of SA and one patient with 3 reports of SA). Maternal age for these SA events ranged from 22 – 36 years (mean and median of 30.6 and 31, respectively). The distribution of events by country included 11 SA events reported from Germany, 6 from the Czech Republic, 2 from the Netherlands, and 1 for each of the following countries: Belgium, Finland, France, Greece, Italy and the United Kingdom.

Five of the 22 patients did not have prior disease modifying therapy (DMT) reported. Of the 17 patients who reported prior treatment with one or more DMTs, all but one of these patients received prior interferon-beta and/or glatiramer acetate, and one patient received prior fingolimod.

Table 33 Gestational age at Last Exposure to Tysabri and at Outcome for Pregnancies in TOP Resulting in Spontaneous Abortion (n=25)

Gestational period reported[1]	Distribution of SA events	
	By gestational age at last exposure to Tysabri (number (%))	By gestational age at time of spontaneous abortion (number (%))
Preconception	8 (32%)	NA
< 8 weeks gestation	8 (32%)	6 (24%)
8-11 weeks gestation	1 (4%)	8 (32%)
1st trimester	0	1[2] (4%)
12-16 weeks gestation	0	2[3] (8%)
Unknown	8 (1%)	7 (28%)
22 weeks gestation	0	1 (4%)

[1]Derived from SAE narratives reported to the MAH
[2]Gestational age reported as 1st trimester, number of weeks not provided
[3]Gestational ages were 12 and 14 weeks

Further detail on the Tysabri exposure in pregnancies that resulted in spontaneous abortion is provided in Table 34. The mean Tysabri exposure was similar for the SA events in which the last exposure to Tysabri occurred prior to conception and those in which the last exposure to Tysabri occurred at less than 8 weeks of gestation; however, the median exposure varied.

Table 34 Mean and median Tysabri Exposure in Women whose Pregnancies Resulted in Spontaneous Abortion in TOP (n=25)

Gestational age at last exposure	Number of events	Mean exposure to Tysabri(months)	Median exposure to Tysabri(months)
Preconception	8	10.5	8
< 8 weeks gestation	8	10.1	12
8 to 11 weeks gestation	1	NA	NA
Unknown	8	17.1	13

There were 215 pregnancies in the TOP study based on the number of pregnancies reported during the follow up visit. The rate of spontaneous abortions in TOP, using the number of reported pregnancies in the denominator, is 25/215 or 11.6%. This rate is consistent with the rate of spontaneous abortions estimated from the following populations:

1. Tysabri Pregnancy Registry (9% for all pregnancies and 15.9% for those pregnancies enrolled in the Registry prior to week 22 of gestation) (101MS401 CSR EMEA/H/C/000603/II/0074),
2. MS populations treated with glatiramer acetate and interferon beta (10 to 17% Alwan et al 2015; Coyle et al 2003, Coyle et al 2013, Richman et al 2012; Sandberg-Wollheim 2011)

3. General population (15.9 to 17%, Anokute 1987; Ventura 2009).

Discontinuation due to adverse events

A total of 2104 subjects discontinued Tysabri (37.4%). Among those 2104 patients discontinued Tysabri, 1246 patients stayed on study, 855 withdrew from TOP, and 3 discontinued Tysabri after withdrew from TOP as of the date cut-off. 131 patients (2.3%) discontinued due to Non-Serious Adverse Events, 62 patients (1.1%) discontinued due to Serious/Other Serious Adverse Event.

The overall rate of complete withdrawal from the study was 21.3%. For comparison the discontinuation rates in other EU registries such as Sweden, Austria and Denmark in 2014 were reported to be 48%, 38% and 42%, respectively.

The 5 most common reasons for discontinuation of Tysabri, in order of descending frequency were:

1. positive anti-JCV antibody status (14.1% of patients enrolled)
2. patient decision (7.7% of patients enrolled)
3. medication change (7.0% of patients enrolled)
4. insufficient efficacy (6% of patients enrolled)
5. physician decision (4.6% of patients enrolled)

The 5 most common reasons for withdrawal from TOP, in order of descending frequency were:

1. patient decision (4.8% of patients enrolled)
2. lost to follow up (3.1% of patients enrolled)
3. medication change (3.0% of patients enrolled)
4. withdrawal of consent (2.8% of patients enrolled)
5. positive anti-JCV antibody status (2.7% of patients enrolled)

The reasons for discontinuation and the proportion of patients who discontinue Tysabri treatment appeared to be similar across groups and independent of the previous DMT used before initiating Tysabri treatment

Post marketing experience

Natalizumab is available in USA and all EU markets. In addition the drug is also approved in Australia, New Zealand, Canada, Israel, India, Russia, Switzerland, Japan and some Middle East, North African, South American and South East Asian countries. In USA the drug is also approved for the indication Crohn's Disease.

With regards to identified and potential risks several safety postmarketing actions have been initiated which include conduct of clinical trials, MS Re-dosing protocol, TOUCH Surveillance Programme, TYGRIS Observational Cohort Study and a Pregnancy registry. Furthermore local country specific registries (Sweden, Denmark, Italy, France, Austria, Ireland) are being performed in Europe, with the majority being run by independent investigators.

As a result risk minimisation measures have been implemented, e.g. Updates to SmPC, Package Leaflet and Educational Guidance, Revisions to the Patient Alert Card and Implementation of Treatment Initiation and Continuation forms to be used prior to the start of treatment and at the 2-year treatment point.

2.5.1. Discussion on clinical safety

The TOP study patient population was generally well balanced between the subgroups with regard to patient and disease characteristics.

The MAH presented data from an interim analysis (up to 01 May 2015) to update the current safety dataset. However, the updated safety data did not significantly increase the relevant safety dataset, likely

due to the closure date for enrollment from TOP (December 2013, except for Mexico and the Czech republic where enrollment continues) compared to the recent EMA marketing authorization for the new DMT [Teriflunomide (August 2013); Dimethyilfumarate (January 2014); Alemtuzumab (September 2013)]: the number of patients who switched from teriflunomide to Tysabri increased from 6 to 7; the number of patients who switched from dimethyl fumarate to Tysabri remained 5; the number of patients who switched from fingolimod to Tysabri increased from 130 to 147. The total person-years of Tysabri exposure in the subgroup of patients who switched from fingolimod increased from 135.56 to 212. There were no subjects enrolled in TOP with previous exposure to alemtuzumab. For the SOCs with the greatest number of SAEs (infections and infestations and in nervous system) 3 events each occurred in the fingolimod subgroup. SAEs in the SOC of Infections and Infestations in patients who previously received fingolimod, GA and interferon were 1.41, 1.32 and 1.19 per 100 patient years, respectively. The incidence rates for the SOC of Nervous system disorders were 1.41, 0.84 and 0.67 per 100 patient years, respectively. For the remaining SOCs which contained only a single SAE, the incidence rates were somewhat less similar among subgroups who last used fingolimod, GA or interferon.

For the 5 patients who switched to Tysabri from dimethyl fumarate, there were no SAEs reported. For the 7 patients who switched to Tysabri from teriflunomide, one SAE occurred (PT: sepsis and urinary tract infection). This single SAE with a PT of sepsis and urinary tract infection in the subgroup last exposed to teriflunomide (subject year exposure = 16 patient years) results in an incidence rate of 6.21 per 100 patient years for the infections and infestations SOC. Although this rate is considerably greater than the incidence rate for those previously exposed to GA and interferon (1.32 and 1.19 per 100 patient years, respectively), it is acknowledged that due to the small sample size of those last exposed to teriflunomide it is not possible to draw conclusions on this comparison.

The distribution of the type of malignancies as well as the rate of spontaneous abortions in natalizumab-treated TOP patients was in general comparable to that observed in a general population.

In the initial submission, with a data cut of 01 May 2014, the MAH reported 30 cases of PML in the TOP study including 26 confirmed cases and 4 suspect cases. Based on the updated review as of 1 May 2015, 35 confirmed cases of PML have been reported from the TOP study. None of the 35 confirmed PML patients in TOP received fingolimod, dimethyl fumarate, teriflunomide or alemtuzumab at any time prior to initiating Tysabri. However –due to the limited exposure to these new DMTs in the overall TOP population - this provides only very limited reassurance.

Safety findings were generally consistent with the current safety profile of Tysabri.

However, only a limited group of MS patients (147) in the TOP study received fingolimod prior to Tysabri and only 7 and 5 patients were treated with teriflunomide and dimethyl fumarate prior to Tysabri, respectively. 3.8% of patients (n=215) received "traditional" immunosuppressants (mitoxantrone, n=77, azathioprine, n= 90, cyclophosphamide, n=24) as last treatment prior to starting Tysabri. The small number of patients and the low natalizumab exposure to new DMTs prevents a conclusive safety evaluation.

As potential source of additional safety data in patients switching from other disease modifying therapies (DMT) to Tysabri the MAH identified the TOUCH prescribing program in the US and proposed that data from it be used. The MAH provided data on SAEs by SOC and by PT listed for the overall TOUCH population (73.968 patients, total person years of Tysabri exposure: 192.641) and for the subgroup of patients who switched from fingolimod (1.710 patients, total person years of Tysabri exposure: 2.691), for the subgroup who switched from Dimethyl fumarate (1.783 patients, total person years of Tysabri exposure: 2.691) and for the subgroup of patients who switched from Teriflunomide (274 patients, total person years of Tysabri exposure: 309).

TOUCH data provide only a rough safety estimate as no information has been provided with regard to

patient and disease characteristics, thus it is unknown whether the patient population is balanced between subgroup with regard to patient and disease characteristics.

The incidence density of at least 1 SAE was similar in the Overall TOUCH population (3.98 per 100 patients-years) and in the subgroups according to prior DMT (switched from fingolimod: 3.60 per 100 patients-years; switched from dimethyl fumarate 3.27 per 100 patients-years; switched from teriflunomide 3.23 per 100 patients-years).

The incidence density of SAEs by SOCs in the subgroups of patients who switched from fingolimod or from Dimethyl fumarate do not seem to exceed those of the overall TOUCH population; the Applicant states that the incidence of SAEs by SOC in the subgroup of patients who switched from teriflunomide is less comparable due to due to the relatively small sample size (N=274) compared to the overall TOP population (N=73.968) and the small number of events (4 or fewer) of events within each SOC and this is acknowledged.

The comparison of SAEs by PT in the three above mentioned subgroups compared to the overall TOUCH population is difficult due to the small number of events within each PT in the prior fingolimod, dimethyl fumarate and teriflunomide subgroups, thus no conclusions may be drawn.

The major safety concern elicited by the therapy with new DMTs, all endowed with immunosuppressive activity, prior to switching to Tysabri is the occurrence of opportunistic infections, and above all the risk of developing PML.

Indeed PML cases have been recently recorded also in patient treated with fingolimod and dimethyl fumarate containing products, independently of Tysabri exposure.

Post marketing data indicate that PML occurs in about 0.1/1000 in JCV negative patients treated with natalizumab and ranges from 1 to 11/1000 in JCV positive patients according to treatment duration and prior immunosuppressant use. In addition, natalizumab withdrawal because of progressive multifocal leukoencephalopathy almost always triggers an immune reconstitution inflammatory syndrome that may lead to neurological complications or even death.

35 PML confirmed cases were recorded in the TOP study. 6 patients (17.1%) received prior IS therapy. The prior IS therapies included mitoxantrone in 4 patients, azathioprine in 3 patients and cyclophosphamide in 1 patient. Two patients received more than one IS therapy including 1 patient who received cyclophosphamide and azathioprine, and another patient who received mitoxantrone and azathioprine. One patient received 2 different treatment regimens of mitoxantrone (approximately 31.5 months apart). None of the 35 PML patients in TOP received prior fingolimod, dimethyl fumarate or teriflunomide at any time prior to initiation of Tysabri.

Of the 35 confirmed PML patients in the TOP study, 25 patients (71.4%) had anti-JCV antibody testing performed prior to the PML diagnosis and all tested positive; 3 patients had anti-JCV antibody tested positive at an unspecified time; and 7 PML patients did not have available anti- JCV antibody test results. In these 7 PML patients (all from the EU), the diagnosis of PML occurred before the anti-JCV antibody assay became commercially available in the EU.

As a risk minimization measure for PML, the MAH proposed to insert, in section 4.4 of the SmPC, information on the need to consider the half-life and mode of action of the previous DMT when switching patients from another DMT to Tysabri, in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. Furthermore, the MAH proposed to list the 5 specific IS therapies (mitoxantrone, methotrexate, azathioprine, cyclophosphamide and mycophenolate mofetil) used more frequently among PML and non-PML Tysabri-treated patients in the TOP, TYGRIS and STRATA studies. A Complete Blood Count is recommended prior to initiating Tysabri to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved. As alemtuzumab has a profound prolonged

immunosuppressive effect and as the actual duration of these effects is unknown, initiating treatment with Tysabri after alemtuzumab will not be recommended.

In principle, the proposed risk minimization measures are deemed appropriate. However, for the moment it is unknown whether use of new DMTs with an immunosuppressive mechanism of action prior to switching to Tysabri is associated with the same increased PML risk as "traditional immunosuppressants". Indeed, complete safety information on a rare event such as PML may be acquired only with post marketing clinical experience over years, and thus it is impossible to evaluate and quantify at present the added risk of new DMTs to the development of PML following Tysabri exposure.

As acknowledged by the Applicant in previous PSURs, the available information on prior IS use in the overall Tysabri treated population and in confirmed PML cases is very limited. The limited data available do not allow to identify any pattern or trend with regard to PML risk and the specific types of IS therapies. In this regard, the addition of 5 specific IS therapies in the SmPC and Educational material is considered inappropriate.

Based on the available PSUR data (coming from STRATA, TOP and TYGRIS), no specific pattern or trend on duration of the wash-out period for "traditional immunosuppressants" therapy prior to Tysabri has been observed. PML risk appears to be present with both short and long wash-out periods.

In line with these previous findings, the TOP data submitted for this variation show that the frequency of ever prior "traditional immunosuppressants" use in PML patients enrolled in the TOP study was 26.7%, compared to 13.8% in the overall TOP population. Conversely, the frequency of "traditional immunosuppressants" use as last therapy prior to switching to Tysabri was similar between PML patients (3.3%) and overall TOP population (3.6%). At present, this is accounted for in the Tysabri SmPC by a dedicated warning in section 4.4.

It is at present not known if ever prior use of new DMTs is a risk factor for PML occurrence after Tysabri treatment independently of the time at which the exposure occurred. The proposed risk minimisation measures (to consider the half-life and mode of action of the other therapy in order to avoid an additive immune effect) are endorsed. However, it is currently unknown if these measures are sufficient to avoid an increased PML risk in patients treated with new DMTs. Furthermore, lymphocyte cell count alone may not be a sufficient risk minimisation measure. Also number and/or function of lymphocyte subsets may be important for immune function recovery to occur. Only future additional data coming from post-marketing activities will allow to determine whether further specific risk minimization measures will be necessary for instance to better evaluate patients' immunocompetence status.

The MAH provided on request from the CHMP a comparative analysis on the similarity between US and EU patients on Tysabri. The comparison provided by the MAH of the US and EU patient-subgroups included in STRATIFY-2 (all patients from US), TOP (all patients from EU) and TYGRIS (patients from EU and US) showed some differences in demographic characteristics between EU and US patient population; furthermore, between-study and between-geographic variation was observed for the three known risk factors for PML in Tysabri treated patients (positive anti-JCV antibody status, prior immunosuppressant use and duration of treatment), in particular for the proportion of prior IS use in the TYGRIS EU population. A direct comparison of the baseline disease characteristics in the EU and US patient population is not possible from available data, as the baseline disease characteristics (as measured by EDSS and ARR) data have not been collected within TOUCH

In light of the higher number of patients with prior IS use and anti-JCV antibodies in the TYGRIS EU population and considering that differences in PML incidences between EU and US patients have been observed in the past it is considered mandatory to also include patients with prior IS use in the planned analysis. This will also allow for the investigation of a potential cumulative risk for PML in patients with prior IS use switching from newer DMT's to Tysabri.

In conclusion, the comparability of EU and US patients was not fully demonstrated. The MAH plans to assess the feasibility of including EU data.

Regarding the strategy proposed by the MAH to collect post-authorisation safety data relying mainly on the TOUCH program mainly data from US patients will be used to assess the PML risk for patients switching from newer DMT's to Tysabri. In order to assess infrequent events such as PML and other opportunistic infections in patients switching from the newer DMTs, the MAH has proposed to undertake an observational cohort study utilizing all available data fields collected within the Tysabri TOUCH prescribing program in the US. However, collection of data beyond the dataset agreed with the FDA (e.g. EDSS, ARR), is not feasible in this cohort because the MAH does not unilaterally control the TOUCH program which is carried out in conjunction with the FDA. This is a prospective study which will include all TOUCH MS patients and will run for a period of 8 years, with an anticipated end-date of 2023.

Additionally the MAH should also commit to review the feasibility of including EU-patient data utilising existing registries, and should this be unfeasible, commit to set up a dedicated registry in the EU, in order to address the issue of missing data from EU patients. Even though it is acknowledged that this will require additional time to set-up, it is considered mandatory to gain safety data in the long term in European Tysabri-treated patients switching from a new DMT.

2.5.2. Conclusions on clinical safety

The safety profile of Tysabri evaluated in TOP did not show major differences regarding SAEs (incidence, type, frequency), malignancies or PML incidence rates compared to the currently known safety profile of Tysabri. Safety findings were consistent within the subgroups. The lower incidence of SAEs observed in the fingolimod subgroup compared to the total population could be a result of the lower exposure to natalizumab in this subgroup. However, the overall safety of Tysabri after the use of **new DMTs** is at present incompletely characterized mainly because of the limited number of patients who received fingolimod treatment prior to Tysabri and to the extremely low number of patients who received teriflunomide or dimethyl fumarate, the short Tysabri exposure after fingolimod treatment, the lack of data on duration of exposure to first-line DMTs.

Currently PML represents the main safety concern for treatment with Tysabri also with regards to a possible increase in the frequency of PML events due to the sequential use and possible cumulative effect of new DMTs with immunosuppressive activity and Tysabri. In this regard it has to be mentioned that PML cases have also been reported for DMF and fingolimod. However, due to the recent approval status only limited data are currently available on the risk for PML with these drugs.

Adequate information on the limited-absence of data for patients switching from new DMTs to Tysabri should be provided in the SmPC for the prescriber.

As long as conclusive data are not available, patients with prior use of another DMT with an immunosuppressive effect, in a conservative approach must be considered as having a PML risk equal to patients who received immunosuppressants prior to receiving Tysabri. This information should be adequately reflected in the SmPC, Physician Information and Management Guidelines.

Since safety information on a rare event such as PML may be acquired only with post marketing clinical experience over years, the Applicant committed to collect post-authorisation safety data on Tysabri treatment in MS patients who were previously treated with at least one DMT including teriflunomide, dimethyl fumarate, alemtuzumab, fingolimod.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 18 with the following content:

Safety concerns

Important identified risks	Infections Progressive Multifocal Leukoencephalopathy Herpes infections Hypersensitivity Reactions Anti-Natalizumab Antibody Formation Hepatic Injury
Important potential risks	Malignancies
Missing information	Effects of natalizumab on fertility and outcome of pregnancy Patients over the age of 65 years Children and adolescents PML risk following switch from DMTs with immunosuppressant effect Pharmacokinetic and safety profiles of natalizumab in patients with renal and hepatic impairment

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Tysabri Global Observational Program in Safety (TYGRIS) Study 101MS402 (US, Canada) Study 101MS403 (ROW) **Category 3**	To obtain long-term safety data on subjects with MS treated with Tysabri in a clinical practice setting. Collection of data concerning progression of MS.	PML and other infections Malignancies Anti-natalizumab antibody formation Hypersensitivity Reactions	Ongoing	2016
101JC402 (STRATIFY 2) **Category 3**	The primary objective is to demonstrate that the incidence of progressive multifocal leukoencephalopathy (PML) in Tysabri-treated patients who do not have detectable antibodies to John Cunningham	PML risk	Ongoing	2016

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	virus (JCV) (antibody negative) is lower than in patients who have detectable antibodies to JCV (antibody positive)			
Tysabri Observational Study (TOP) Study IMA-06-02 **Category 3**	To assess the long-term safety and impact on disease activity and progression of TYSABRI® (natalizumab) in patients with relapsing remitting multiple sclerosis (RRMS) in a clinical practice setting	PML and Other Infections Malignancies Anti-Natalizumab Antibody Formation Hypersensitivity Reactions	Ongoing	Annually

In addition to the studies referred in the table above, the MAH is requested to update the RMP with the inclusion of the following category 3 PASS:

Study/activity type, title and category: Observational cohort study utilizing the Tysabri TOUCH programme (5 year enrolment: January 2016-December 2020 + 3 year follow up) including a feasibility assessment for inclusion of EU registry data. Category 3.

Objectives: to estimate the risk of PML among patients on Tysabri switching from the newer DMTs (including fingolimod,dimethyl fumarate, teriflunomide) and from established DMTs (interferon beta and glatimer acetate).

Safety concerns addressed: PML risk in patients switching from DMTs with immunosuppressant effect.

Status: planned

Data for submission of interim or final reports:

1) Report on the assessment of the feasibility of including data from the EU utilising existing registries: ***December 2016***

2) Annual interim analysis from August 2017 (updated risk estimates of PML among the DMT groups of interest, stratified by JCV, duration of exposure to Tysabri, prior IS) to be submitted with the annual PSUR.

3) Final report: **End Q2 2024**.

Risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
PML	Contraindication for use in patients with PML in section 4.3 of the SmPC. Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC. Effects of prior history of immunosuppressant use on risk of PML added to SmPC and Package Leaflet Increased risk of PML with positive anti-JCV antibody status and in particular for those patients who have all three risk factors (anti-JCV antibody positive, prior IS use and duration of Tysabri treatment >2 years) added to SmPC, and Package Leaflet. Recommend initial anti-JCV antibody testing for all patients, and repeat antibody testing every 6 months for those patients who are anti-JCV antibody negative added to SmPC, Package Leaflet, and physician education documents including treatment forms. Information concerning continued vigilance for signs and symptoms of PML for approximately 6 months post-discontinuation of treatment added to SmPC and physician education document. Information indicating that anti-JCV negative patients may still be at risk	Physician Education via Physician Information and Management Guidelines (Annex 11). Update to testing frequency included. Update to include continued vigilance for signs and symptoms of PML for approximately 6 months post-discontinuation Publishing the latest PML data on company websites Details of IRIS diagnosis and management during recovery from PML added to SmPC, PIL and physician education Patient Alert Card Treatment initiation and continuation forms. Template patient information document to be completed before initiation of Tysabri treatment and Tysabri treatment continuation after 24 months treatment included in physician education documentation to ensure patients are fully informed about risks (implementation to be discussed with local regulators) Publishing an MRI learning module on the differentiation of MS relapse from PML.

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity reactions	Recommendation for management of hypersensitivity in section 4.2 of the SmPC. Contraindication in section 4.3 of the SmPC. Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC.	Physician Education via a Physician Information and Management Guidelines
Anti-Natalizumab Antibody formation	Recommendation that therapy be carefully reconsidered in patients showing no evidence of therapeutic benefit beyond 6-months and check of antibody status if infusion events occur and before re-dosing in section 4.2 of the SPC. Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC.	
Herpes/Other Infections	Contraindication in patients with increased risk of opportunistic infections in section 4.3 of the SmPC. Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC. Addition of herpes infection to SmPC	Addition of herpes infection educational materials including physician prescribing guidelines
Hepatic injury	Inclusion of hepatic reactions in warnings section and ADR section of SmPC.	.

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential Risks		
Malignancy	Contraindication in patients with known active malignancies (except for patients with cutaneous basal cell carcinoma) in section 4.3 of the SmPC.	
Unknown Information		
Pregnancy and Pregnancy Outcome	Recommendations for discontinuation of Tysabri with occurrence of pregnancy as listed in section 4.6 of the SmPC.	
PML risk in patients switching from DMTs with immunosuppressant effect	Warning in section 4.4 that it is unknown if patients switching from DMTs with immunosuppressant effects to Tysabri have an increased risk of PML. Such patients should be monitored more frequently using an abbreviated MRI protocol Guidance on laboratory tests and washout periods prior to starting Tysabri in section 4.4	Physician Education via a Physician Information and Management Guidelines
Special Populations	Information on use of drugs in elderly, and patients with renal and hepatic impairment in section 4.2 of SmPC. Information on posology in children and adolescents in section 4.2 of SmPC. Contraindication for children and adolescents in section 4.3 of SmPC	

NB: Considering the ongoing parallel procedures involving Tysabri at the present time, the MAH is requested to consolidate the approved updates to the RMP within each procedure.

2.7. Update of the Product information

The CHMP adopted changes to the existing indication as follows:

"TYSABRI is indicated as single disease modifying therapy in **adults with** highly active relapsing remitting multiple sclerosis for the following patient groups:

- ~~Adult~~ Patients ~~aged 18 years and over~~ with high**ly active** disease ~~activity~~ despite **a full and adequate course of** treatment with **at least one disease modifying therapy**

(DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1) ~~a beta-interferon or glatiramer acetate~~.

~~These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon or glatiramer acetate. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.~~

or

- ~~Adult~~ Patients ~~aged 18 years and over~~ 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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI".

Additionally and as a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

To support the change to the approved indication for Tysabri, efficacy data are derived from the ongoing Tysabri Observational Program (TOP), an observational study of patients receiving Tysabri, through an interim Clinical Study Report using a cut-off date of May 1, 2014.

In the overall TOP population, ARR decreased from 1.99 (95% confidence interval [CI]: 1.96, 2.01) in the pretreatment year to 0.22 (95% CI: 0.21, 0.24) while on natalizumab therapy ($p < 0.0001$) and remained stable over 5 years. A significant reduction in ARR with natalizumab occurred in patients who were either DMT naïve, had taken only 1 DMT or had taken >1 DMT prior to dosing with natalizumab ($p < 0.0001$), with greater reductions seen in patients who were either DMT naïve or had taken only 1 DMT prior to dosing with natalizumab.

When looking at the three subgroup of patients with interferon, glatiramer acetate or fingolimod as last therapy received prior to natalizumab, in all three subgroups there was a significant reduction in ARR while on natalizumab treatment compared to pretreatment year (GA subgroup ARR decreased from 1.98 in the pre-treatment year to 0.24 while on natalizumab therapy; beta interferon subgroup ARR decreased from 1.98 to 0.21; fingolimod subgroup ARR decreased from 2.06 to 0.38; $p<0.0001$).

For the subgroups of patients whose last therapy prior to dosing with natalizumab was GA or beta interferon the reduction in ARR remained stable over 5 years. For patients whose last therapy prior to dosing with natalizumab was fingolimod, the reduction in ARR remained stable over 2 years. Data for the fingolimod subgroup after the 2 year period are less meaningful due to the smaller sample size (n=22 at 3 years; $n \leqslant 4$ after 3 years).

Mean EDSS scores were similar from Baseline (3.5) to Year 5 (3.2) in the overall TOP population patients treated with natalizumab. Similar results were seen for the subgroups of patients whose last therapy prior to dosing with natalizumab was GA or beta interferon. For the fingolimod subgroup, less meaningful conclusions may be obtained due to the limited sample size ad due to the shorter Tysabri exposure (n=51 at year 1, n=15 at year 2 and $n \leqslant 4$ after the 2 year period). From the limited data available, mean EDSS scores were similar from Baseline to Year 2.

Uncertainty in the knowledge about the beneficial effects

The majority of patients treated with natalizumab in the TOP study received as last treatment prior to starting Tysabri either beta interferon (n= 3210, 57%) or glatiramer acetate (GA) (n= 1354, 24%); only a small subgroup of patients received fingolimod (n=130, 2.3%); very few patients received teriflunomide or dimethyl fumarate (6 and 5 patients, respectively); 215 patients (3.8%) received "traditional" immunosuppressants (mitoxantrone, n=77, azathioprine, n= 90, cyclophosphamide, n=24). Furthermore, the subgroup of patients who received fingolimod as last therapy before natalizumab was exposed to a lower number of Tysabri infusions (mean 14.29) compared to the subgroups of patients whose last therapy before natalizumab was GA or beta interferon; (mean 29 and 31 natalizumab infusions, respectively). In particular, only 21 patients out of 130 (16%) were exposed to Tysabri for >24 months.

No efficacy data have been provided for patients switching from other DMTs (teriflunomide, DMF) to Tysabri but efficacy of Tysabri could be expected due to disease related indication for these drugs

(teriflunomide, DMF for mild to moderate RRMS, Tysabri for highly active disease).

Risks

Unfavourable effects

The TOP study was designed as a safety non-interventional/ observational study. No data have been provided from a randomized controlled clinical trial to support the proposed extension of indication for Tysabri.

On the basis of available data coming from the observational TOP study, in a small subgroup (n=147) of patients treated with fingolimod prior to switching to natalizumab, the Applicant stated that safety findings were generally consistent regardless if the patient's last therapy before natalizumab infusion was GA, beta-interferon or fingolimod.

The incidence density of at least 1 SAE was similar in the Overall TOUCH population (3.98 per 100 patients-years) and in the subgroups according to prior DMT (switched from fingolimod: 3.60 per 100 patients-years; switched from dimethyl fumarate 3.27 per 100 patients-years; switched from teriflunomide 3.23 per 100 patients-years). However, the incidence density of SAEs by SOCs in the subgroups of patients who switched from teriflunomide is less comparable due to the relatively small sample size and the small number of events (4 or fewer) of events.

The major safety concern with natalizumab treatment is the risk of developing PML, as reflected by the 35 PML cases that occurred in TOP study. Among risk factors for PML there is the previous use of immunosuppressive drugs. The new DMTs are all endowed with immunosuppressive activity and thus may increase the risk of PML following Tysabri especially for patients switching from fingolimod and DMF. Moreover, PML cases have been reported both in patients treated with fingolimod as well as after the administration of dimethyl fumarate containing products, independently of Tysabri exposure.

Of the 35 confirmed cases of PML in the TOP study, 6 (17.1%) received prior IS therapy. The prior IS therapies included mitoxantrone, azathioprine and cyclophosphamide. None of the 35 confirmed PML patients in TOP received fingolimod, dimethyl fumarate, teriflunomide or alemtuzumab at any time prior to initiating Tysabri. However –due to the limited exposure to these new DMTs in the overall TOP population this provides only very limited reassurance.

Among important Tysabri potential risks, there is the occurrence of malignancies. In the TOP interim analysis there were 60 patients (1.1%) diagnosed with a neoplasm, and 41 of these events in 39 patients (0.7%) were malignant. Further data with longer exposures are needed in order to assess whether the use of other DMT with an immunosuppressive effect prior to switching to Tysabri are associated with an increased risk of malignancies. This issue will need discussion in upcoming PSURs.

In the TOP study there were two deaths due to pulmonary embolism, a total of 8 SAEs of pulmonary embolism, and 5 SAEs of deep vein thrombosis.

Uncertainty in the knowledge about the unfavourable effects

The Applicant updated safety data from the TOP study (last interim analysis up to 1 May 2015). However, these safety data did not significantly increase the relevant safety dataset. TOP data include only a limited number of patients (147) who switched from fingolimod to Tysabri, followed up for a relative short time (212 person-years of exposure). Only 7 patients included in TOP switched from teriflunomide to Tysabri and only 5 switched from dimethyl fumarate to Tysabri. As potential source of additional safety data in patients switching from other disease modifying therapies (DMT) to Tysabri the MAH identified the TOUCH prescribing program in the US.

It is at present not known if differences exist between "traditional" immunosuppressants and "new DMT"-endowed with immunosuppressive activity as risk factors for the occurrence of PML events following Tysabri administration. Currently, no conclusive safety data for patients switching from other DMTs (teriflunomide, DMF, fingolimod) to Tysabri are available.

Due to the variability in duration and washout periods of prior traditional immunosuppressants use between the PML and non-PML TOP population no conclusions may be drawn on this comparison.

Weight was not collected in TOP, thus the MAH is unable to provide data regarding the weight of patients with PML

Present data do not allow for comparison of the frequency and type of malignancies observed in natalizumab-treated TOP patients with those occurring in the patient population with MS of comparable age not treated with natalizumab. Further data with longer exposures are needed in order to assess whether the use of other DMT with an immunosuppressive effect prior to switching to Tysabri are associated with an increased risk of malignancies. Further post-authorisation safety data should be collected.

Effects Table

	Effect	Short Description	Unit	previous treatment before Tysabri	Uncertainties/ Strength of evidence	References
Favourable	ARR	Comparison of pre- and post-Tysabri infusion ARR	No. of relapses (N)	-Overall population from 1.99 (1.96, 2.01) to 0.22 (0.21, 0.24) - GA from 1.98 (1.93, 2.03) to 0.24 (0.22, 0.27) - Beta-interferon from 1.98 (1.94, 2.01) to 0.21 (0.19, 0.22) - fingolimod from 2.06 (1.88, 2.26) to 0.38 (0.28, 0.52)	• Reduction in ARR was shown of Tysabri in patients with prior GA / beta-interferon therapy • ARR decrease remained stable over 5 years for GA and IFN-β and over 3 years for fingolimod • data are limited but a trend towards efficacy in patients with prior fingolimod therapy is seen	Discussion on clinical efficacy Benefit-Risk Balance
	Cumulative probability of sustained EDSS improvement and progression		Percentage (%)	- Overall population (at 24 months) Improvement: 21.75% Progression: 9.43% - Overall population (at 5.5 years) Improvement: 30.34% Progression: 19.70%	• Mean EDSS scores in the overall TOP population were similar from Baseline (3.5) to Year 5 (3.2) in patients treated with Tysabri. • Similar results were seen for the subgroups of patients whose last therapy prior to dosing with	

Effect	Short Description	Unit	previous treatment before Tysabri	Uncertainties/ Strength of evidence	References
			- GA (at 24 months) Improvement: 31.43% Progression: 15.87% - GA (at 5.5 years) Improvement: 31.43% Progression: 15.87% - IFN-β (at 24 months) Improvement: 21.39% Progression: 9.48% - IFN-β (at 5.5 years) Improvement: 29.43% Progression: 21.44% - fingolimod (at 24 months) Improvement: 23.02% Progression: 5.53%	natalizumab was GA or beta interferon. • For the fingolimod subgroup, less meaningful conclusions may be drawn due to the limited sample size and the shorter Tysabri exposure. • • Due to the open label nature of the TOP study and due to the very high dropout rate, no conclusion may be drawn on a endpoint such as time to sustained improvement on EDSS • Uncertainty: very few patients received teriflunomide or dimethyl fumarate • Uncertainty: the subgroup of patients who received fingolimod as last therapy before natalizumab was exposed to a lower number of Tysabri infusions compared to the subgroups of patients whose last therapy before natalizumab was GA or beta interferon • Uncertainty: 40% of subjects did not receive Tysabri every month.	

	Effect	Short Description	Unit	previous treatment before Tysabri	Uncertainties/ Strength of evidence	References

	Effect	Description	Unit	Value	Uncertainties/Strength of evidence	Referrences
Unfavourable	SAEs	Incidence of SAEs	Percentage (%) of patients involved	At least 1 SAE Overall: 9.8% Treatment-related: 3.5% (Primarily infections, nervous and immune system disorders and neoplasms)	• Potentially increased risk for PML in patients with sequential therapies switching from other DMTs (especially from fingolimod and DMF) to Tysabri	Discussion on clinical safety Benefit-Risk Balance
	Most common SAEs	Incidence of PML	Rate/1000 patients	4.6 (3, 6.8)	• Insufficient characterisation of PML cases in TOP with regards to DMT types and duration of exposure • Only limited safety data for patients switching from other DMTs (teriflunomide, DMF) to Tysabri are available • • 2 deaths due to pulmonary embolism • TOP is a safety non-interventional/ observational study. No data from a randomized controlled clinical trial are available	
			No. (N) and Percentage (%) of patients involved	N = 35 [all confirmed]		
		Incidence of individual SAEs	No. (N) and Percentage (%) of patients involved	- Hypersensitivity N = 26 (0.5 %) - IRIS N = 20 (0.4%) - pneumonia N = 16 (0.3%) - spontaneous abortion N = 16 (0.3%) - herpes zoster N = 15 (0.3%)		
	Deaths	Incidence of deaths	No. (N) and Percentage (%) of patients involved	N = 17 (0.3%)		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Efficacy of Tysabri has been demonstrated in the past and is supported by the TOP study. Treatment options for patients with highly active RRMS are limited. Efficacious treatment is important in this patient population. Insufficient therapy can lead to an increase of relapse rates and disabilities. The possibility of switching to Tysabri after only one DMT could contribute to the patient's benefit.

Currently, the indication of Tysabri is limited to patients who have failed to respond to a full and adequate course of IFN-β or GA. The MAHs proposal to extend the indication for Tysabri is comprehensible considering the introduction of new therapeutic options in the MS treatment over the past years and the corresponding changes to current MS treatment guidelines.

From a biological perspective, there is no reason to suspect that Tysabri efficacy should be different according to the type of first line DMT. Thus the administration of Tysabri after any first line DMT would allow a larger number of MS patients to benefit from the treatment with a very efficacious drug.

Safety information on a rare event such as PML may be acquired only with post marketing clinical experience over years, so, at present, it is not possible to definitely evaluate the risk of PML for new MS DMTs or to quantify the potential increase in PML events following administration of different DMTs and Tysabri.

Conclusive data for patients with prior use of recently approved DMT switching to Tysabri are currently limited/ not available. Consequently, estimation of the PML risk for these patients is not possible. Therefore, patients with prior use of these DMT must be considered and treated as having a PML risk equal to patients with prior use of immunosuppressants.

Adequate information on the limited/absence of data for patients switching from new DMTs to Tysabri should be provided in the SmPC for the prescriber.

Benefit-risk balance

The clinical course of RRMS is characterized by a high inter-individual variability. A subset of patients presents with severe disease activity, defined by a high load of active lesions and frequent relapses that are very likely to progress to sustained disability with all related complications. If these patients show an inadequate response to a first-line therapy the treating physician should have the possibility to administer a second-line treatment such as Tysabri, after careful consideration of the individual benefit/risk balance.

Conversely, there is also a subset of MS patients for whom sequential courses with more than one disease modifying agent could be reasonably considered before starting a second-line therapy with a worse safety profile. This is correctly reflected in the wording of the indication which states after "at least one" disease modifying treatment. Because of its safety profile, Tysabri should be used when other treatments are viewed as not appropriate or inefficacious, on a case by case basis.

The main safety concern that the use of Tysabri after treatment with new DMTs generates is the potential increase in PML frequency due to the fact that previous treatment with "traditional" immunosuppressants is a known risk factor for PML occurrence. Due to the rarity of PML further information may only be acquired with post marketing clinical experience over years and the MAH committed to systematically gather additional data on the safety of Tysabri treatment in MS patients who were previously treated with at least one DMT including teriflunomide, dimethyl fumarate, alemtuzumab, fingolimod.

Discussion on the Benefit-Risk Balance

DMTs like GA, beta-interferon, teriflunomide and DMF are first line treatment options for mild to moderate forms of RRMS. In case of disease worsening DMTs are usually insufficient and these patients are in need for more effective treatment options. For patients with highly active RRMS these options include natalizumab. In the past efficacy of Tysabri has been demonstrated in the treatment of highly active RRMS. TOP provided additional efficacy data (ARR, EDSS) for patients with prior GA, beta-interferon and fingolimod therapy although for the latter the dataset is limited.

Although data on the efficacy of Tysabri after failure of first-line treatment with the newest DMTs were limited they were considered sufficient. Moreover it was recognized by the CHMP, that given the current situation, and the available therapeutic options in clinical practice, it would be unreasonable to expect separate efficacy data to be provided in patients treated with each of the marketed drugs before switching to Tysabri.

However, the main safety concern elicited by the sequential therapy of new DMTs, all endowed with immunosuppressive activity, and Tysabri is the occurrence of infections, and above all the risk of developing PML. Indeed PML cases have been recently recorded also in patient treated with fingolimod and dimethyl fumarate containing products, independently of Tysabri exposure. A recent abstract presented at the American Academy of Neurology in Washington (Herbert et al, 2015) suggested that increasing Tysabri dosing interval may be a strategy for mitigating risk of PML while maintaining efficacy. In this regard, it is of note that about 40% of patients in the TOP study did not receive Tysabri every month.

A Complete Blood Count is recommended prior to initiating Tysabri to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved. As alemtuzumab has a profound prolonged immunosuppressive effect and as the actual duration of these effects is unknown, initiating treatment with TYSABRI after alemtuzumab is not recommended unless the benefits clearly outweigh the risks for the individual patient.

In general, it is agreed that in case of sequential use of new DMTs and Tysabri, information in the SmPC on how to avoid additive immunosuppression is needed. However, up to now it is unknown whether new DMTs with an immunosuppressive mechanism of action are associated with the same increased PML risk as "traditional immunosuppressants" when administered prior to Tysabri. Indeed, complete safety information on a rare event such as PML may be acquired only with post marketing clinical experience over years, and thus it is impossible to evaluate and quantify at present the added risk of new DMTs to the development of PML following Tysabri exposure. The limited data available do not allow to identify any pattern or trend with regard to PML risk and the specific types of IS therapies. In this regard, the addition of specific recommendations with regard to specific prior immunosuppressant therapies in the SmPC of Tysabri and the Educational material is considered inappropriate.

Based on the available PSUR data (coming from STRATA, TOP and TYGRIS), no specific pattern or trend on duration of the wash-out period for "traditional immunosuppressants" therapy prior to Tysabri has been observed. PML risk appears to be present with both short and long wash-out periods.

As long as more complete data are not available, patients with prior use of another DMT with an

immunosuppressive effect should be considered as having a PML risk equal to patients who received immunosuppressants prior to receiving Tysabri.

The Applicant committed to systematically gather additional data on the safety of Tysabri treatment in MS patients who were previously treated with at least one DMT including teriflunomide, dimethyl fumarate, alemtuzumab, fingolimod.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new indication for Tysabri
As a consequence, sections 4.1 and 4.4 of the SmPC were updated in order to provide physicians with more options for treating RRMS patients with high disease activity who fail a full and adequate course of treatment with disease modifying therapy (DMT). Consequential changes were also introduced in sections 4.2, 4.3, 5.1 of the SmPC.

The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP) version 18.

This CHMP recommendation is subject to the following condition:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Based on how patients treated with TYSABRI are currently monitored at national level, the Marketing Authorisation Holder (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 Marketing Authorisation Holder must, following discussions and agreement with the National Competent Authorities in each Member State where TYSABRI is marketed, ensure that all physicians who intend to prescribe TYSABRI are provided with a physician pack containing the following elements:

- Summary of Product Characteristics and Package Leaflet
- Physician information about TYSABRI
- Patient alert card
- Treatment initiation and treatment continuation forms
- Treatment discontinuation form

The physician information about TYSABRI shall contain the following key elements:

- That TYSABRI therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.
- Information that atypical/opportunistic infections, in particular PML, may occur with TYSABRI and include:
    - That the risk of PML increases with increasing duration of treatment and that treatment beyond 24 months carries additional risk Other factors associated with an increased risk for the development of PML
        - Presence of anti-JC virus antibodies
        - Level of the antibody response (index) for patients without a history of immunosuppressant treatment
        - Immunosuppressant treatment prior to the use of Tysabri
    - A stratification of the risk of developing PML based on the identified risk factors and presentation of the PML risk in a given time interval of treatment as well as the cumulative PML risk
    - Diagnosis and prognosis of symptomatic and asymptomatic PML
    - □ differentiation between PML and MS
    - PML management algorithm
    - Possibility of other opportunistic infections
    - The recommendation that patients should have MRI scans at the following times

        - Within 3 months prior to starting TYSABRI
        - Annually during treatment with TYSABRI
            - More frequent MRIs (e.g. on a 3 to 6 monthly basis) for patients at high risk for PML.
        - At the first sign of any symptoms indicative of the possibility of PML.

Description of MRI protocols for baseline, routine screening and in case of PML suspicion

Anti-JCV antibody testing, frequency of testing, interpretation of qualitative and quantitative results, seroprevalence of JCV-antibodies and seroconversion rate over time

Monitoring strategy after discontinuation of TYSABRI treatment

    - The need to inform patients about the benefits and risk of TYSABRI and provide them with:
        - A copy of the treatment initiation form
        - A patient alert card including a core text agreed by the CHMP
    - If treatment is to be continued for longer than 24 months, the need to inform patients about the increased risk of PML and provide them with a copy of the treatment continuation form
    - Possibility of other opportunistic infections
    - The need to inform the National Competent Authority about any cases of PML

- Information about the following adverse reactions:
    - Infusion reactions
    - Hypersensitivity reactions
    - Antibody formation
- Information about any registry or other monitoring system set up in the Member State and how to enter patients

The treatment initiation form should contain the following elements:

- That the aim of the treatment initiation form is to provide patients with information on PML and IRIS
- Information on PML and IRIS including the risk of developing PML during Tysabri treatment stratified by prior treatment with immunosuppressants and JC virus infection.
- Confirmation that the doctor has discussed the risks of PML and the risk of IRIS if treatment is discontinued following suspicion of PML
- Confirmation of patient understanding of the risks of PML and that they have received a copy of the form and a patient alert card
- Patient details, signature and date
- Prescriber name, signature and date
- Date treatment started

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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new indication for Tysabri
As a consequence, sections 4.1 and 4.4 of the SmPC were updated in order to provide physicians with more options for treating RRMS patients with high disease activity who fail a full and adequate course of treatment with disease modifying therapy (DMT). Consequential changes were also introduced in sections 4.2, 4.3, 5.1 of the SmPC.

The Package Leaflet is updated in accordance.

Summary

Please refer to the scientific discussion of Tysabri H-000603-II-077-AR.