25 July 2013
EMA/492191/2013
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Tysabri

International non-proprietary name: natalizumab

Procedure No. EMEA/H/C/000603/II/0059/G

This withdrawal Assessment Report is based on the latest assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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List of abbreviations

ARR	Annualised Relapse Rate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidential Interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DMT	Disease modifying treatment
EBV	Epstein Barr virus
EDSS	Expanded disability status scale
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
GA	Glatiramer Acetate
IFN-beta	Interferon Beta
IMSE	Swedish MS registry
IS	Immunosuppressant
JCV	John Cunningham virus
MA	Marketing authorisation
MAH	Marketing authorisation holder
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale
MSQLI	Multiple Sclerosis Quality of Life Inventory
MSSS	Multiple Sclerosis Severity Score
PI	Product Information
PID	Physician Information and Management Guidelines
PML	Progressive Multifocal Leukoencephalopathy
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMS-reg	Swedish MS quality registry
STRATA	Safety of Tysabri re-dosing and treatment study
STRATIFY	JCV antibody program in patients with relapsing multiple sclerosis receiving or considering treatment with Tysabri
SDMT	Symbol Digit Modalities Test
TOP	Tysabri observational program
TYGRIS	Tysabri global observational program in safety
TYSEDMUS	French Tysabri Registry
US	United States
VAS	Visual Analogue Scale
VLA-4	Very-late- activation antigen 4

1. Background information on the procedure

1.1. Type II and group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Elan Pharma International Ltd. submitted to the European Medicines Agency on <date> an application for a group of variations including extension of indications.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Tysabri	Natalizumab	See Annex A

The following variations were requested in the group:

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

The MAH applied for a grouped extension of indications for the treatment of multiple sclerosis as follows:

1) extension of indication in RRMS population without high disease activity, those patients who are negative for anti-JCV Antibodies.

2) extension of indication in RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure.

Consequently, the MAH proposed the update of section 4.4 of the SmPC to update the warning on the risk of PML regarding anti-JCV antibody negative patients. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH proposed to include the paediatric deferral statement in accordance with QRD template version 8.

The group of variations proposed amendments to the SmPC and Package Leaflet.

This application concerns:

This application concerns a product with:

☒ a PIP ☐ a class waiver

☐a product specific waiver

☐not applicable

The PIP is ☐ completed ☒ not yet completed as some measures were deferred

The applicant received:

☐ CHMP Scientific Advice ☐ CHMP Protocol Assistance on <date> pertaining to

☐Quality ☐ non clinical ☐ clinical aspects ☐ paediatric development

☒The applicant did not seek scientific advice or Protocol assistance at the CHMP.

2. Scientific discussion

2.1. Introduction

Natalizumab (Tysabri) is a recombinant humanized monoclonal antibody that binds to the α4 chain of the α4β1 and α4β7 integrins. In multiple sclerosis (MS), the rationale for natalizumab therapy is the reduction of leukocyte migration into the central nervous system (CNS) by specifically targeting α4β1, or very-late-activation antigen 4 (VLA-4).

With increasing post-marketing experience and duration of exposure to Tysabri, the continued reporting of MS patients diagnosed with progressive multifocal leukoencephalopathy (PML) raised concerns, especially since data suggest that the risk of developing PML increases significantly after two years of continuous exposure. On 22 October 2009, the CHMP requested a review of the benefits and risks for Tysabri. In view of this, the European Commission requested the opinion of the CHMP on measures necessary to ensure the safe use of Tysabri, and a procedure under Article 20 of Regulation (EC) No 726/2004 was initiated on 26 October 2009. 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 committed to further activities for risk minimization.

PML is caused by JC virus (JCV) which is among the most prevalent viruses in the human population (Agostini 1996). Primary infection by archetype JCV is asymptomatic and occurs early in life, typically in childhood or adolescence. It appears as if a benign form of JCV remains asymptomatic in the kidney and in lymphoid organs throughout life. For the time being, it is not clear how variables, such as host factors (eg, genetics and immune status), presence of viral mutations, and therapeutic interventions (immunosuppressives, biologics) may contribute to the development of PML.

Since infection by JCV is a prerequisite for PML development, serologic detection of past infection allows for identifying patients at higher risk of developing PML (Gorelik 2010). While exposure to JCV can be confirmed by directly measuring JCV DNA in body fluids, the absence of detectable JCV DNA does not correlate with a lack of exposure to JCV, and viremia appears to be transient.

In the meantime, a validated 2-step ELISA antibody assay for the detection of anti-JCV antibodies in human serum and plasma has been developed and is now commercially available in Europe. In addition, a quantitative risk stratification algorithm which added anti-JCV antibody status to the previously established risk factors was included into the SmPC for Tysabri, and information on PML risk and JCV antibody status was also added to the Physician Information and Management Guidelines (PID) and Treatment Forms. This included a recommendation for re-testing antibody negative patients every 12 months (EMEA/H/C/00603/II/41).

Subsequently, further information on the clinical utility and testing of the anti-JCV antibody status to stratify the risk of developing PML prior or during treatment with Tysabri were introduced into the SmPC including a reference to the physician information and management guidelines for the quantification of PML risk in the different patient groups (EMEA/H/C/00603/II/54).

The CHMP also recommended to update of section 4.4 of the SmPC to include recommendations on testing frequency for anti-JCV antibody negative patients every 6 months based on review of post-marketing PML cases and clinical trial data in relation to the frequency of re-testing of anti-JCV antibody status in anti-JCV antibody negative patients (EMEA/H/C/00603/II/57, October 2012) and that patients and healthcare professionals should continue to be alert for any new signs and symptoms

that may be suggestive of Progressive Multifocal Leukoencephalopathy (PML) for approximately 6 months following discontinuation of Tysabri since PML has been reported following discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation (EMEA/H/C/00603/II/58, January 2013).

Within the present grouped variations application, the MAH initially applied for the following:

1) extension of indication in RRMS population without high disease activity, those patients who are negative for anti-JCV Antibodies.

2) extension of indication in RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure.

Consequently, the MAH proposed the update of section 4.4 of the SmPC to revise the warning on the risk of PML regarding anti-JCV antibody negative patients. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH proposed to include the paediatric deferral statement in accordance with QRD template version 8.

This withdrawal assessment report relates to the latest assessment report as adopted by the CHMP on Part 1 of the grouped variation described above i.e the withdrawn extension of indication for RRMS population without high disease activity, those patients who are negative for anti-JCV antibodies.

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

No new clinical data have been submitted in this application. The MAH refers to the main pivotal study from the initial marketing authorisation (MA), **C-1801**, a multicenter, randomized, double-blind, placebo-controlled, parallel- group trial in patients with RRMS to establish the safety and efficacy of once monthly IV infusions of natalizumab. Approximately 900 patients were to be randomized at baseline using a 2:1 allocation to receive either 300 mg of natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks.

Efficacy parameters assessed included MS relapses, brain Magnetic Resonance Imaging (MRI) scans, Expanded Disability Status Scale (EDSS) scores, Multiple Sclerosis Functional Composite (MSFC) scores, visual function tests, and quality of life as measured by Multiple Sclerosis Quality of Life Inventory (MSQLI) and a Subject Global Assessment as rated using a visual analogue scale (VAS). Visual Function and MSFC practice tests were performed three times prior to randomization to remove any learning effect and to determine baseline values. EDSS and MSFC are measured every 12 weeks, brain MRI scans at baseline and every year, and MS relapses on an ongoing basis at unscheduled visits.

2.4. Clinical efficacy

2.4.1. RRMS population without high disease activity, those patients who are negative for anti-JCV antibodies

2.4.1.1. Results

The study population evaluated in study C-1801 represented a population with mild to moderate disease activity and minimal disability at baseline despite a disease history of several years.

70% of patients were treatment naïve at baseline. In the small group of pre-treated patients (30%), one half had a history of prior immunomodulatory treatment, but the moiety had received steroids only.

Treatment with 300 mg natalizumab resulted in a 42% decrease in the risk of disability progression, as measured by sustained changes on EDSS, when compared to placebo over a 2-year period ($p<0.001$). These results were confirmed by an alternative scoring system, the Multiple Sclerosis Functional Composite (MSFC). The highly significant reduction in the annual relapse rate (ARR) that was the central argument for efficacy of the initial submission was confirmed after 2 years: Treatment with 300 mg natalizumab resulted in a 68% decrease in the annualized relapse rate versus placebo over both 1 and 2 years ($p<0.001$ for both time points). Through year 2, there was a highly statistically significant 83% reduction in the number of new or newly enlarging T2-hyperintense lesions in natalizumab-treated subjects compared to placebo. 96% of subjects in the natalizumab group were free of Gd-enhancing lesions after 1 year of treatment, and 97% after 2 years.

The effect was consistent across all subgroups regardless of age, gender, race, weight, baseline disease activity, and MS disease history, including the subgroup of treatment naive patients:

Table 1

Table 14.2-43: Efficacy Endpoints by Prior MS Medication - ITT Population - One-year Analysis

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	Placebo		Natalizumab		Rate Ratio for Relapse Rate (95% CI) (a)
	n		n		
Annualized relapse rate (95% CI) (a)					
Any Prior Therapy	87	0.730(0.547,0.974)	196	0.283(0.208,0.385)	0.388(0.254,0.592)
Any Prior Therapy Excluding Steroids	46	0.703(0.480,1.027)	103	0.396(0.282,0.557)	0.564(0.338,0.940)
Any Prior Therapy Excluding Steroids/Misc	40	0.787(0.541,1.145)	81	0.398(0.275,0.575)	0.506(0.299,0.856)
No Prior Therapy	228	0.675(0.563,0.810)	431	0.214(0.170,0.269)	0.316(0.237,0.422)
Mean number of new or newly-enlarging T2 hyperintense lesions (s.d.)					
Any Prior Therapy	87	5.43(7.39)	196	1.32(7.11)	
Any Prior Therapy Excluding Steroids	46	5.49(7.33)	103	0.75(1.29)	
Any Prior Therapy Excluding Steroids/Misc	40	6.01(7.71)	81	0.83(1.37)	
No Prior Therapy	228	6.31(9.41)	431	1.19(2.93)	

Table 2

MRI: Number of New or Newly Enlarging T2 Hyperintense Lesions by the Four Baseline Factors
ITT Population
One-year Analysis
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	Placebo	Natalizumab
Baseline number of T2 lesions		
< 9		
n	16	31
Mean (s.d.)	1.43 (1.816)	0.19 (0.578)
Median	1.00	0.00
>= 9		
n	299	596
Mean (s.d.)	6.31 (9.052)	1.29 (4.764)
Median	3.00	0.00
Baseline Gd-enhancing lesions		
Absent		
n	172	311
Mean (s.d.)	2.98 (4.488)	0.69 (1.468)
Median	1.00	0.00
Present		
n	143	316
Mean (s.d.)	9.78 (11.189)	1.76 (6.351)
Median	6.00	0.00

Table 3

.2-31: **Proportion of Subjects Relapse-free by Subgroup - ITT Population - One-year Analysis**

Page 1 of 2

	Placebo	Natalizumab
Number of subjects randomized	315	627
Number of relapses in the year prior to screening		
1 relapse		
n (%)	180 (100)	368 (100)
n (%) relapse free	104 (58)	285 (77)
2 relapses		
n (%)	102 (100)	197 (100)
n (%) relapse free	52 (51)	145 (74)
>2 relapses		
n (%)	27 (100)	56 (100)
n (%) relapse free	8 (30)	40 (71)

Discussion

The majority of patients (approximately 70%) randomized to one of the two arms in the pivotal trial C-1801 were treatment-naive. Natalizumab treatment resulted in a 68% reduction in the annualized relapse rate versus placebo (P<0.001), 80% reduction in new or newly enlarging T2-hyperintense lesions, and 92% reduction in number of Gd-enhancing lesions.

Similarly, there was a relative increase of 43% in the proportion of subjects who remained relapse free on treatment (P<0.001). The effect was rapid in onset, with differences between the groups becoming apparent after just 6 weeks of treatment. The effects were consistent in a variety of pre-specified subgroups, including weight, age, prior MS therapy, and baseline disease characteristics such as the number of T2 hyperintense lesions at baseline, the number of Gd- enhancing lesions at baseline, or the prior annual relapse rate, indicating the robustness of the result. Further, there was a significant reduction in the proportion of patients treated with corticosteroids for relapse.

After over 6 years of post-marketing experience, Tysabri continues to demonstrate a high level of efficacy, comparable to what has been demonstrated in the pivotal clinical trial C-1801.

These results confirm the efficacy of Tysabri as a first-line therapy in treatment-naive RRMS patients with mild to moderate disease activitiy.

2.4.1.2. Conclusions

On the basis of the available data, the CHMP concluded that the efficacy of Tysabri is demonstrated in the RRMS population without high disease activity. Given the modest efficacy of the currently approved first line therapies interferon beta and copaxone with ARR reductions of approximately 0.3, it can be concluded that Tysabri may confer substantial benefit in this patient population.

2.5. Clinical safety

The most important adverse event affecting Tysabri's benefit-risk profile is the occurrence of progressive multifocal leukoencephalopathy (PML). Three established risk factors have been identified and are currently included in the product labelling for risk stratification. These are anti-JCV antibody status, treatment duration and prior use of immunosuppressant therapy.

As JCV infection is a known and necessary precursor for PML development, identification of patients who are anti-JCV antibody negative, and who are therefore at very low risk for PML, provide an opportunity for physicians and patients to consider Tysabri earlier in the treatment of MS.

In order to characterize the incidence of PML in patients who are anti-JCV antibody negative, the MAH have collected data on anti-JCV antibody status from patients in clinical trials, observational studies, and the post-marketing setting. The MAH has utilized the analytically and clinically validated anti-JCV antibody ELISA to detect and confirm the presence of antibodies to JCV. The assays utilize identical methodologies and have demonstrated concordance of approximately 90% or greater for both anti-JCV antibody negative and positive samples. In addition, the assays demonstrated 100% concordance for all pre-PML samples tested. As such, the results from the assays are considered interchangeable. The assays have been CE-marked in the EU.

The data presented included: 1) STRATIFY-2 (Study 101JC402) and 2) Results of a pooled clinical study population of approximately 26,000 MS patients from STRATIFY-2, STRATIFY-1, STRATA, and TYGRIS-US with available anti-JCV antibody data. See Table 4.

Table 4

Table 1: Overview of Patients in Studies included in Pooled Clinical Study Analysis

Data Source	# of Tysabri-Treated Patients with Known Anti-JCV Antibody Status	Number of PML Cases with Known Pre-PML Antibody Status at least 6 months Prior to PML Diagnosis
STRATIFY-2 (101JC402)	23356	20#
STRATIFY-1 (101JC401)	1029	2
TYGRIS-US (101MS402)	1772	2
STRATA (101MS321 & 101MS322)	687	10
Total	**26633**	**34**

#A total of 10 PML patients were excluded from STRATIFY-2; 9 patients had anti-JCV antibody testing within 6 months of PML diagnosis and 1 patient converted from antibody negative to positive and developed PML symptoms 2 months later. Because the patient changed antibody status at some point between the 2 test results, the patient's antibody status at ≥6 months prior to PML diagnosis is not known (see Section 1.4.2 for further details).
*Population in the TYGRIS-US and STRATA studies are based on the total number of patients enrolled at the start date of the protocol amendment for anti-JCV antibody testing.
Data are included based on the following cut off dates: STRATIFY-1: August 17, 2012; STRATIFY-2: August 1, 2012; STRATA: May 20, 2012; TYGRIS-US: May 23, 2012

Source: Pooled Analysis Report, Appendix Table 4

The PML incidence in the anti-JCV antibody negative patients in the post-marketing setting was estimated, based on results from the PML cases from all global sources in the post-marketing setting (including PML cases from clinical studies and spontaneous reports) with known pre-PML anti-JCV antibody status at least 6 months prior to diagnosis.

The proportion of patients who change antibody status annually from anti-JCV antibody negative to anti-JCV antibody positive has been evaluated based on the AFFIRM and STRATIFY-1 studies examining longitudinal antibody status over 18 months.

The false negative rate of the STRATIFY JCV Dx Select assay has been determined based on STRATIFY-1 data over 18 months.

2.5.1.1. Results

Results are presented in Tables 5-13.

Data from STRATIFY-2 demonstrate that the risk of PML in anti-JCV antibody negative patients is significantly lower than the risk in anti-JCV antibody positive patients. The incidence of PML for anti-JCV antibody negative patients in this study is estimated to be approximately 0.09/1,000 (95% CI:0-0.5). See Tables 5 and 6.

Table 5

Table 2: Incidence of PML Stratified by Anti-JCV Antibody Status in STRATIFY-2

Anti-JCV Antibody Status [1]	No. of PML Cases	Total Patients Treated with ≥1 month of Tysabri	Incidence per 1,000 patients (95% CI) treated with >=1 month of Tysabri
JCV Ab+	20	12237	1.63 (1.00, 2.52)
JCV Ab–	0	11119	0 (0, 0.33)
Total	20	23356	0.86 (0.52, 1.32)
p-value*	< 0.0001		
RR (95% CI**)	∞ (5.63, ∞)		

[1] Anti-JCV antibody testing performed using STRATIFY JCV assay
* 1-sided Fisher's exact p-value comparing incidence of PML in patients tested anti-JCV antibody positive to the incidence in antibody negative patients
** 2-sided exact 95% confidence interval (CI) of relative risk (RR) based on binomial distribution
Analysis includes PML cases in STRATIFY-2 with known pre-PML anti-JCV antibody status

Table 6

Table 3: Incidence of PML by anti-JCV antibody status (21 PML cases, 20 tested positive and 1 tested negative) - Hypothetical Scenario

Anti-JCV Antibody Status [1]	No. of PML Cases	Total Patients Treated with ≥1 month of Tysabri	Incidence per 1,000 patients (95% CI) treated with >=1 month of Tysabri
JCV Ab+	20	12237	1.63 (1.00, 2.52)
JCV Ab–	1	11120	0.09 (0.00, 0.50)
Total	21	23357	0.90 (0.56, 1.37)
p-value*	< 0.0001		
RR (95% CI**)	18.20 (2.91,755)		

[1] Anti-JCV antibody testing performed using STRATIFY JCV assay
* 1-sided Fisher's exact p-value comparing incidence of PML in patients tested anti-JCV antibody positive to the incidence in antibody negative patients
** 2-sided exact 95% confidence interval (CI) of relative risk (RR) based on binomial distribution
Analysis includes PML cases in STRATIFY-2 with known pre-PML anti-JCV antibody status and utilizes 1 hypothetical anti-JCV antibody negative PML case.

Data from a pooled clinical study population from the STRATIFY-2, STRATIFY-a, STRATA, and TYGRIS-US studies also demonstrate that the risk of PML is significantly lower in anti-JCV antibody negative patients than in anti-JCV antibody positive patients. The incidence of PML in the pooled study population for anti-JCV antibody negative patients is estimated to be approximately 0.08/1,000 (95% CI: 0-0.45). See Tables 7 and 8.

Table 7

Table 4: Incidence of PML Stratified by Anti-JCV Antibody Status in Pooled Clinical Trial/Observational Study Data Set

Anti-JCV Antibody Status [1]	No. of PML Cases	Total Patients Treated with ≥1 month of Tysabri	Incidence per 1,000 patients (95% CI) treated with >=1 month of Tysabri
JCV Ab+	34	14250	2.39 (1.65, 3.33)
JCV Ab–	0	12383	0 (0, 0.30)
Total	34	26633	1.28 (0.88, 1.78)
p-value*	<0.0001		
RR (95% CI**)	∞ (9.45, ∞)		

[1] Anti-JCV antibody testing performed using STRATIFY JCV assay
* 1-sided Fisher's exact p-value comparing incidence of PML in patients tested anti-JCV antibody positive to the incidence in antibody negative patients
** 2-sided exact 95% confidence interval (CI) of relative risk (RR) based on binomial distribution

Table 8

Table 5: Incidence of PML Stratified by Anti-JCV Antibody Status in Pooled Clinical Trial/Observational Study Data Set - Hypothetical Scenario

Anti-JCV Antibody Status [1]	No. of PML Cases	Total Patients Treated with ≥1 month of Tysabri	Incidence per 1,000 patients (95% CI) treated with >=1 month of Tysabri
JCV Ab+	34	14250	2.39 (1.65, 3.33)
JCV Ab–	1	12384	0.08 (0.00, 0.45)
Total	35	26634	1.31 (0.92, 1.83)
p-value*	<0.0001		
RR (95% CI**)	29.5 (4.97, 1204)		

[1] Anti-JCV antibody testing performed using STRATIFY JCV assay
* 1-sided Fisher's exact p-value comparing incidence of PML in patients tested anti-JCV antibody positive to the incidence in antibody negative patients
** 2-sided exact 95% confidence interval (CI) of relative risk (RR) based on binomial distribution

Cumulative data from a total of 86 PML cases from all global sources in the post-marketing setting (including clinical studies and spontaneous reports) with known pre-PML samples at least 6 months prior to PML diagnosis estimated the overall PML incidence in anti-JCV antibody negative patients to be approximately 0.07/1,000 (95% CI:0-0.38). See Table 9.

Table 9

Table 6: Incidence of PML Stratified by Anti-JCV Antibody Status in Tysabri-treated Patients in the Post-marketing Setting as of September 5, 2012

	No. of PML Cases with Pre-PML Antibody Status	Total Patients Treated with ≥1 month of Tysabri	Incidence per 1,000 patients (95% CI) treated with >=1 month of Tysabri
JCV Ab+	85	18012	4.72 (3.77, 5.83)
JCV Ab–	1	14737	0.07 (0.00, 0.38)
Total	86	32749	2.63 (2.10, 3.24)
p-value*	<0.0001		
RR (95% CI)**	69.6 (12.2, 2792)		

* 1-sided Fisher's exact p-value comparing incidence of PML in patients tested anti-JCV antibody positive to the incidence in antibody negative patients

** 2-sided exact 95% confidence interval (CI) of relative risk (RR) based on binomial distribution

A sensitivity analysis examining the effect of increasing the number of anti-JCV antibody negative PML cases on PML risk, demonstrates that with a hypothetical scenario of up to 4 antibody negative PML cases out of a total of 89 PML cases, anti-JCV antibody negative patients continue to have a 17-fold lower risk of PML than anti-JCV antibody positive patients. See Table 10.

Table 10

Table 7: PML Incidence Estimates with Increasing Number of Anti-JCV Antibody Negative PML Cases

Number of PML cases		PML incidence per 1000 (95% CI) in Patients Treated with ≥1 month of Tysabri		Relative risk (Ab+ vs Ab-) with 95% CI	1-sided p-value: Ab+ vs Ab -
JCV Ab+	JCV Ab-	JCV Ab+	JCV Ab-		
85	1	4.72 (3.77, 5.83)	0.07 (0.00, 0.38)	69.6 (12.2, 2792)	<0.0001
85	2	4.66 (3.73, 5.76)	0.13 (0.02, 0.48)	34.8 (9.37, 293)	<0.0001
85	3	4.61 (3.69, 5.70)	0.20 (0.04, 0.58)	23.2 (7.70, 115)	<0.0001
85	4	4.56 (3.64, 5.64)	0.26 (0.07, 0.67)	17.4 (6.57, 65.6)	<0.0001

Sensitivity analysis includes the one PML patient who tested anti-JCV antibody negative 9 months prior to PML diagnosis and also includes an additional hypothetical second, third and fourth antibody negative PML patient

The proportion of patients with available samples at each time point stratified by anti-JCV antibody status at the prior time point for STRATIFY -1 are presented in Table 11.

Table 11

Table 8: Proportion of Patients with Available Samples at each time point stratified by Anti-JCV Antibody Status at the Prior Time Point for STRATIFY-1*

Timepoint	Anti-JCV Antibody Positive	Anti-JCV Antibody Negative	Total
6 Month	87% (534/614)	89% (427/482)	88% (961/1096)
12 Month	86% (433/506)	86% (390/455)	86% (823/961)
18 Month	87% (396/457)	88% (343/392)	87% (739/849)
24 Month	69% (301/435)	85% (329/387)	77% (630/822)

*Anti-JCV antibody results above reflect testing using STRATIFY JCV assay. Anti-JCV antibody status is based on the antibody status in the previous time point. The numerator is the number of patients with available samples at the specified time point in the study; the denominator is the number of patients who tested anti-JCV antibody positive or negative at the previous time point in the study.
Source: Longitudinal Analysis Report, Appendix Table 5

Longitudinal data collected over 18 months from the AFFIRM and STRATIFY-1 studies demonstrate that the proportion of patients who test antibody positive at any time point in the studies is approximately 60-62%, and the proportion of patients who test antibody negative at all timepoints in the studies is approximately 38-40%. The proportion of patient who change antibody status annually ranges from 3.3% in AFFIRM to 7.5% in STRATIFY-1. The proportion of patients who test intermittently positive annually ranges from 3.3% in AFFIRM to 3.5% in STRATIFY-1. See Tables 12 and 13.

Table 12

Table 9: Longitudinal Evaluation of Anti-JCV Antibody Status in STRATIFY-1 using Patients with Samples Available for Testing at all 6 month interval Time Points Through Month 18

Anti-JCV Antibody Status[1]	Number of Patients (%) (n=720)
Ever positive at any time point	446 (61.9%)
• Consistently Positive at all timepoints	373 (51.8%)
• Seroconverter	37 (5.1%)
• Seroreverter	7 (1.0%)
• Intermittent Positive - Positive at baseline - Negative at baseline	29 (4.0%) 12 17
Consistent Negative at all time points	274 (38.1%)

[1] Anti-JCV antibody testing performed using STRATIFY JCV Dx Select assay

*Note that the grouping "Ever positive at any time point" includes all of the following groups: "Consistently positive at all timepoints", "Seroconverter", "Seroreverter", and "Intermittent Positive"

Source: Longitudinal Analysis Report, Appendix Table 6

Table 13

Table 11: Longitudinal Evaluation of Anti-JCV Antibody Status in AFFIRM using Data Collected for up to 18 months with Comparison to Data Collected for up to 18 months from STRATIFY-1

Anti-JCV Antibody Status[1]	AFFIRM Number of Patients (%) (n=540)	STRATIFY-1 Number of Patients (%) (n=720)
Ever positive at any time point	322 (59.6%)	446 (61.9%)
• Consistently Positive at all time points	283 (52.4%)	373 (51.8%)
• Seroconverter	12 3.3% per year	37 7.5% per year
• Seroreverter	11	7
• Intermittent Positive -Positive at baseline -Negative at baseline	16 4 12 3.3% per year	29 12 17 3.5% per year
Consistent Negative at all time points	218 (40.4%)	274 (38.1%)

[1] Anti-JCV antibody testing performed using STRATIFY JCV Dx Select assay

*Note that the grouping "Ever positive at any time point" includes all of the following groups: "Consistently positive", "Seroconverter", "Seroreverter", and "Intermittent Positive"

Source: Longitudinal Analysis Report, Appendix Table 6 and Table 7

Based on STRATIFY-1 data through 18 months, the false negative rate of the STRATIFY JCV Dx Select assay has been determined to be 2.4%, which is consistent with the false negative rates reported for other similar ELISAs (Jacobson 1998).

2.5.1.2. Discussion

The safety profile of Tysabri has been well characterized with over 6 years of marketing experience. Infusion and hypersensitivity reactions and anti-natalizumab antibody production are important safety concerns; however, they are manageable in routine clinical practice. Serious herpes infections and hepatic events are additional safety concerns, but the incidence of these adverse events is very low. The most important adverse event affecting Tysabri benefit-risk considerations is the occurrence of PML.

The data presented here indicate that the estimated incidence of PML in anti-JCV antibody negative patients treated with Tysabri is approximately 1/10,000.

Even though, a low risk of PML has been estimated in MS patients negative for anti-JCV antibodies tested by ELISA Stratify JCV Dx Select assay, several concerns on the applied methodology still persist.

The calculation of the risk estimate by the MAH is based on the following assumptions:
- only individuals infected with JC Virus can develop PML;
- the search of JC Virus DNA in urines is a reliable method to identify latently infected patients;
- sensitivity and predictive values of the Stratify JCV Dx Select test can be reliably evaluated identifying latently infected individuals by presence of JC Virus DNA in urine.

However, the following issues, impacting on the reliability of the methodology used for the calculation of the risk estimate need to be taken into account:
- direct Virus DNA amplification from urines may not be a sensitive enough marker of JC Virus latent infection as in this compartment JC Virus DNA is present only during the productive phase of the infection, which occurs irregularly;
- the frequency of natalizumab treated patients shedding JCV in urine was similar to the incidence observed in healthy individuals (20-50%). (Rudick et al., Annals of Neurology 2010).
- the frequency of positive JCV DNA isolation, in Natalizumab-treated patients, may vary according to the compartment selected for JCv DNA amplification. Up to now, available data (both from literature and MAH studies) suggest that the optimal compartment for searching JCV DNA is still controversial as whole blood might give different results from urines (Major E., NEJM 2009;, comment to Chen T. NEJM, 2009; Chen T et al, reply to Major and to other, NEJM, 2009). This may be due to the higher number of circulating leucocytes observed during therapy administration.
The MAH estimated the false negative rate (2.7%) of the Stratify JCV Dx Select test (STRATIFY-1 data) by looking for latent JC Virus infection, only in DNA extracted from urines and not in DNA extracted from whole blood (PBMCs). Differences in DNA amplification results according to the selected compartment would hamper the sensitivity and specificity of the analysis and thus the estimated false negative rate of the the Stratify JCV Dx Select test and the overall PML risk stratification.
-In addition, since the frequency of JCV DNA may increase after prolonged natalizumab treatment (longer than 18 months), the reported data up to 18 months do not allow to estimate a potential PML risk increase over time. Anticipating the start of Tysabri treatment would hence increase this still not characterized risk.

Taken together these data suggest that the estimate of the risk in RRMS patients undergoing Tysabri treatment based on STRATIFY JCV DX Select test might be underestimated and therefore a number of PML cases higher than those shown (n=1) could be expected in antibody seronegative patients. Moreover, the low number of PML reported by the MAH in this population of MS could be due to a non representative number of PML cases included (34 +86=120) which are less than half of the total registered thus far. Therefore, further data on PML incidence in STRATIFY JCV DX Select test negative patients and on sensitivity and predictive value of the test are needed before allowing Tysabri extension of indication to all seronegative patients as first line therapy.

There are concerns pertaining to the group of seroconverters which change antibody status from negative to positive over time. The following issues remain unclear and need to be addressed further:

- Seroprevalence studies have demonstrated conflicting results regarding the distribution of JCV antibodies. Data indicate that there are differences in both the geographic and age distributions of the antibody, suggesting that seroprevalences increase with age. Therefore, longitudinal data on JCV seroconversion rates over time are needed to assess the probability for anti-JCV antibody negative patients to change antibody status from negative to positive over time. Recent data suggest higher seroconversion rates than the presented estimation by the MAH (A. Etxeberria et al., 2012: Annual rate of JCV seroconversion in a French Cohort of MS Patients under Natalizumab; R. Lanzillo et al., 2012: JCV antibodies seroconversion on natalizumab treatment and predictive factors: preliminary data).

- It remains unclear whether patients acquiring primary JCV infection whilst on Tysabri therapy may differ in their risk of developing PML and in the clinical course of the PML disease compared to patients with previous JCV infection which reactivates. Further understanding of this issue is essential to estimate the PML risk for patients being tested anti-JCV antibody negative prior to initiation of Tysabri therapy.

- As already discussed with the MAH, presentation of PML risk in form of incidence rates is not considered ideal. PML risk calculations should be depicted as Kaplan-Meier graphs, which are considered superior in illustrating the cumulative risk over time.

- In general, the calculation of the PML risk in the anti-JCV antibody negative and positive patients is based on incomplete and retrospective data.

2.5.1.3. Conclusions

At the present time, the CHMP concluded that the safety profile in the RRMS population without high disease activity, for those patients who are negative for anti-JCV antibodies, is not sufficiently characterised.

2.5.2. PSUR cycle

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider the PSUR cycle at the present time.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 16.0 the PRAC considers by consensus that the risk management system for natalizumab (TYSABRI) as single disease modifying therapy in adult patients aged 18 years and over with relapsing remitting multiple sclerosis in the following patient groups:

- Patients who are negative for anti-JCV antibodies (see section 4.4) with or without high disease activity.
- Patients who are positive for anti-JCV antibodies or have unknown anti-JCV antibody status (see section 4.4) with high disease activity, which may be defined as:
    - o Patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of alternative immunomodulatory therapies for example, 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

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

<u>is not acceptable</u> since the proposed pharmacovigilance and risk minimisation activities cannot adequately manage the risk of PML in the newly included patient population (i.e. patient with relapsing remitting multiple sclerosis without high disease activity who are anti-JCV antibody negative), especially in patients who experience JCV seroconversion. Details are provided in Section 2. The applicant is requested to submit an updated risk management plan and satisfactory responses to the questions detailed in Section 4.

The PRAC also considers that for a robust benefit-risk assessment for the newly included patient population of relapsing remitting multiple sclerosis patients without high disease activity who are anti-JCV antibody negative, additional information is warranted.

Advice on conditions of the marketing authorisation

As there are outstanding issues regarding the RMP to be resolved, only preliminary advice can be provided at this stage. The preliminary PRAC advice is:

Risk management system

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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

The PRAC considers that the existing conditions in the Marketing Authorisation relating to the safe and effective use of the product are sufficient.

Other conditions: obligation to conduct post-authorisation measures

Not applicable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of the Safety Concerns

Summary of safety concerns	

Important identified risks	• Infections
	  o Progressive Multifocal Leukoencephalopathy (PML)
	  o Herpes infections
	• Hypersensitivity Reactions
	• Anti-Natalizumab Antibody Formation
	• Hepatic Injury

Important potential risks	• Malignancies • Venous Thrombosis
Important missing information	• Effects of natalizumab on fertility and outcome of pregnancy • Patients over the age of 65 years • Children and adolescents • Pharmacokinetic and safety profiles of natalizumab in patients with renal and hepatic impairment

The PRAC considers that the following issues should be addressed:

- The PRAC considers that long-term exposure in patients with relapsing remitting multiple sclerosis without high disease activity who are anti-JCV antibody negative should also be a safety concern and classified as important missing information.

Pharmacovigilance plans

On-going and planned studies in the pharmacovigilance development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Tysabri Observational Program (**TOP**) Study IMA-06-02 **Category 3**	To obtain long-term safety data on subjects with MS treated with Tysabri in a clinical practice setting the collection of data concerning progression of MS.	PML and Other Infections Malignancies Anti-Natalizumab Antibody Formation Hypersensitivity Reactions	Started	2023
Tysabri Global Observational Program in Safety (**TYGRIS**): Study 101MS402	To obtain long-term safety data on subjects with MS treated with Tysabri in a clinical practice	PML and Other Infections Malignancies Anti-Natalizumab Antibody	Started	2014

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
(US, Canada) Study 101MS403 (ROW) **Category 3**	setting	Formation Hypersensitivity Reactions		
Epidemiology of JCV Antibody Seroprevalence in Multiple Sclerosis Patients **(JEMS)** Study 100JC401	Epidemiology of JCV antibodies as risk factor for PML	PML and Other Infections	Started	2013
Treatment Interruption of Natalizumab **(RESTORE)** Study 101MS205 **Category 3**	Clinical study to investigate drug interruption to further investigate effects of drug withdrawal on lymphocyte trafficking and return of MS activity to determine whether drug interruption might possibly reduce risk of PML	PML and Other Infections	Complete	CSR Q3 2012
A Randomized, Blinded, Parallel-Group, Phase 2 Study Exploring the Safety, Tolerability, and Efficacy of Multiple Regimens of Natalizumab in Adult Subjects With Relapsing Multiple Sclerosis **(REFINE)** Study 101MS206 **Category 3**	Clinical dose-ranging study comparing the safety, tolerability, and efficacy of Tysabri (standard dose regimen of 300mg q4 weeks) to lower dose regimens (300mg q12 weeks, 150mg q12 weeks).	PML and Other Infections	Started	2015
JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri® **(STRATIFY-1)**	To define the prevalence of anti-JCV antibodies in serum and plasma and to confirm the false negative rate of the anti-JCV	PML and Other Infections	Started	2012

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Study 101JC401 **Category 3**	antibody assay.			
JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri® **(STRATIFY-2)** Study 101JC402 **Category 3**	To evaluate whether the incidence of PML in Tysabri-treated patients who are anti-JCV antibody negative is lower than in patients who are anti-JCV antibody positive.	PML and Other Infections	Started	2015
Corticosteroids for Immune Reconstitution Inflammatory Syndrome (**IRIS**) Study 101JC404 **Category 3**	To examine the effect of 2 different corticosteroid treatment schedules in the setting of Immune Reconstitution Inflammatory Syndrome (IRIS) in patients who have developed PML while on treatment with natalizumab.	PML and Other Infections	Completed	CSR Q4 2012
Genetic Evaluation of Natalizumab-Treated Patients With Progressive Multifocal Leukoencephalopathy (**GENETICS**) Study 101JC403 **Category 3**	Cross-sectional study to examine host genetic variation and possible genetic susceptibility to PML.	PML and Other Infections		2013
Pregnancy Registry Study 101MS403 **Category 3**	Tysabri Pregnancy Exposure Registry	Pregnancy and Pregnancy outcome	Started	
Re-dosing study **(STRATA)** North American protocol: Study 101-MS-322 European/ROW	To evaluate the risk of hypersensitivity and immunogenicity upon redosing with natalizumab, and to confirm	PML and Other Infections Anti-Natalizumab Antibody Formation Hypersensitivity	Started	2018

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
protocol : Study 101-MS-321 **Category 3**	the safety of switching treatment from other MS therapies to natalizumab	Reactions		

*Category 1 are imposed activities considered key to the benefit risk of the product. Category 2 are specific obligations. Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures).

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product in the new indication.

The PRAC considered that the limited information on the long-term seroconversion rates and PML risk in patients with relapsing remitting multiple sclerosis without high disease activity who are anti-JCV antibody negative will be addressed by the on-going STRATIFY-2 study which objectives include the investigation of JCV seroprevalence and seroconversion and PML prevalence under Tysabri treatment.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Progressive Multifocal Leukoencephalopathy (PML)	Contraindication for use in patients with PML in section 4.3 of the SmPC. Warning in Section 4.4 of SmPC with the addition of a 6 month vigilance post discontinuation of Tysabri 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 of PML for approximately 6 months post-discontinuation of treatment added to SmPC and physician education document.	**Physician education** • Physician Information and Management Guidelines updated on testing frequency and continued vigilance for signs of PML for approximately 6 months post-discontinuation. • DHCP letter when new information becomes available. • 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. • Publishing an MRI learning module on the differentiation of MS relapse from PML. **Patient 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).
Herpes infections/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.	Physician Education via a Physician Information and Management Guidelines (see above).
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 (see above).
Anti-natalizumab antibody	Recommendation that therapy be	None.

formation	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.	
Hepatic reactions	Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC.	DHCP letters issued to prescribers in EU.
Malignancy	Contraindication in patients with known active malignancies (except for patients with cutaneous basal cell carcinoma) in section 4.3 of the SmPC.	None.
Immunisation response	Information included in section 4.5 of the SmPC summarising results of trial (no impact of Tysabri on immune response to recall or neoantigen).	None.
Venous thrombosis	None.	None.
Pregnancy and pregnancy outcome	Recommendations for discontinuation of Tysabri with occurrence of pregnancy as listed in section 4.6 of the SmPC.	None.
Special Populations: • Patients over the age of 65 years • Children and adolescents • Pharmacokinetic and safety profiles of natalizumab in patients with renal and hepatic impairment	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.	None.

As there are many outstanding issues regarding the RMP, the preliminary view of the PRAC is that the proposed risk minimisation measures are not sufficient to minimise the risks of the product in the proposed indication and supplementary risk minimisation measures are required relating to:

- PML risk management strategy for patients who do test seropositive after starting Tysabri including guidance on actions to take for these patients stratified by age. All educational materials should be updated accordingly.
- If the indication is not approved, there remains an important potential risk of off-label use in the treatment naïve, mild or moderate disease/seronegative MS population. There should be measures in place to evaluate and minimise this risk.
- Concerning the proposals for risk minimisation activities in special populations the MAH is reminded to update this section, and to provide additional PK data and a summary of the efficacy data

available from post-marketing experience. This is an agreed commitment summarised in the Opinion on the paediatric investigation plan (PIP) (EMEA-001095-PIP02-12).

The CHMP endorsed this advice without changes.

2.7. Update of the product information

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider the proposed update of the product information at the present time.

3. Benefit-risk balance

3.1.1. Beneficial effects

Tysabri confers a highly significant reduction in the annual relapse rate (ARR) and the risk of disability progression. Treatment with 300 mg natalizumab resulted in a 68% decrease in the annualized relapse rate versus placebo over both 1 and 2 years ($p<0.001$ for both time points). Through year 2, there was a highly statistically significant 83% reduction in the number of new or newly enlarging T2-hyperintense lesions in natalizumab-treated subjects compared to placebo. 96% of subjects in the natalizumab group were free of Gd-enhancing lesions after 1 year of treatment, and 97% after 2 years. The effect was consistent across all subgroups, including the subgroup of treatment naive patients.

3.1.2. Uncertainty in the knowledge about the beneficial effects

A risk of over-treatment in patient with “benign forms” of MS, who can remain fully functional in all neurological systems for several years after MS onset, is possible as these patients are a subgroup of the general MS population without high disease activity which is the target of the sought indication.

3.2. Risks

3.2.1. Unfavourable effects

The most important adverse event affecting Tysabri benefit-risk considerations is the occurrence of PML. Current data indicate that the estimated incidence of PML in anti-JCV antibody negative patients treated with Tysabri is approximately 1/10,000. Additional safety concerns include infusion and hypersensitivity reactions, the production of anti-natalizumab antibodies, infections (including serious herpes infections).

3.2.2. Uncertainty in the knowledge about the unfavourable effects

The occurrence of false-negative anti-JCV antibody test results cannot completely be eliminated, although the rate of false-negative results was demonstrated to be low (2.4%) this estimate still has some uncertainty as there is no gold standard for confirming JCV positivity. It must also be noted that patients (6.6% in AFFIRM, and 11% in STRATIFY-1) will change antibody status over time, again there is uncertainty on the true conversion rate. Regular re-testing on a 6-monthly basis is therefore recommended. However, it is not completely clear yet, what should be recommended to patients whose antibody status has changed to positive, since the following questions have arisen:

- Seroprevalence studies have demonstrated conflicting results regarding the distribution of JCV antibodies. Data indicate that there are differences in both the geographic and age distributions of the antibody, suggesting that seroprevalences increase with age. Therefore, longitudinal data on JCV

seroconversion rates over time are needed to assess the probability for anti-JCV antibody negative patients to change antibody status from negative to positive over time.

- It remains unclear whether patients acquiring primary JCV infection whilst on Tysabri therapy may differ in their risk of developing PML and in the clinical course of the PML disease compared to patients with previous JCV infection which reactivates. Further understanding of this issue is essential to estimate the PML risk for patients being tested anti-JCV antibody negative prior to initiation of Tysabri therapy.

- As already discussed with the MAH, presentation of PML risk in form of incidence rates is not considered ideal. PML risk calculations should be depicted as Kaplan-Meier graphs, which are considered superior in illustrating the cumulative risk over time.

- In general, the calculation of the PML risk in the anti-JCV antibody negative and positive patients is based on incomplete and retrospective data.

3.3. Benefit-risk balance

3.3.1. Importance of favourable and unfavourable effects

Early treatment with disease modifying therapies has become the cornerstone of MS therapy, with prevention of disability progression being the major goal of treatment. Tysabri has demonstrated the ability to significantly reduce both, annual relapse rate (ARR) and the risk of disability progression. This effect is assumed to be more pronounced than with alternative disease modifying treatments, such as beta-INF or GA. The proven efficacy of Tysabri as a first-line therapy in treatment-naive RRMS patients can therefore be considered.

The most important adverse event affecting Tysabri benefit-risk considerations is the occurrence of PML. The incidence of PML in the proposed population of anti-JCV antibody negative RRMS patients is estimated to be approximately 1/10,000, which would be remarkably low. However, as detailed above, additional information and data are deemed necessary for proper risk stratification.

3.3.2. Benefit-risk balance

Tysabri confers a highly significant reduction in annual relapse rates (ARR) and the risk of disability progression. First-line treatment with 300 mg natalizumab resulted in approximately 70% decrease in annualized relapse rates versus placebo and in an approximately 80% reduction in the number of new or newly enlarging T2-hyperintense lesions. These beneficial effects are faced by various safety concerns, such as infusion and hypersensitivity reactions, the production of anti-natalizumab antibodies, infections (including serious herpes infections), and – most importantly- the occurrence of PML. Current data do not indicate new safety concerns for Tysabri if used as first-line therapy. A low risk of PML in anti-JCV antibody negative patients and the proven high efficacy of Tysabri in the treatment of RRMS argue for a positive benefit-risk balance for the use of Tysabri as a first line therapy in treatment naïve RRMS patients that are anti-JCV antibody negative. A risk of over-treatment in patient with “benign forms” of MS, who can remain fully functional in all neurological systems for several years after MS onset, is possible as these patients are a subgroup of the general MS population without high disease activity which is the target of the sought indication. Over-treatment would unnecessary expose patients to the risk of PML, which is considered unacceptable in light of the benign course of the disease in these patients and will only rarely develop a more severe course of the disease. Therefore, some patients in the first line setting may have a benign course and might therefore not be considered as good candidates for a therapy with a higher degree of uncertainty as regards the occurrence of severe ADR such as PML and other (opportunistic) infections (e.g. viruses of

the herpes group), as patients initially tested anti-JCV antibody negative may change antibody status over time or might have been tested false-negative. Benefit-risk for this group of patients has not been adequately appraised yet.

4. Recommendations

☒ The application for the group of variations II/59 for Tysabri® (natalizumab) , in the treatment of multiple sclerosis, for the following proposed change to the indication statement in section 4.1 of the SmPC,

1) extension of indication in RRMS population without high disease activity, in those patients who are negative for anti-JCV Antibodies

is not approvable since major objections have been identified, which preclude a recommendation at the present time.