

11 February 2016 EMA/PRAC/171485/2016 Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Tysabri

INN: natalizumab

Procedure number: EMEA/H/A-20/1416/C/000603/0083

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.



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1. Information on the procedure

1.1. Referral of the matter to the PRAC

Scientific evidence on progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri is rapidly growing. New information has become available on three key issues: risk estimates; the diagnosis of PML before the development of clinical symptoms; and anti-JC virus antibodies. There is a need to consider whether regulatory action is necessary in light of the new elements.

In view of the above, on 29 April 2015 the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and asked the Agency to assess the above elements and their potential impact on the benefit-risk balance of Tysabri. The EC requested the Agency to give its opinion on whether a regulatory action with regard to the marketing authorisation for this product is necessary.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use (CHMP) on the basis of a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC).

2. Scientific discussion

2.1. Introduction

Natalizumab is a humanized monoclonal antibody targeting the a-chain of the a4 β 1 adhesion molecule. Tysabri (natalizumab) was approved in the EU on 27 June 2006 and is currently indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS) for the following patient groups:

• Adult patients aged 18 years and over with high disease activity despite treatment with a betainterferon 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.

Natalizumab is associated with the onset of progressive multifocal leukoencephalopathy (PML), which is caused by John Cunningham Virus (JCV). The onset of PML in MS has serious prognostic implications, as it leads to death in about 20% of patients or to serious disability in 40% of survivors (Sørensen PS et al, 2012). The clinical presentation of natalizumab-associated PML is considered not distinct from

classical PML, and consists in cognitive disorders in more than half of the patients together with motor symptoms, ataxia, neurovisual disturbances, and dysphasia or agnosia in more than 40% of cases (Brew BJ et al, 2010, Berger JR et al, 2013).

Pathomechanism

The high prevalence of asymptomatic JC polyomavirus (JCV) infection (50 %- 90 %) in the general population indicates coexistence with the human host and efficient immune control in healthy individuals. For unknown reasons, kidney-resident archetypic JCV strains can turn into neurotropic JCV strains which in immunodeficient patients can cause opportunistic infection and cytolytic destruction of glial cells or granule cell neurons resulting in progressive multifocal demyelination in the central nervous system (CNS) or cerebellar atrophy, respectively. Symptomatic JCV infection of the CNS is assumed to be associated with disturbances of adaptive immunity affecting B cells, antibodies, and CD4⁺ and/or CD8⁺ T cells.

Two general mechanisms have been suggested to explain the association between natalizumab treatment and PML. The first is that blocking alpha-4 integrin decreases lymphocyte trafficking, and the subsequent reduction in immune surveillance allows for the activation of a latent infection in the brain. However, it is assumed that the natalizumab action is not simply caused by the inhibition of the passage of activated T-lymphocytes through the blood brain barrier (BBB). Indeed, the impact on immune functions of natalizumab is apparently broader and includes interactions various players of the innate and adaptive immune system such as antigen presenting cells (APC) and natural killer (NK) cells. The second suggested mechanism is associated with the finding that deletion of alpha 4 integrin is associated with increased numbers of B cells and immature CD34+progenitor cells released from the bone marrow. Both of these cell populations may be reservoirs of latent JC virus (Warnke C et al, 2011, Frohman EM et al, 2014, Monaco MC et al, 1996, Chalkias S et al, 2014).

Diagnosis

According to the current case definitions, a possible PML case the definite diagnosis of PML requires clinical symptoms and either the detection of JCV DNA in cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) amplification or a brain biopsy to detect JCV DNA on histological examination and/or characteristic MRI findings (Berger JR et al, 2013, Mentzer D et al., 2012)

On MRI, PML lesions of symptomatic cases are generally large (more than 3 cm) and can affect supratentorial and infratentorial white matter. These lesions are usually hyperintense on T2 and FLAIR (fluid-attenuated inversion recovery) MRI sequences and hypointense on T1 sequences. Diffusion weighted imaging (DWI) can help in the diagnosis of PML in natalizumab-treated patients to differentiate active PML lesions from MS plaques. In contrast with non-natalizumab-PML lesions, natalizumab-associated PML lesions frequently show gadolinium enhancement (43% of cases) (Brew BJ et al, 2010).

Despite improved sensitivity of the newest quantitative PCR techniques for JCV detection in the CSF (Iacobaeus E et al, 2009), the result is sometimes negative, especially in early stages of the disease, justifying repeated CSF analysis and the use of ultra-sensitive methods that enable the detection of a very small number of copies with a detection limit up to 10 copies JCV DNA/ml (Brew BJ et al, 2010).

Therapy

To date, no specific therapy to overcome PML is available, although several therapeutic options are currently investigated. The only way to eliminate the virus from the CNS is to reconstitute global immune function. Therefore it is of inherent importance to diagnose PML as early as possible and to stop treatment immediately.

Due to the long half-life of natalizumab, the majority of PML patients underwent either plasma exchange (PLEX) or immunoadsorption (IA) in order to remove natalizumab from the plasma and accelerate immune surveillance. In most cases, within days to weeks but generally about four to six weeks following PLEX or IA, there was evidence of the development of Immune Reconstitution Inflammatory Syndrome (IRIS) associated with worsening neurologic deficits which have been sometimes rapid, severe and at times fatal. As IRIS can be life-threatening it is important to monitor patients for development of symptoms and institute appropriate treatment. Treatment of IRIS with steroids was undertaken in most cases, usually consisting of high dose intravenous therapy often followed by an oral tapering regime. However, the optimal steroid regimen for treatment of IRIS is controversial and dose and duration of steroid treatment used after development of IRIS have varied. Some evidence suggests that high dose intravenous steroids with oral taper over relatively prolonged periods and sometimes repeated may be required to adequately control the inflammation of IRIS.

Risk Factors for PML

Since the authorisation of natalizumab, three main risk factors for PML have been identified:

- the presence of JCV-specific antibodies,
- the increasing duration of treatment (treated > 24 months),
- a history of immunosuppressive therapy.

Patients who have all three risk factors for PML have a significantly higher risk of PML. Therefore a number of risk minimisation measures in relation to PML are in place for Tysabri.

However, these risk factors do not allow for a reliable individual prediction of PML. For example 50-60 % of the MS population is anti-JCV antibody positive (Lee P et al, 2013), but only as small proportion develops PML.

The absolute prerequisite for PML development is previous contact with JCV. Hence, a two-step serological assay consisting of an enzyme-linked immunosorbent assay (ELISA) was developed and is available for testing patients.

Whereas a number of risk minimisation measures are in place for Tysabri, scientific evidence on PML rapidly growing and new elements have com e to light in relation to three key issues: risk estimates; the diagnosis of PML before the development of clinical symptoms; and anti-JCV antibodies.

1) Risk estimates

Decisions on initiation and continuation of treatment by physicians and patients are currently based on an algorithm included in the educational material, and in which the estimated PML incidences are calculated in a static way and by pooling data from all sources (clinical studies, registries, spontaneous reports). The interim data from the STRATIFY 2 study for patients with positive anti-JVC antibody status with and without a history of immunosuppressive treatment seems to indicate a higher risk of PML based on Kaplan Meier curves than currently described in the algorithm. It is therefore appropriate to review the calculations to ensure that accurate risk estimates are available for treatment decisions.

2) Diagnosis of PML before the development of clinical symptoms

Currently, approximately 11 % of PML patients were clinically asymptomatic at the time of diagnosis. Asymptomatic PML patients are associated with unilobar lesions reflecting a more localised disease. The data also seems to indicate that asymptomatic PML cases have a higher survival rate compared with symptomatic cases.

Current recommendations are for a MRI to be performed within 3 months before treatment initiation, and annually thereafter. Recent literature suggests that more frequent MRI testing may contribute to increase the proportion of cases detected in the asymptomatic stage.

3) Anti-JCV antibodies

Initial interpretations of the serological anti-JCV antibody test suggested that a negative status could be used to reassure patients that the probability of developing PML is very low (approximately 1/10000). However longitudinal serological follow-up from the combined AFFIRM and STRATIFY-1 studies showed that nearly 13% of patients who were anti-JCV antibody negative at baseline could become positive during follow-up. Therefore, negative JCV serology at treatment initiation is not sufficient for long-term reassurance. The current recommendation in the product information is to retest these patients every 6 months for antibodies. Since this recommendation was put in place, a more sensitive second generation ELISA assay has been developed, and there is a need to assess whether this impacts on current recommendations for antibody testing.

In addition, in the literature it is suggested that an anti-JCV antibody index >1.5 may be interpreted as a risk factor for PML, therefore, it may be necessary to review the surveillance strategy when therapy is pursued.

2.2. Diagnosis of PML before the development of clinical symptoms

Overview

As of May 2015, 142,958 patients had received natalizumab worldwide with 432,814 patient-years of exposure. A total of 566 PML cases have been reported globally (clinical studies, registries and spontaneous reports) as of 04 June 2015, of which 133 patients died (23.5 % 0f PML patients). Patients who survive often have serious morbidity associated with serious and permanent disability.

Out of the 566 cases, 62 cases (10.9%) had abnormal brain MRI findings consistent with, and subsequently attributed to PML. Asymptomatic (sometimes also called pre-symptomatic) PML is defined as the absence of recognisable new symptoms attributable to PML at the time of PML diagnosis with PML lesion visible on MRI.

The majority of asymptomatic cases (n= 52/62) were reported from EU/Rest of the World (ROW), while 10 were from the US (table 1). The proportion of asymptomatic PML case reports has increased over years in particular in the EU/ROW, where approximately 20 % of PML cases since 2013 were asymptomatic at the time of diagnosis. While the apparent discrepancy between the EU/ROW and the US might in part be related to the higher incidence of PML overall in EU/ROW, a possible contributing factor might be the more frequent acquisition of MRIs in EU/ROW compared to the US. The SmPC for natalizumab recommends annual MRIs, but it is noted that some EU/ROW countries and EU hospitals have instituted more frequent MRI protocols (Alroughani RA, 2014, Fernández O; 2015; McGuigan C 2016, Wattjes MP 2015).

	All PML	Total	EU/ROW		(US	
	patients n=	asymptomatic					
			Symptomatic	Asymtomatic	Symptomati	Asymtomatic	
					с		
2008	4	0 (%)	3	0	1	0	
2009	30	1 (3.3 %)	20 (95.2 %)	1 (4.8 %)	9	0	
2010	69	8 (8.7 %)	35 (89.7 %)	4 (10.3 %)	28 (93.3 %)	2 (6.7 %)	
2011	107	10 (9.3)	59 (86.8 %)	9 (13.2 %)	38 (97.4 %)	1 (2.6 %)	
2012	125	6 (4.8)	83 (94.3 %)	5 (5.7 %)	36 (97.3 %)	1 (2.7 %)	
2013	110	19 (17.3)	67 (80.7 %)	16 (19.3 %)	24 (88.9 %)	3 (11.1 %)	
2014	94	16 (17)	59 (81.9 %)	13 (18.1 %)	19 (86.4 5)	3 (13.6 %)	
2015*	27	4 (14.8)	16 (80 %)	4 (20 %)	7	0	
Total	566	62 (10.9 %)	342	52	162	10	

 Table 1 Number of asymptomatic and symptomatic (confirmed) cases reported per year 2008-2015

 according to the case definition of the MAH

*as of 4 June 2015

Upon suspicion of PML, natalizumab was discontinued in all 62 PML cases classified as asymptomatic. Follow-up data was available for 77.4% (48/62) of the cases, with a median of 11.8 months (mean: 12.4 months, range 1 – 33.6). At the time of this analysis, 63% (39/62) of PML patients with asymptomatic onset had at least 6 months of follow-up data available. The majority (70.8%; 34/48) remained free from clinical symptoms, while 29.1% (14/48) became symptomatic subsequent to PML onset. Among this latter group, the median time from first suspect MRI to the onset of symptoms was 17 days (mean: 32.2 days, range: 1- 151). IRIS (Immune Reconstitution Inflammatory Syndrome) was reported in 83.9% (52/62) of the cases. At the time of last follow-up, 95% (59/62) of patients were alive and three had a fatal outcome.

All available MRI images and MRI reports for confirmed PML cases were reviewed, and the PML lesions were classified as follows: 1) unilobar - confined to 1 lobe; 2) multilobar - involving 2 or more contiguous lobes; 3) widespread - involving 2 or more non-contiguous lobes and/or present in both hemispheres.

Both cohorts of patients had similar baseline MS disease characteristics (table 2), but pre-PML EDSS was higher for the symptomatic group. Time from suspicion of PML (either by reported symptom onset or by date of suspect MRI) to PML diagnosis date was shorter in the asymptomatic PML patients. Another difference between asymptomatic and symptomatic PML patients is the extent of PML on brain MRI, with asymptomatic patients having a higher proportion of localized (unilobar) PML and a lower proportion of widespread PML (p-value: 0.0005). Finally, the survival rate was higher in asymptomatic patients than in patients who were symptomatic at diagnosis (p-value: <0.0001).

		US PML Patients		EU/ROW PML Patients			
	Asymptomatic	Symptomatic		Asymptomatic	Symptomatic		
Mean / Median; (range) [n]	(n=10)	(n=162)	P-value	(n=52)	(n=342)	P-value	
Age at Diagnosis				-			
	41.6 / 37.5	49.3 / 49.5	0.02	42.2 / 41	42.3 / 43	0.05	
	(23-60) [n=10]	(26-73) [n=162]	0.02	(22-72) [n=47]	(15-61) [n=257]	0.93	
Gender, n (%)							
Female	4 (40.0)	119 (73.5)		34 (65.4)	235 (68.7)		
Male	6 (60.0)	43 (26.5)	0.03	18 (34.6)	106 (31.0)	0.61	
Unknown	(0)	(0)	1	(0)	1 (0.3)		
Duration of MS a	t PML diagnosis (y	ears)					
	14.8 / 13.5	15.1 / 13	0.04	10.8 / 10	12.4 / 11	0.36	
	(4-29) [n=6]	(2-51) [n=67]	0.94	(2-21) [n=25]	(0-35) [n=142]		
Natalizumab exp	osure at time of PM	L Diagnosis (doses)					
	56.2 / 52	46.6 / 46	0.11	45.3 / 44	43.0 / 41	0.4	
	(27-92) [n=10]	(8-110) [n=162]	0.11	(22-91) [n=52]	(8-103) [n=341]	V.T	
Prior IS use, n (%	% yes)						
	3 (33.3)	42 (30.2)	0.01	10 (20.8)	79 (25.5)	0.49	
	[n=9]	[n=139]	0.91	[n=48]	[n=310]	0.48	
EDSS on Nataliza	umab pre-PML	-					
	2.5 / 2	3.9 / 4	0.28	3.0 / 3	3.7 / 3.5	0.02	
	(1.5-4) [n=3]	(0-8) [n=50]	0.28	(1-6) [n=36]	(0-8.5) [n=212]	0.02	
Karnofsky on Na	talizumab pre-PMI	_					
	90 / 90	78.8 / 80	0.28	82.5 / 90	78.4 / 80	0.15	
	(80-100) [n=3]	(40-100) [n=49]	0.28	(50-100) [n=24]	(40-100) [n=140]	0.15	
Duration of follow	w-up after PML Dia	ignosis, months		-			
Mean	8.4	12.4		11.9	13.1		
Median	7.2 (1.6-24.8)	12.6 (0.3-25.1)	0.10	10.3 (2.9-29.5)	12.6 (0.3-54.1)	0.52	
N	[n=8]	[=n=87]		[n=40]	[n=253]	1	
PML Extent on M	IRI at Diagnosis, n	(%)					
Unilobar	4 (40%)	57 (38.5%)	0.52	29 (64.4%)	106 (35.8%)	0.0002	
Multilobar	4 (40%)	39 (26.4%)	0.52	9 (20.0%)	64 (21.6%)	0.0003	

 Table 2 Demographic and clinical characteristics of asymptomatic and symptomatic onset PML patients

 stratified by geographic region

		US PML Patients		EU/ROW PML Patients			
	Asymptomatic	Symptomatic		Asymptomatic	Symptomatic		
Mean / Median; (range) [n]	(n=10)	(n=162)	P-value	(n=52)	(n=342)	P-value	
Widespread	2 (20%) [n=10]	52 (35.1%) [n=148]		7 (15.6%) [n=45]	126 (42.6%) [n=296]		
CSF JCV viral lo	ad, copies/mL				1	•	
Mean	1899	377,691		218,161	67,609		
Median (Range)	297 (12-9900)	987 (10-10,243,280)	0.1	622 (10-4,972,331)	386 (1-3,074,234)	0.28	
N	[n=6]	n=[106]		[n=32]	[n=241]		
Duration of first	suspect MRI/PML	symptom onset date to PM	L diagnosis	s date, days	•	-	
Mean	16	51		46	51		
Median (Range)	2 (0-73)	36 (0-264)	0.007	13.5 (0-367)	36 (0-329)	0.001	
N	[n=9]	n=[159]		[n= 52]	[n=338]		
Received PLEX,	yes, n (%)						
	7 (100%) [n=7]	108 (95.6%) [n=113]	0.43	36 (92.3%) [n=39]	250 (96.5%) [n=259]	0.26	
Reported IRIS, y	es, n (%)						
	8 (100%) [n=8]	113 (88.3%) [n=128]	0.16	44 (95.7%) [n=46]	279 (93.6%) [n=298]	0.58	
Clinical Outcome	**, n (%)						
Alive	10 (100%)	97 (59.9%)	0.002	49 (94.3%)	277 (81.0%)	0.000	
Died	0 (0%)	65 (40.1%)	0.002	3 (5.8%)	65 (19.0%)	0.009	

EDSS= Expanded Disability Status Scale; KPS = Karnofsky Performance Scale; PML = progressive multifoc leukoencephalopathy. Bold text indicates statistical significance.

*P-values are provided using two-sample t-test or Wilcoxon rank sum test depending on the distribution of data for continuous variables and Chi-square test for categorical variables. These P-values are strictly of an exploratory nature as the assumptions on the underlying probability structure are unlikely to hold and the multiplicity issue has not been addressed.

**Confirmed PML cases are followed until final outcome. This reflects clinical outcome as of the most recent follow-up report at the time of the analysis.

Disability outcomes of asymptomatic and symptomatic PML patients

Treating physicians for all confirmed PML patients were queried via a standardized PML Data Collection Tool (DCT) to provide assessments of the PML patient's disability status (as measured by both EDSS and KPS) prior to PML diagnosis, at the time of diagnosis, and every 6 months for up to 24 months post PML diagnosis. Functional disability scores were not reported at every requested time point for all PML patients. EDSS scores were available for 80% (457/566) of confirmed PML patients overall, with 67% of patients having available EDSS reported at the time of PML diagnosis and 49% reported at 6 months post PML diagnosis. KPS scores were available for 78% (444/566) of confirmed PML patients overall, with 49% of patients having available KPS scores reported at the time of PML diagnosis and 49% at 6 months post diagnosis. At 12 months post PML diagnosis, 37% and 38% of confirmed PML patients had available assessments of disability status as measured by EDSS and KPS, respectively. In general, asymptomatic PML patients had less functional disability after PML diagnosis when compared with symptomatic PML patients, as reflected by lower EDSS scores and higher KPS scores at all time points after PML diagnosis (Figures 1 and 2). However, disability in terms of pre-PML EDSS and KPS was slightly numerically higher for the symptomatic group.



Figure 1 EDSS and Figure 2 KPS scores for symptomatic and asymptomatic PML patients measured over time. The EDSS and KPS scores for symptomatic and asymptomatic PML patients are shown for time points prior to PML diagnosis, at PML diagnosis, and post-PML diagnosis. Each symbol represents a single patient measurement at a single time point. EDSS and KPS scores were not available for all patients at all time points. Data prior to diagnosis were gathered from medical records. The red lines represent the mean evolution of EDSS and KPS scores over time for the asymptomatic PML patient population, while the blue line represents the mean evolution of EDSS and KPS scores over time for symptomatic PML patient population.

Frequency of MRI testing of asymptomatic and symptomatic PML cases

Current recommendations for MRI testing in the EU for MS patients receiving natalizumab are outlined in the Summary of Product Characteristics (SmPC) and EU Educational material (Physician Information and Management Guidelines for Multiple Sclerosis patients on TYSABRI Therapy Version 14, dated 22 May 2015) and specify that a pre-treatment cranial MRI scan should be performed as a reference within 3 months before starting natalizumab and should be repeated on a yearly basis to update this reference. Natalizumab-treated patients should have regular clinical follow-up to allow for early detection of changes in neurological status, and if any new neurological symptoms develop, a brain MRI scan is recommended; PML should always be considered as part of the differential diagnosis.

MRI frequency in symptomatic PML cases is not available for analysis, and consequently a comparison cannot be made with MRI frequencies in PML cases having asymptomatic onset. Nonetheless, treating physicians for the 62 cases of asymptomatic onset PML were queried for MRI testing frequency and the rationale for MRI testing. In the majority of cases (92%; 57/62), the MRI that prompted PML suspicion was reported to be part of a "routine assessment". The frequency and/or rationale for these MRIs (e.g. MS standard of care or PML monitoring or other reason) were not specified in many cases. There were five cases (8%; 5/62) for which the reason for the MRI was not reported to be a routine assessment. In one case, the MRI was performed as part of a work up for headaches (reported as unrelated to PML)

and in the other four cases, the patients had discontinued natalizumab and underwent an MRI prior to starting another disease modifying therapy.

Brain MRI frequency was available in only 24 out of the 62 PML cases classified as having asymptomatic onset. MRI frequency was reported as every 12 months in 2 patients (consistent with the recommendation in the SmPC); every 6 months in 10 patients; every 4 months in 5 patients; and every 3 months in 7 patients. Thus, of the 62 PML cases classified as having asymptomatic onset, 22 PML cases were known to have undergone MRIs more frequently than the annual MRI recommendation in the SmPC, and the reported MRI testing frequencies varied between every 3-6 months; the percentage of symptomatic onset PML cases who have undergone MRIs more frequently than annually is unknown. The duration of the reported MRI testing frequency was not provided for the 24 asymptomatic onset patients. The rationale for the MRI testing frequency was reported as "routine" with no further specifications in 17 cases and as part of clinical trial study protocol in 1 case; while in 6 cases the rationale was reported to be "due to the presence of PML risk factors". Of the 6 cases where MRI testing frequency was "due to the presence of PML risk factors", one patient was receiving a 4-month MRI testing frequency, 2 patients were receiving a 3-month MRI testing frequency, and 3 patients were receiving a 6-month MRI testing frequency.

Evaluation of the time interval between the last brain MRI scan without signs of PML and the onset of PML symptoms and clinical outcome in symptomatic PML patients

As of 04 June 2015, there were 504 symptomatic PML patients, and of those, brain MRI reports or images pre-dating the onset of PML were available for a total of 251 (50%). Only cases where the report included the radiologist's description of the MRI and/or impression were included in this analysis. Of the 251 cases, 232 (92%) were considered to have met this criterion and were included in the analysis. The survival rate in these symptomatic PML patients was 75% (174/232). There were 58 fatal PML reports with median time from PML diagnosis to fatal outcome of 77 days (mean: 149, range: 1-1067). To evaluate the time interval between the last MRI scan reported as being without evidence of PML and the onset of PML in symptomatic PML patients, time intervals for MRI testing in relation to PML onset were categorised as follows: 1 to 3 months, > 3 to 6 months, > 6 to 9 months, > 9 to 12 months, and > 12 months. Thirty eight percent of patients (89/232) had an MRI reported as being without evidence of PML between 1 to 3 months prior to PML onset; 25.4% (59/232) between 3 to 6 months; 12.9% (30/232) between 6 to 9 months; 11.6% (27/232) between 9 -12 months and 11.6% (27/232) more than 12 months.

The patients within the five time interval cohorts between MRI and PML onset were very similar in terms of PML extent on MRI at the time of PML onset and clinical outcome, and no trends or patterns were identified. The data in this sub-analysis have many limitations inherent to the fact that these are spontaneously reported cases. There is incomplete information on MRI dates and MRI reports/ interpretations on these cases. It is also possible that patients may have had additional MRIs performed prior to the onset of symptoms which were not reported and therefore would have influenced which time interval the patient was placed in for the analysis. Therefore, an MRI monitoring frequency should not be assumed in these cases based on the reported time interval between MRI and PML onset. Lastly, the reason for the MRI scan to have been performed in these patients remains unknown.

An analysis of cases for which there was a negative brain MRI scan up to 16 weeks before onset of PML symptoms does not suggest a clear pattern across biweekly intervals.

2.3. Anti JCV antibodies

Anti-JCV antibody index and antibody index cut-off

The presence of anti-JCV antibodies is one risk factor for PML which, alone, due to the high prevalence of anti-JCV antibodies (50-60%) in the population, is not useful for predicting the risk of PML, but when combined with the other two identified risk factors for natalizumab associated PML (treatment duration especially more than 2 years and prior immunosuppressant [IS] use), has proven clinical utility for risk stratification and provides physicians with an estimate of PML risk for individual patients receiving natalizumab.

Detection of anti-JCV antibodies is currently performed using a 2-step ELISA (STRATIFY JCV Dx Select, Focus Diagnostics, Cypress, CA). Results are expressed as a binary output (positive or negative) based on an assay cut-point. The index value is derived from the optical density value for a sample normalized to an assay calibrator within the STRATIFY JCV Dx Select ELIS (Plavina et al, 2014). Samples that are below an index of 0.20 are considered negative, and samples above an index of 0.40 are considered positive. For samples with an index between 0.20 and 0.40, inclusive (an indeterminate response), the sample is further evaluated in the second step of the ELISA (the confirmation test) and a positive or negative result is provided. In the EU, anti-JCV antibody testing via STRATIFY JCV Dx Select is performed by Unilabs in Denmark (Lee P et al, 2013). Although the results are provided as a binary output, a physician in the EU can obtain the index value for a patient's sample upon request.

In order to investigate the link between antibody index and PML risk, Anti-JCV antibody index data was collected using the STRATIFY JCV Dx Select assay from anti-JCV antibody positive MS patients from three natalizumab clinical studies: AFFIRM (n=359), STRATIFY-1 (n=680) and STRATIFY-2 (n=7131). Samples were obtained from clinical study patients who were receiving natalizumab as well as those who were not receiving natalizumab. The STRATIFY-2 data used in the main index analysis was extracted as of March 2014 and the STRATIFY-2 data over 4 years used in the longitudinal index stability analysis was extracted as of 18 May 2015. In total, there were 8,112 non-PML anti-JCV antibody positive MS patients with available data (total of 12,932 samples). Because PML is an uncommon adverse reaction in natalizumab-treated patients, PML patient samples were obtained from all available post-marketing sources including spontaneous reports and clinical studies (n=101, with a total of 442 samples); only pre-PML samples collected at least 6 months prior to PML diagnosis were included in the analysis. The association of index and PML risk was initially explored using a test set of samples and then confirmed using a validation set. The test data set consisted of 1030 non-PML anti-JCV antibody positive MS patients from AFFIRM and STRATIFY-1 and 52 MS patients who developed PML from clinical studies (excluding STRATIFY-2) and post-marketing sources. The validation data set consisted of 7082 non-PML anti-JCV antibody positive MS patients from STRATIFY-2 and 49 MS patients who developed PML from STRATIFY-2. Integrated analyses of the combined data sets were performed on 8112 non-PML anti-JCV antibody positive MS patients and 101 MS patients who developed PML. For cross-sectional analyses, the lowest index was used for patients with more than one available index sample.

The distribution of index in non-PML anti-JCV antibody positive MS patients was compared with the distribution of index in PML patients. Figure 3A represents the distribution of index values in the test data set utilizing the lowest index value for non-PML patients who tested anti-JCV antibody positive from AFFIRM and STRATIFY-1 and PML patients (from all available post-marketing sources excluding STRATIFY-2) with pre-PML samples collected and tested for index at least 6 months prior to PML diagnosis. The distribution of index suggests that the index values were significantly higher in the pre-PML samples from natalizumab-treated PML patients compared to non-PML anti-JCV antibody positive patients (p<0.0001). The same type of analysis was performed using samples collected from

STRATIFY-2. Figure 3B represents the distribution of index values in the validation data set from non-PML patients who tested anti-JCV antibody positive at baseline from STRATIFY-2 and PML patients from STRATIFY-2 with pre-PML samples collected and tested for index at least 6 months prior to PML diagnosis. Similar to Figure 3A, the distribution of index indicates significantly higher index values in the pre-PML samples from the STRATIFY-2 PML patients compared to the non- PML anti-JCV antibody positive patients (p=0.0013).





The impact of the established PML risk factors on index was evaluated. Data indicate that natalizumab treatment duration does not have a statistically significant impact on index in the test data set (p=0.1824). When stratifying the data in the test data set by prior IS use, there was a statistically significant difference (p<0.0001) in the distribution of index between PML and non-PML patients with no prior IS use; the difference was not seen in patients with prior IS use (p=0.8037) as shown in Figures 4 and 5 (p=0.0010).





Index by PML and Prior IS Use

Box = interquartile range; thick white horizontal line = median; horizontal bars = range; x = mean. P-values from Wilcoxon rank-sum test

Box = interquartile range; thick white horizontal line = median; horizontal bars = range; x = mean. P-values from Wilcoxon rank-sum test

Figure 5 Anti-JCV antibody index in non-PML and PML patients stratified by prior IS use in the validation data set



Index by PML and Prior IS Use

When the test and validation data sets were combined, the median index in patients with no prior IS use was significantly higher for PML patients than for non-PML patients (p<0.0001), while there was no significant difference in the median index for non-PML and PML patients with prior IS use (p=0.6424).

It must be noted that the point estimate for the median index in the prior IS cohort is numerically higher in the PML cases compared with the non-PML cases, but the 95% confidence intervals are wide and the overall number of PML patients with prior IS use and available anti-JCV antibody index is small (n=26). Therefore, the ability to reach firm conclusions on the lack of an association of index and PML in the prior IS population is limited. Because pooling the IS and non-IS patient populations might underestimate the risk of PML in patients with prior IS use, subsequent analyses of index and PML risk were limited to patients with no prior IS use.

Figure 6 Anti-JCV antibody index in non-PML and PML patients (combined test and validation data set) stratified by prior IS use



P-values for the comparison in index values between PML and non-PML patients were based on a Wilcoxon ranksum test; p-value for the interaction was based on a general linear model of the ranked index values.

A scatterplot of the distribution of index in the combined test and validation data sets of non- PML and PML patients with no prior IS use demonstrates the overall higher index in PML patients with no prior IS use compared with non-PML patients with no prior IS use (p<0.0001) (Fig. 7). These results remain significant after 1,731 patients who had not been treated with natalizumab at the time of sample collection were removed from the non-PML, no prior IS use cohort (p<0.0001).

Figure 7 Index distribution in anti-JCV antibody positive non-PML and PML patents with no prior IS use (combined test and validation data sets)



P-values from Wilcoxon rank-sum test

Given the overall distribution of index values in PML patients, with most PML patients having index above 1.5 and few PML patients (n=3) having index below 0.9, the proportion of PML and non-PML patients having index values above or below index thresholds ranging from 0.9 to 1.5 was explored. The estimated proportions of anti-JCV antibody positive non-PML and PML patients with no prior IS use who fell at or below index thresholds ranging from 0.9 to 1.5 (and the associated 95% CIs) are shown in Table 3. The odds ratio of PML comparing patients with index above the thresholds ranging from 0.9 to 1.5 with those patients with index at or below the thresholds is \geq 7 (range ~7-15) with wide 95% CIs.

Anti- JCV antibody index	% of non- PML patients below threshold	95% CI	% of PML patients below threshold	95% CI	Odds ratio	95% CI
≤0.9	31.0	30.0 – 32.1	2.9	0.8 – 10.3	15.2	3.9 – 58.8
≤1.0	33.8	32.7 – 34.9	3.6	1.2 – 10.6	13.6	4.3 – 43.1
≤1.1	36.4	35.3 – 37.6	5.1	1.9 – 12.9	10.7	3.9 – 29.2
≤1.2	38.9	37.7 – 40.0	6.6	2.8 – 14.8	9.0	3.7 – 22.0
≤1.3	41.2	40.1 – 42.3	8.1	3.8 – 16.4	8.0	3.6 – 17.9
≤1.4	43.5	42.3 - 44.6	9.0	4.5 – 17.4	7.7	3.6 – 16.4
≤1.5	45.7	44.5 - 46.9	9.9	4.9 – 18.9	7.7	3.6 – 16.4

Table 3 Estim	ated proporti	ions of anti-JCV	antibody pos	sitive non-PML	and PML pati	ients with no pri	or IS
use by Index	threshold						

In order to identify the optimal cut-off level, the receiver operating characteristics (ROC) curve method was used to compare sensitivity and specificity across a range of possible antibody index thresholds based on all currently available data from ongoing and completed clinical studies and relevant post-marketing data (see above). The results of the ROC analysis confirm that the risk of PML is a continuum associated with increasing index values. The range of index thresholds assessed in Table 3 generally fall on a flat part of the ROC curve and show very limited difference in sensitivity/specificity.

Therefore, although higher anti-JCV antibody index is associated with higher PML risk compared to lower index values, all index cut-points evaluated are close to the optimal densitivity/specificity balance defined by the distance to the diagonal line. Therefore, it is unclear whether a single index cut-point with optimal clinical utility can be identified.

Anti-JCV Aantibody Index Cutpoint	Estimated Prob of non- PML Patients ≤ Threshold	Estimated Prob of PML Patients ≤ Threshold	Sensitivity	Specificity	Sensitivity + Specificity -1 (D)	PPV	NPV
0.8	27.7%	2.5%	0.975	0.277	0.252	1.34%	99.9%
0.9	31.0%	2.9%	0.971	0.310	0.281	1.40%	99.9%
1.0	33.8%	3.6%	0.964	0.338	0.302	1.46%	99.9%
1.1	36.4%	5.1%	0.949	0.364	0.313	1.49%	99.9%
1.2	38.9%	6.6%	0.934	0.389	0.323	1.53%	99.8%
1.3	41.2%	8.1%	0.919	0.412	0.331	1.54%	99.8%
1.4	43.5%	9.0%	0.910	0.435	0.345	1.60%	99.8%
1.5	45.7%	9.9%	0.901	0.457	0.358	1.64%	99.8%
1.6	47.8%	11.7%	0.883	0.478	0.361	1.68%	99.8%
1.7	49.9%	12.7%	0.873	0.499	0.372	1.72%	99.7%
1.8	51.8%	21.0%	0.790	0.518	0.308	1.63%	99.6%
1.9	53.9%	23.8%	0.762	0.539	0.301	1.59%	99.5%
2.0	55.9%	29.8%	0.702	0.559	0.261	1.34%	99.4%

Table 4 Sensitivity/specificity of index cut-points in anti-JCV antibody positive non-PML and PML patients with no prior immunosuppressant use

Figure 8 ROC Curve of index cutpoints in anti-JCV antibody positive non-PML and PML patients with no prior immunosuppressant use



It should also be noted that the index cut-point of 1.5 has a D value of 0.36, nearly indistinguishable from the maximum of 0.37, while limiting the false negative rate (1-sensitivity) to be below 10%.

Risk associated with increasing anti-JCV antibody index is a continuum, and identification of a single cut-off point appears to be difficult. The cut-off of 0.9 has the highest sensitivity but specificity is rather low. The cut-off of 1.5 has a somewhat better specificity but is less sensitive.

To further assess the clinical utility of the antibody index, PML risk was stratified by antibody index for patients with positive anti-JCV antibodies and no prior IS use from STRATIFY-2. Consistent with the results of the ROC analysis, lower index cut-points show higher sensitivity in identifying patients who developed PML in this data set (97.3 % with cut-off of 0.9 and 89.2 % with a cut-off of 1.5), but at the

expense of lowering specificity. With a cut-off of 0.9 approximately 73 % of patients who did not develop PML would be classified as being at higher risk, whereas with a data-cut off of 1.5 approximately 58 % of non-PML patients would be classified at higher risk.

Table 5 Number (%) of JCV antibody positive patients with no prior immunosuppressant use in antibody index categories - STRATIFY-2 study

	Non-PML	PML
Total N of Subjects	4678	37
Index* ≤ 0.9	1276 (27.3%)	1 (2.7%)
Index* > 0.9	3402 (72.7%)	36 (97.3%)
Index* ≤ 1.5	1986 (42.5%)	4 (10.8%)
Index* > 1.5	2692 (57.5%)	33 (89.2%)

*The highest index value prior to the PML for PML cases and the highest index value at any point for non-PML cases.

PML risk estimates and index

PML risk estimates in anti-JCV antibody positive patients were derived using Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of immunosuppressant were derived from combining the overall yearly risk with the antibody index distribution. The resulting PML risk estimates per 1,000 patients for anti-JCV antibody positive patients with no prior IS use are shown in the table below.

Table 6 New PML risk estimates, including stratification by index threshold in anti-JCV antibody positive patients with no prior immunosuppressant use



Positive Antibody Status											
	PML risk estimates per 1000 patients										
Natalizumab Exposure		Patients witho	ut prior IS use		Dationts with						
	No index value	ex value Antibody Index ≤ 0.9 Antibody Index > 0.9 ≤ 1.5 Antibody Index > 1.5									
1-12 months	0.1	0.1	0.1	0.2	0.3						
13-24 months	0.6	0.1	0.3	0.9	0.4						
25-36 months	2	0.2	0.8	3	4						
37-48 months	4	0.4	2	7	8						
49-60 months	5	0.5	2	8	8						
61-72 months	6	0.6	3	10	6						

The second column (patients without prior IS use with 'no index value') describes the PML risk of anti-JCV antibody positive patients without stratification by index.

In anti-JCV antibody positive Tysabri treated patients who have not used prior immunosuppressants, the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e. the risk is greater in those with a high antibody index compared to those with a low index). Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with Tysabri for longer than 2 years.

Longitudinal stability of anti-JCV antibody index

Longitudinal stability of anti-JCV antibody index was evaluated using data from the ongoing STRATIFY-2 clinical study as of 18 May 2015. Patients who had index values at least two time points were included in this analysis. Time to the first high index value from a baseline anti-JCV antibody negative status, from a baseline anti-JCV antibody negative status or a baseline anti-JCV antibody positive status with low index combined, or from a baseline anti-JCV antibody positive status with low index is plotted over time. Baseline is defined as the first available anti-JCV antibody result in STRATIFY-2. Sample collection in STRATIFY-2 was initially performed annually and then changed to every 6 months. 14% of baseline anti-JCV antibody negative patients became antibody positive high index (index above 0.9) over 4 years corresponding to an approximately 4% annualized serostatus change rate from negative to high index. If the cut-off index was 1.5, 11.3% of baseline anti-JCV antibody negative patients became antibody positive high index over 4 years corresponding to an approximately 3% annualized serostatus change rate from negative to high index.

41.3% of anti-JCV antibody positive low index (index ≤ 0.9) patients became antibody positive high index (index above 0.9) over 4 years which resulted in an approximately 12% annualized rate of change from antibody positive low to high index above 0.9. If index point is 1.5, 33.9% of anti-JCV antibody positive low index patients became antibody positive high index over 4 years which resulted in an approximately 10% annualized rate of change from antibody positive low index to high index above 1.5.

A summary of the longitudinal stability data for anti-JCV antibody index from STRATIFY-2 collected over 4 years is shown below in the table below for index thresholds of 0.9 and 1.5.

Index threshold	Annual rate of	Annual rate of change	Annual rate of
	change from	from antibody negative	change from
	antibody negative to	or positive low index to	antibody low index to
	high index	high index	high index
0.9	4 %	5 %	12 %
1.5	3 %	4 %	10 %

 Table 7 Longitudinal stability data for anti-JCV antibody index for index thresholds of 0.9 and 1.5 in

 STRATIFY-2 collected over 4 years

Data from STRATIFY-2 show that antibody index change from negative or low index to high index occur in 4-5 % of patients per year. The majority (>80%) of patients having a baseline negative anti-JCV antibody status or baseline positive low index value had their index value remain below the index threshold (0.9 or 1.5) over 4 years.

Anti-JCV antibody ELISA

The first generation anti-JCV antibody ELISA assay (STRATIFY JCV) became commercially available in the EU in March 2011. The second generation ELISA assay (STRATIFY JCV Dx Select) was developed to enhance the robustness and performance characteristics of the assay and to provide improved

efficiency (limit of detection = 60 ng/mL versus 350 ng/mL, respectively) at the diagnostic testing lab by translating it into a ready-to-use kit format. STRATIFY JCV Dx Select became commercially available in the EU in March 2012. Currently, all testing globally for anti-JCV antibodies both commercially and in clinical studies utilizes the second generation assay. Because the published PML algorithm is based on the first generation ELISA anti-JCV antibody assay, seroprevalence data for the second generation ELISA anti-JCV antibody assay by age, history of MS treatment and country (da Silva AM et al, 2014, Bhan V et al, 2014) was analised.

The second-generation anti-JCV antibody assay was shown by Focus Diagnostics to have positive percent agreement of greater than 97% and a negative percent agreement of greater than 90% when compared with the first-generation assay. Focus Diagnostics has received 510(k) clearance from the Centers for Diagnostics and Radiological Health for this device and the device has a CE Mark in the EU. The anti-JCV antibody assay is currently performed in 3 laboratories: Focus Diagnostics (Cypress, CA), Unilabs (Copenhagen, Denmark), and Cirion Central Laboratory (Laval, Canada). At the time that the PML risk algorithm was first included in the Physician Information and Management Guidelines in 2011, the anti-JCV antibody status of the overall natalizumab-treated population was unknown, and an assumption of 55% positive serostatus was utilized in the calculation of the risk estimates. This number was based on the anti-JCV antibody prevalence in approximately 6,000 MS patients from natalizumab clinical trials (baseline samples) and a national MS registry testing for the presence of anti-JCV antibodies using the first generation assay.

Currently available data demonstrate that anti-JCV antibody prevalence was generally similar using the first and second generation assay and ranged from approximately 50-60%. Baseline data from STRATIFY-1 reported 56% positive serostatus using the first generation assay and 55% positive serostatus using the second generation assay. The positive serostatus in STRATIFY-1 using the first and second generation assays remained similar when stratified by age or prior IS use. Real-world serostatus data from Unilabs in six EU countries (Austria, France, Germany, Italy, Portugal and Spain) showed that positive serostatus is generally consistent across the individual countries and between the two assays ranging from 53%-59% on cross sectional analysis and ever positive analysis in the first generation assay and 51%-60% on cross sectional analysis and 53%-61% on ever positive analysis in the second generation assay.

The analysis of anti-JCV antibody serostatus change using samples from STRATIFY-2 over 4 years (initially collected every 12 months and later collected every 6 months within the study) demonstrates that approximately 9% of patients change from anti-JCV antibody negative to positive per year. A 12-16% serostatus change rate is observed in Unilabs real-world data from EU countries collected and tested using the second generation assay over a median duration of 12 months. The current Physician Information and Management Guidelines mentions an 11% annual serostatus change rate based on 18 month data from STRATIFY-1 (where samples were collected every 6 months throughout the study).

The assumption of 55% positive serostatus for the overall natalizumab-treated population utilized in the PML risk algorithm calculations remains acceptable. In general, the positive serostatus results using the first and second generation assays were similar. There is no significant impact of the second generation assay on the risk estimates within the algorithm.

The available longitudinal data from the STRATIFY-2 study in patients who changed serostatus from baseline anti-JCV antibody positive to negative using the second generation STRATIFY JCV Dx Select assay was also reviewed. In the second generation STRATIFY JCV Dx Select assay, index levels below 0.2 are considered antibody negative and index levels above 0.4 are considered antibody positive; index levels between 0.2 and 0.4 are considered indeterminate and are retested in the second step of

the ELISA to determine the binary test result. A presentation of the last index level for the STRATIFY-2 patients who changed serostatus from positive to negative in STRATIFY-2 is shown in the table below.

			Time in Study		
	1-12 Months	13-24 Months	25-36 Months	37-48 Months	Overall
Number of Subjects at the beginning of the interval	10,666	8,952	5,496	4,089	10,666
Number (%) of subjects with at least one incidence of serostatus change from positive to negative	91 (0.9%)	213 (2.4%)	130 (2.4%)	147 (3.6%)	561 (5.3%)*
Number (%) of subjects with more than one incidence of serostatus change from positive to negative	0	0	1 (0.02%)	2 (0.05%)	22 (0.2%)**
The last Index level before serostatus changed to negative					
Mean (SD)	0.72 (0.72)	0.51 (0.40)	0.52 (0.43)	0.45 (0.21)	0.53 (0.44)
Median	0.47	0.44	0.44	0.43	0.44
(25th quartile, 75th quartile)	(0.42, 0.64)	(0.40-0.53)	(0.33, 0.54)	(0.29, 0.54)	(0.34, 0.55)
Min, Max	0.21 - 3.83	0.20-3.75	0.20-3.73	0.20-1.33	0.20-3.83

Table 8	Index	levels	in pa	atients	who	changed	serostatus	from	positive	to r	negative	in th	e STI	RATIFY	(-2
study															

SOURCE: TYSABRIMS/PRAC-ART20/STRATIFY2-SEP15/T-JCV-POSTONEG1.SAS

* The patients who had >= 1 change in each yearly interval are not unique, i.e. there are patients who changed status in more than one yearly interval. Therefore, the number of patients with >= 1 change for the entire period does not equal to the sum of the number in each interval.

** The likelihood of having status change more than once within yearly interval is low; but the likelihood of changing more than once over the entire 4 year period is much higher. Therefore, the number of patients with >=2 changes for the entire period does not equal to the sum of the number in each period.

In the patients who changed serostatus from positive to negative, the median last index level before testing antibody negative was 0.44 (25th quartile = 0.34; 75th quartile = 0.55), which was close to the cut-off index level of 0.4 (above which is reported as antibody positive in the STRATIFY JCV Dx Select assay).

2.4. PML development after discontinuation of natalizumab

Almost all PML patients were diagnosed while on natalizumab treatment, but some patients have been diagnosed after discontinuation. As of 4 June 2015, 566 confirmed cases of PML were reported in natalizumab-treated patients. The time to PML onset after last natalizumab infusion was known for 98% (555/566) of patients; the majority (481/555, 87%) had PML onset prior to or within 4 weeks of their last infusion of natalizumab. Of these 481 patients, 232 had PML onset prior to the last infusion of natalizumab and 249 had PML onset within 4 weeks of their last infusion of natalizumab. The remaining 74 (13%) patients had PML onset more than 4 weeks after their last infusion of natalizumab and were classified as having occurred after natalizumab discontinuation. In 11/566 (2%) patients, the time of

PML onset relative to the last natalizumab infusion was unknown. In 8 of these cases, the date of last natalizumab infusion was unknown while in 3 cases, the date of PML onset was unknown.

Of the 74 patients with PML onset more than 4 weeks after last natalizumab infusion, 57 were reported spontaneously in the post marketing setting and 17 were reported from clinical or observational studies.

Eight patients (11%) were asymptomatic and initial suspicion of PML was based on MRI findings. Nine patients (12%) died and 65 (88%) were alive at the time of the analysis. Natalizumab exposure ranged from 8 to 90 months (mean 43 and median 42.5), with the majority of the patients (81%; 60/74) having received >24 months of treatment. The time between the last natalizumab infusion and the onset of PML ranged from 1 to 6 months, with a mean and median of 2.1 and 1.8 months, respectively; the majority of cases (88%; 65/74) occurred within 3 months of the last infusion of natalizumab. A graphical presentation of the time of PML onset in relation to the last natalizumab infusion is presented in Figure 1. The time between the last natalizumab infusion and PML diagnosis (defined as the date of CSF with positive JCV DNA or brain biopsy positive for JCV) ranged from 1 to 7 months, with a mean and median of 2.8 and 2.6 months, respectively.



Figure 9 Time to PML onset from last natalizumab infusion

For 11 cases, Time After Last Dose could not be calculated

*For 1 case, although first suspicion of PML was at approximately 6 months after last natalizumab infusion, in retrospect, MRI from 3 months after last natalizumab infusion was consistent with PML

Among the 74 patients whose PML onset was > 4 weeks after the last infusion of natalizumab, suspicion of PML was the most common reason for drug discontinuation (25 patients; 33.8%).

Other reasons for natalizumab discontinuation included the following: presence of risk factors for PML including the presence of anti-JCV antibodies (16 patients; 21.6%), lack of effect (5 patients; 6.8%), switch to an alternative MS therapy (3 patients; 4.1%), initial alternative diagnosis other than PML, pregnancy, drug holiday, urinary tract infection, sinusitis, and end of clinical study treatment (1 patient each). In addition, 3 patients had been receiving natalizumab at 8 week intervals (1 patient for the last 4 infusions and 2 patients for the last 2 infusions) and 1 patient missed a dose of natalizumab for

"logistical reasons"; these 4 patients may not have intended to discontinue natalizumab treatment, but reported PML onset more than 4 weeks after their last natalizumab infusion. For the remaining 15 patients (20.3%), the reason for natalizumab discontinuation was unknown. Fifty nine patients (80%) had anti-JCV antibody test results reported.

Prior immunosuppressant (IS) use was unknown in 4 patients (5.4%). For the remaining 70 patients, 49 patients (70%) had no prior IS use and 21 patients (30%) had prior IS use. Sixteen patients (22%) reported receiving another MS therapy at the time of PML onset: 10 patients were receiving fingolimod (including one patient who switched from fingolimod to glatiramer acetate between onset of symptoms and diagnosis of PML), 2 patients were receiving rituximab, 2 patients were receiving glatiramer acetate, 1 patient was receiving mycophenolate, and 1 patient was receiving dimethyl fumarate.

Among the 13% (74/555) of PML cases who developed symptoms more than 4 weeks after the last infusion of natalizumab, all occurred within 6 months of the last natalizumab infusion.

The reversal of PK and PD (a4-integrin saturation and markers of immune function) effects of natalizumab and the temporal pattern of return of disease activity (as an indicator of return of central nervous system [CNS] immune surveillance) in natalizumab-treated MS subjects who discontinued natalizumab was explored in the prospective clinical study RESTORE (101MS205). In this study, subjects were randomized to 1 of 3 groups:

(1) continued to receive natalizumab infusions every 4 weeks for 24 weeks;

(2) received infusions of placebo every 4 weeks for 24 weeks; or

(3) discontinued natalizumab for 24 weeks, but received an alternative immunomodulatory treatment.

After the last dose of natalizumab in the non-natalizumab groups, values for PD markers (including a4integrin saturation and total leukocyte counts) declined, and soluble vascular cell adhesion molecule (sVCAM) concentrations and very late antigen-4 (VLA4) expression increased concordantly. The **average predose** a4-integrin saturation levels (an indicator of target engagement) at Week 0 (when last natalizumab dose was administered), were above 80% for all treatment groups, consistent with what has been measured at steady-state. Pre-dose saturation began to fall from the steady-state values in the nonnatalizumab groups such that by week 16 (4 months after last natalizumab infusion) values were consistent with subjects who had not received natalizumab. Study subjects who were on natalizumab throughout the study maintained consistently high a4 integrin saturation.

In addition, immunological markers of immune competence (lymphocyte count, leukocyte subset counts [CD4, CD8, CD19, CD34, and CD56], and leukocyte functional assessment as measured by adhesion) were assessed, and by Week 16, mean values were consistent with those observed in subjects who had not received natalizumab.

The occurrence of MRI disease activity was assessed by regular 4-weekly MRI scans during the randomized period, as it is more sensitive than clinical activity (relapse). Natalizumab treatment interruption resulted in the occurrence of gadolinium enhancing (Gd+) lesions in subjects randomised to the placebo or alternate immunotherapy groups beginning 12 weeks after the last natalizumab dose (n=3). In all, 49 of 122 (40%) non-natalizumab subjects met protocol defined MRI rescue criteria (1 new Gd+ lesion >0.8 cm3 or 2 or more Gd+ lesions of any size) during the randomized treatment period. None of the subjects in the natalizumab group met MRI rescue criteria. The majority of non-natalizumab subjects (76%, 37 of 49 subjects) who met MRI rescue criteria had their first MRI meeting rescue criteria at week 16 or week 20.

The data from the RESTORE study indicate that serum concentrations of natalizumab decrease following last infusion such that levels are no longer detectable by week 16. The pharmacodynamic effects of natalizumab are also reversed by approximately week 16 after last natalizumab infusion when means values are consistent with those of patients who have never received natalizumab. MRI disease activity returns within similar timeframes, peaking at 16-20 weeks after last infusion. Published reports support that reductions of CSF WBCs and lymphocyte subsets associated with natalizumab treatment are reversible upon natalizumab discontinuation, though these effects may persist up to 6 months after last dose.

All PML cases in patients who had received natalizumab occurred within 6 months of the last infusion. These findings support the current SmPC recommendation that physicians should remain vigilant for signs and symptoms of PML for approximately 6 months after natalizumab discontinuation.

2.5. PML risk estimation

The risk stratification algorithm currently included in the educational material is based on PML incidences (Bloomgren et al, 2012). The incidence calculation is derived by the confirmed number of PML cases among patients in a certain time period (e.g. 0-24 months) and the total number of patients ever exposed to natalizumab during that same period. The PML risk estimates of the incidence based algorithm present risk as a forward-looking interval risk at the beginning of the specified period (e.g. over the next 2 year treatment interval), and differ from the Kaplan-Meier (KM) analysis which presents the cumulative risk of PML over time.

The KM analysis and the life-table method (also called the actuarial method) are similar methodologies used to estimate the failure time function with censoring taken into account (exposure stopped without observing events). The KM analysis estimates the cumulative probability of PML risk over time with risk updated at each event time, and the lifetable method estimates the conditional probability of risk within each pre-defined time interval for the subjects that had no event up to the beginning of the given time interval. Both methods adjust the denominator to account for censoring within each time interval.

Supplemental presentations of PML risk using different methodologies may be complementary to the information within the current algorithm and will provide additional information to physicians as they engage in benefit/risk discussions with their patients.

Therefore, two new presentations of PML risk that are derived from a pooled study cohort (STRATIFY-2, TOP, TYGRIS and STRATA studies) of natalizumab-treated patients - a KM analysis of PML risk and a table of PML risk estimates by year of natalizumab exposure using the standard actuarial method – will be included in the educational material.

2.6. Biomarkers for PML development

L-selectin expression on CD4+ T cells

Schwab et al (Schwab et al, 2013) investigated the expression of T lymphocytes surface markers and suggested that L-selectin (CD62L) expression on CD4+ T cells might identify in addition to known risk factors MS patients at high risk for PML, since all 8 patients in their study who developed PML had a previous blood sample showing levels of CD62L expression below a hypothetical threshold. CD62L is a key adhesion molecule which regulates the migration of leukocytes at sites of inflammation and the recirculation of lymphocytes between blood and lymphoid tissue. The MAH was not able to confirm the published results with regard to L-Selectin/ CD62L as a potential biomarker for PML risk assessment. The reasons for the conflicting results (e.g. handling problems such as storage transport etc.) remain

unknown. Interestingly Spadaro M et al (Spadaro M et al, 2015) have found that natalizumab treated MS patients showed a lower percentage of CD62L compared to patients treated with first line MS therapy. One patient with asymptomatic PML associated with natalizumab belonged also to the group with low levels of CD62L. Basnayat et al (Basnayat et al, 2015) investigated soluble L-selectin in patients with relapsing-remitting MS. The results of their small study support the hypothesis of sL-selectin being connected to the anti-JCV antibody index values and possibly cellular L-selectin. Thus additional studies are considered important to investigate whether CD62L might be a suitable biomarker for PML risk.

IgM Oligoclonal bands for risk stratification prior to initiating natalizumab

IgG Oligoclonal bands (OCBs) are routinely used as an MS diagnostic test, with high IgG OCBs linked to high disease activity. IgM OCBs to myelin lipids are not routinely assessed but are also linked to aggressive disease (Villar et al. 2005). Recently, Luisa Villar *et al.* (Villar et al. 2015) reported that Lipid-specific IgM OCBs in CSF may also be a potential marker for reduced risk of PML by analysing 176 anti-JCV antibody positive patient's CSF and paired serum samples from MS patients. High risk for PML was observed in patients that where negative for lipid-specific IgM OCBs; 22 of 23 PML (>95%) natalizumab-associated cases were IgM OCB negative prior to treatment. However, IgM OCB evaluation also showed a significant false positive rate, 49 of 71 (69%) anti-JCV antibody positive, lipid-specific IgM OCB negative patients with similar duration of natalizumab treatment never developed PML (Villar et al. 2015).

The most compelling observation of the Villar study is that only 1 PML case (0.6% of all JCV+ patients tested) was positive for IgM OCBs. Anti-JCV antibody patients that are also positive for lipid-specific IgM OCBs had a similar PML risk to anti-JCV antibody negative patients (Villar et al. 2015). These data, if reproduced more widely, would suggest that the lipid specific IgM antibodies may protect from the pathogenic infection of glial cells in the brain and that natalizumab could be used safely in this subset of anti-JCV antibody positive patients.

3. Expert consultation

The PRAC consulted the neurology scientific advisory group (SAG) which provided advice on a number of issues.

The SAG confirmed that current medical practice in the EU has changed to a clear trend to recommend more frequent MRIs. In particular UK, Spain, Belgium, NL and France seem to be applying a risk stratification approach with more frequent MRI scans for patients considered at high risk for PML.

SAG experts were asked to comment on the reliability of MRI in the detection of pre-clinical PML lesions. The experts agreed that the sensitivity of the MRI in this situation is high and this is sufficient as low specificity is not an issue, since any suspicious MRI lesion will lead to further investigations (CSF fluid JCV testing or repeated MRI). For the purpose of PML screening, the SAG recommended abbreviated sequences (T2, FLAIR, DWI). T1 Gadolinium-enhancement was not considered necessary for screening purposes, but could still be used in case of PML suspicion. The SAG acknowledged that it is not easy to recognise an early PML lesion on MRI (specially a small one, early in the development of the condition) and that interrater variability is considerable even among neuroradiologists.

The SAG was also asked whether it was possible to identify specific sub-groups of patients on Tysabri that might benefit from more frequent MRIs in the context of early detection of pre-clinical PML lesions, and what would be the appropriate MRI scan schedule for such patients. The experts agreed that different risk groups exist depending on the combination of risk factors present, such as: duration of

treatment, JCV status, previous therapy with immunosuppressants and anti-JCV antibody index value. The SAG considered that there may be a need for a different approach to monitoring depending on risk level. While there are limited data available to help determine appropriate MRI frequency, the SAG experts agreed that more frequent MRIs may improve the chances of detecting asymptomatic PML cases and that a frequency of around 3-4 months was a reasonable interval to realistically allow detection of early PML cases in higher risk patients. These were considered to be:

- Patients exposed to prior immunosuppressant therapy and positive for anti-JCV antibodies (and treatment duration > 2 years)
- Patients with anti-JCV antibody index > 0.9 (regardless of previous exposure to immunosuppressant therapy), and treatment duration > 2 years

The SAG also recommended that when patients are switched to other therapies, close monitoring for at least 6 months should be maintained as per the SmPC.

When asked to consider the feasibility of more frequent MRIs in view of the burden for patients and healthcare systems in the EU, both the experts and the patient representative considered that there were no feasibility issues and supported a view that higher risk patients should be followed preferably in an appropriate setting (i.e. MS experienced neurologist or specialised centre, with full access to MRI facility and experienced neuroradiologist trained for early PML diagnosis).

With regards to the use of anti-JCV antibody index as and additional criterion for risk stratification, the experts agreed that the index could be useful in certain cases but there was no unanimous view on whether using a specific threshold would be appropriate. Some SAG members considered that changes in antibody index should be interpreted in the overall clinical context and therefore it was not appropriate to define thresholds leading to specific actions. For those who did consider it appropriate, there was no unanimous view on the threshold to be used.

The SAG also discussed the available data on the use of %CD62L levels as a marker for individual PML risk stratification, and concluded that while it may show promise it is not yet suitable for clinical use and further studies should be performed.

4. Other data

During the course of the assessment, selected Multiple Sclerosis registries in the EU (which enrolled a considerable number of patients treated with natalizumab for several years) were contacted and invited to submit relevant information on PML cases and PML detection strategy in their registries. Responses were received from registries in France, Germany, Poland and Sweden. Relevant national guidelines were also considered. In addition, the PRAC also considered information provided by third parties during the referral procedure.

5. Overall conclusions

Diagnosis of PML before development of clinical symptoms

As of May 2015, 142,958 patients had received natalizumab worldwide with 432,814 patient-years of exposure. A total of 566 PML cases have been reported globally as of 04 June 2015, of which 133 patients died (23.5 % of PML patients). Patients who survive often have serious morbidity associated with serious and permanent disability.

In sixty-two PML patients (10.9%) asymptomatic onset PML has been reported. While 10 cases have been reported in the US, most of the asymptomatic cases were reported from EU/ROW (83%, 52/62).

Although asymptomatic PML patients had generally similar baseline clinical characteristics compared with symptomatic patients, a higher proportion of asymptomatic patients presented with more localized disease (64% unilobar PML) on MRI at the time of diagnosis compared to symptomatic PML patients (36%). The shorter time to diagnosis of asymptomatic patients compared with symptomatic patients may have enabled earlier immune reconstitution following discontinuation of natalizumab. Most importantly, in terms of outcomes, asymptomatic patients appeared to have less accrual of disability over time and higher survival rates compared with symptomatic patients (95% vs. 74%). These data confirm previous observations that early PML diagnosis is critical in limiting the degree of permanent brain damage before immune reconstitution can be achieved, and reinforces the need to put in place strategies for the earliest possible identification of potential PML cases, if possible before the development of clinical symptoms of PML.

Asymptomatic PML cases were identified via routine MRI. MRI is considered to be a sensitive method to identify even small and asymptomatic PML lesions (Wattjes MP, 2015). Considering the dire diagnosis of PML a high level of vigilance and a low threshold even for invasive diagnostic measures and interventions such as MRI is warranted for managing patients with high risk for PML development. In spite of limitations of the currently available evidence such as small numbers, lack of information about MRI frequency in PML patients, false positive and false negative rate of MRI screenings, patients with a high risk for PML development may in particular benefit from more frequent MRIs because periodic brain MRI are likely to provide earlier detection of PML, even before symptoms develop, and subsequently better outcomes.

Published data (Blair NF, 2012; McGovern E, 2013, Wattjes MP, 2015) suggest that patients considered as having a high risk for PML development and who continue natalizumab treatment beyond 2 years of treatment may benefit from more frequent MRI screening e.g. every 3 to 6 months.

There seems to be consensus among experts that routine MRI screening for suspected PML lesions can be conducted without gadolinium –enhancement (Wattjes MP, 2015, McGuigan C, 2015). For natalizumab-treated patients with MS, who are at high risk of PML, brain MRI screening using a protocol that includes FLAIR, T2-weighted and diffusion –weighted imaging is recommended (Wattjes MP, 2015, McGuigan C, 2015, Rovira et al, 2015). Increasing evidence indicates that T2-FLAIR is the most sensitive sequence for detecting PML (Richert N, 2012). Diffusion –weighted imaging is highly sensitive for depicting acute demyelinisation and can also aid differentiation of acute PML lesions from chronic and subacute demyelinating PML lesions (Richert N, 2012, summary in Wattjes MP, 2015). In patients with MRI lesions suggestive for PML, the MRI protocol should be extended to include contrastenhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-IRIS, particularly during follow up (Yousry TA, 2012, Gheuens S, 2012).

It is acknowledged that high expertise is necessary to identify small and asymptomatic PML lesions via MRI. Thus, adequate guidance needs to be provided in the educational materials, and other tools may also be explored (e.g. web-based) for sharing MRIs and consultation of additional expertise.

Anti-JCV antibody index for guiding MRI monitoring frequency

Available data to date suggest that anti-JCV antibody index is correlated with the risk of PML in anti-JCV antibody positive patients with no prior IS use. However, it is unclear whether a single index cutpoint can be identified within the range of index thresholds assessed that will provide optimal clinical utility in terms of treatment decisions. The balance between sensitivity and specificity in this range needs to be carefully considered. Sensitivity differs very little between the index of 0.9 and 1.5 but there is improved specificity with 1.5. Currently available evidence suggests that the risk of PML is low at an index equal to or below 0.9 (and lower than previously estimated) and increases substantially above 1.5 for patients who have been on treatment with Tysabri for longer than 2 years. For patients with prior immunosuppressant treatment, no significant difference was observed in median index between non-PML and PML patients.

Anti-JCV antibody testing

Currently it is recommended that patients who are anti-JCV antibody negative should be tested for seroconversion twice yearly. Based on the data on antibody index stability from STRATIFY-2 the recommendation should be maintained.

In addition patients without prior immunosuppressant use and a low antibody index should also be tested every 6 months if they are treated beyond 2 years. For patients without prior immunosuppressant use and with high anti-JCV antibody index, no further antibody testing is required, as more frequent MRI screening should be considered if natalizumab treatment is continued for more than 2 years.

Anti-JCV antibody ELISA

The assumption of 55% positive serostatus for the overall natalizumab-treated population utilized in the PML risk algorithm calculations remains acceptable. In general, the positive serostatus results using the first and second generation assays were similar. There is no significant impact of the second generation assay on the risk estimates within the algorithm.

Considering real world data from UNILABS from four EU countries showing that the upper annual serostatus change rate can be as high as 16%, the annual (negative to positive) serostatus change rate in the Physician Information and Management Guidelines needs to be updated. In addition, it needs to be clarified that patients who test anti-JCV antibody positive at any time should be considered to be at an increased risk of PML, independent of any prior or subsequent antibody test result.

PML development after discontinuation of natalizumab

All PML cases in patients who had received natalizumab occurred within 6 months of the last infusion. These findings support the current SmPC recommendation that physicians should remain vigilant for signs and symptoms of PML for approximately 6 months after natalizumab discontinuation, and that the same monitoring strategy should apply for up to 6 months after discontinuation. It is important to update the package leaflet concerning the risk of PML up to 6 months following Tysabri discontinuation.

PML risk estimation

The risk stratification algorithm in the educational material will be revised to include current estimates derived from a pooled study cohort (STRATIFY-2, TOP, TYGRIS and STRATA studies) of natalizumab-treated patients, and to incorporate anti-JCV antibody index.

Supplemental presentations of PML risk using different methodologies may be complementary to the information within the current algorithm and will provide additional information to physicians as they engage in benefit/risk discussions with their patients. In particular, the inclusion of a Kaplan-Meier analysis of PML risk alongside the algorithm would allow to present cumulative risk of PML over time.

Biomarkers for PML development

Recent efforts to identify potential biomarkers are promising but have not resulted, to date, in the identification of new markers that can be used in clinical practice to enhance the existing PML risk stratification.

In view of all of the above, the PRAC concluded that the benefit-risk balance of Tysabri remains favourable subject to amendments to the product information and additional risk minimisation measures as described below.

6. Risk management

The MAH should operate a risk management system described in a Risk Management Plan which has been endorsed as part of the current review procedure.

6.1. Pharmacovigilance activity

The Tysabri data collection tool (DCTs) enhancing the overall MRI data collection for symptomatic and asymptomatic PML cases to include the MRI testing frequency and the reason for MRI testing for all patients. Going forward further data on the optimal MRI testing frequency may therefore become available.

6.2. Risk minimisation activities

6.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk of PML associated with the use of Tysabri. These changes include amendments to section 4.4 of the SmPC.

The Package Leaflet was amended accordingly.

6.2.2. Direct Healthcare Professional Communications/Communication plan

The PRAC adopted the wording of a Direct Healthcare Professional Communication (DHPC) to inform healthcare professionals of the conclusions of this review, including the need to consider more frequent MRIs and the need to retest patients with low anti-JCV antibody index and no prior exposure to immunosuppressant therapy every 6 months once they reach the 2-year treatment point.

6.2.3. Educational materials

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:

- Summary of Product Characteristics and package leaflet
- Physician information about Tysabri
- Patient alert card
- Treatment initiation and treatment continuation forms

The Physician Information and Management Guideline shall be revised to include detailed information on:

• Updated risk estimates for development of PML in Tysabri-treated patients, including presentation of PML risk in a given interval of treatment as well as cumulative PML risk;

- The association between level of anti-JCV antibody response (index) and increased risk for the development of Tysabri in patients without prior exposure to immunosuppressant treatment;
- Prognosis of asymptomatic and symptomatic PML;
- The need to consider more frequent MRIs (e.g. on a 3 to 6 monthly basis) for patients at high risk 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 anti-JCV antibodies and seroconversion rate over time;
- Monitoring strategy after discontinuation of Tysabri treatment.

The patient alert card shall be revised as follows:

• Further emphasise the need remain aware of PML symptoms for up to 6 months after stopping treatment with Tysabri.

The Treatment initiation and treatment continuation forms shall be revised as follows:

• Updated PML risk estimates will be included, including reference to how the level of anti-JCV antibodies may impact on the risk of developing PML.

A treatment discontinuation form is introduced to remind prescribers and inform patients to continue the same MRI monitoring frequency as on treatment for up to 6 months after stopping Tysabri, as well as to remain vigilant for symptoms of PML.

A mock-up of the educational material reflecting these updates can be found annexed to the Risk Management Plan.

7. Grounds for Recommendation

Whereas,

- The PRAC considered Tysabri (natalizumab) in the procedure under Article 20 of Regulation (EC) No 726/2004, initiated by the European Commission
- The PRAC reviewed all data presented by the MAH on the risk of PML in association with Tysabri, as well as other data made available during the procedure and the views expressed by the neurology scientific advisory group.
- The PRAC 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, the PRAC 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.
- The PRAC also concluded that, 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.

- The PRAC 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.
- The PRAC also considered it necessary to update the existing educational material, particularly in relation to the risk estimates for development of PML in Tysabri-treated patients.

In view of the above, the Committee considered that the benefit-risk balance of Tysabri remains favourable subject to the agreed amendments to the product information and additional risk minimisation measures.

The Committee, as a consequence, recommended the variation to the terms of the marketing authorisation for Tysabri.

The agreed DHPC can be found enclosed to this report.

8. EPAR changes

The EPAR will be updated following Commission Decision for this procedure under Article 20 of Regulation (EC) No 726/2004. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

8.1. Scope

Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 29 April 2015 the opinion of the European Medicines Agency further new scientific evidence on progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Tysabri and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

8.2. Summary

Please refer to the assessment report:

Tysabri EMEA/H/A-20/1416/C/000603/0083

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