London, 30 May 2013
EMA/297726/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tysabri

International non-proprietary name: NATALIZUMAB

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

Note

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

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List of abbreviations

ARR	Annualised Relapse Rate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
DMT	Disease modifying treatment
EC	European Commission
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
MSIS-29	Multiple Sclerosis Impact Scale
MSSS	Multiple Sclerosis Severity Score
PID	Physician Information and Management Guidelines
PML	Progressive Multifocal Leukoencephalopathy
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
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
TOP	Tysabri observational program
TYGRIS	Tysabri global observational program in safety
TYSEDMUS	French Tysabri Registry
US	United States
VLA-4	Very-late- activation antigen 4

1. Background information on the procedure

1.1. Type II 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 7 November 2012 an application for a group of variations including 2 extensions of indication.

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	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	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 application containing 2 extensions of indication 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.

On 14 May 2013, on the basis that additional data were required and these were considered still provisional, the MAH withdrew the following variation:

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

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

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Daniela Melchiorri

Submission date:	7 November 2012
Start of procedure:	23 November 2012
Rapporteur's preliminary assessment report circulated on:	15 January 2013
CoRapporteur's preliminary assessment report circulated on:	30 January 2013
PRAC RMP advice and assessment overview adopted by PRAC on :	7 February 2013
Rapporteur's updated assessment report circulated on:	15 February 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 February 2013
MAH's responses submitted to the CHMP on:	27 March 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	2 May 2013
MAH withdrawal letter submitted to the CHMP on:	14 May 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	15 May 2013
PRAC RMP advice and assessment overview adopted by PRAC on :	16 May 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	22 May 2013
CHMP opinion:	30 May 2013

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 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 Relapsing Remitting Muliple Sclerosis (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.

On 14 May 2013, on the basis that additional data were required and these were considered still provisional, the MAH withdrew the variation for the extension of indication in RRMS population without high disease activity, those patients who are negative for anti-JCV Antibodies. Consequently, the scope of this assessment relates to the extension of indication in RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure.

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

The following clinical data are presented to support the proposed extension of indication for " RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure":

1) TOP (Tysabri Observational Program)

TOP, is an ongoing, observational study in the European Union (EU), Canada, and Australia that collects safety and efficacy data from patients prescribed Tysabri in the commercial setting.

The primary endpoint is long-term safety (incidence and pattern of serious adverse events or SAEs) in patients receiving Tysabri. The secondary endpoints include MS disease activity as determined by the occurrence of clinical relapses (annualised relapse rate or ARR, distribution of the total number of relapses over 5 years, time to first relapse, proportions of patients with and without relapse), and disability progression as determined by Expanded Disability Status Scale or EDSS (based on neurological examination, physical EDSS). Furthermore, baseline disease characteristics such as previous use of disease modifying therapy are evaluated as prognostic indicators for disease activity and disability progression over time.

The study population will include approximately 6,000 patients with RRMS, who are naïve to Tysabri at initiation of Tysabri treatment and most of whom have switched from a first line therapy to Tysabri after failing to respond to the first line therapy. Each patient is followed up for approximately 10 years. The collection of efficacy and safety data at 6-month intervals during the TOP observational period coincides with regular clinic visits and routine clinical practice.

An interim analysis of the ARR in 4,434 patients in TOP was conducted with a data cut-off of 01 June 2012.

2) The Swedish Tysabri Registry (IMSE)

In August 2006, at the launch of natalizumab in Sweden, a post-marketing surveillance study was established in Sweden as an academic initiative in collaboration with the Swedish regulatory authorities and industry. The objective of this study was to monitor and analyze the demographic/clinical characteristics together with collection of long-term safety and efficacy data of natalizumab in MS patients via the Swedish MS quality registry (SMS-reg). Nearly all patients prescribed Tysabri in Sweden are entered into the Swedish MS registry (IMSE), approximately >95%, and safety and efficacy data are collected. Data was registered before start of treatment (baseline) and at every six months during treatment. Of the 1152 MS patients for whom information was available as of May 2012, the last disease modifying treatment (DMT) used prior to Tysabri was Avonex in 408 patients (22.7%), Betaferon in 143 patients (8%), Rebif in 230 patients (12.8 %), glatiramer acetate (GA) in 234 patients (13%) and other therapies in the remaining patients. The number of patients who received GA as the last MS therapy prior to starting Tysabri was similar in those patients who continued on Tysabri treatment and those who discontinued Tysabri. Data on the efficacy and safety of Tysabri in 1115 MS patients included in this registry have been published (Holmen et al. 2011).

3) The French Tysabri Registry (TYSEDMUS)

TYSEDMUS is a multicentre observational cohort study aiming at involving all French neurologists prescribing natalizumab and including all patients exposed at least once to Tysabri. Patients' characteristics under natalizumab (including pre-treatment data and clinical evolution), utilisation patterns and occurrence of adverse events are described. This observational study is run by independent investigators in France. A group of non-exposed patients, never treated with natalizumab, receiving or not immuno-active therapies, will be extracted later from the EDMUS databases for comparison. All the data are centralised in the EDMUS Coordinating Center in Lyon. The study duration is planned to be at least 5 years.

An interim analysis of data (as of November 3, 2011) from TYSEDMUS showed that of 3178 MS patients prescribed Tysabri in France, 766 patients (27%) received GA as their last treatment for MS just prior to starting Tysabri; many of these patients had also received other MS therapies in the past.

4) GLANCE

GLANCE is a randomized, double-blind, placebo-controlled parallel group Phase 2 study in which 110 MS patients (ranging in age from 19-55 years) with previous disease activity on GA were randomized to continue receiving GA (20 mg subcutaneous) or to receive Tysabri (300 mg intravenous) in combination with GA.

Although this was primarily a safety study, the primary objective was to determine whether natalizumab in combination with GA lead to an increase in MS disease activity as measured by MRI and clinical relapse or an increase in adverse events as compared to GA alone, whilst this study did not include a Tysabri-alone arm. The study therefore indirectly evaluates whether switching from GA alone to GA plus Tysabri may provide benefit.

5) Patient cohort studies

Several small, independent, patient cohort studies have been conducted in clinical practice to determine the impact of switching MS treatments on ARR. The following studies were analysed:

- A retrospective cohort study was conducted at the MS Centre, Wayne State University School of Medicine, Detroit, USA (Memon et al. 2010) in 46 MS patients treated with Tysabri in clinical practice after previous treatment with GA or Interferon-beta (IFN-beta).
- An observational study (Vokaer et al. 2010; Belachew et al., 2010) was conducted at the CHU Tivoli University Hospital, Liege, Belgium on a cohort of 45 MS patients 18–65 years of age, treated with Tysabri after therapy failure in clinical practice. The last DMT used was Avonex

(42%), GA (27%), Rebif (16%), Betaferon (16%). Only patients who had initiated natalizumab at least 44 weeks before the beginning of this study were eligible. Monthly EDSS evaluation was prospectively planned in accordance with the standard procedures of the two centers.

- In a prospective, multicentre, cohort study in German speaking countries, Austria, Germany, Switzerland (Putzki et al. 2009). Ninety-seven (97) MS patients were treated with Tysabri after therapy failure in clinical practice. The last DMT used was IFN-beta in 73 patients (75%), GA in 10 patients (10%) and other therapies in 14 patients (15%).
- A retrospective multicentre cohort in Switzerland (Putzki et al. 2009) of 85 MS patients was treated with Tysabri after therapy failure in clinical practice. Some of the patients included in this cohort were also included in the 97 patient cohort study described above. The last DMT used was IFN-beta in 57 patients (67%), GA in 11 patients (13%) and other therapies in 18 patients (20%).

2.4. Clinical efficacy

2.4.1.1. Results

1) TOP (Tysabri Observational Program)

The interim data from TOP showed that in 25% of MS patients in normal clinical practice, the last MS therapy used immediately prior to the start of Tysabri treatment was GA. This was comparable to the usage of IFN-beta 1-b (18%), subcutaneous IFN-beta 1-a (23%) and intramuscular IFN-beta 1-a (18%). Overall, one-third of subjects in TOP had used GA at some time prior to starting Tysabri, but some of these patients switched to other MS therapies before beginning Tysabri treatment.

The patients enrolled in TOP had more baseline disease activity (mean baseline EDSS: 3.5, mean ARR in previous year: 2.00) than the patients enrolled in the pivotal AFFIRM (EDSS: 2.3, ARR: 1.53) and SENTINEL (EDSS: 2.4, ARR: 1.44) studies.

The ARR reduction in TOP was maintained over three to four years of treatment (see Figure 1). The efficacy outcomes with respect to the magnitude of the ARR reductions on treatment with Tysabri were similar and consistent with AFFIRM (see Figure 2) and SENTINEL.

Figures 1. ARR reduction per yearly interval overtime

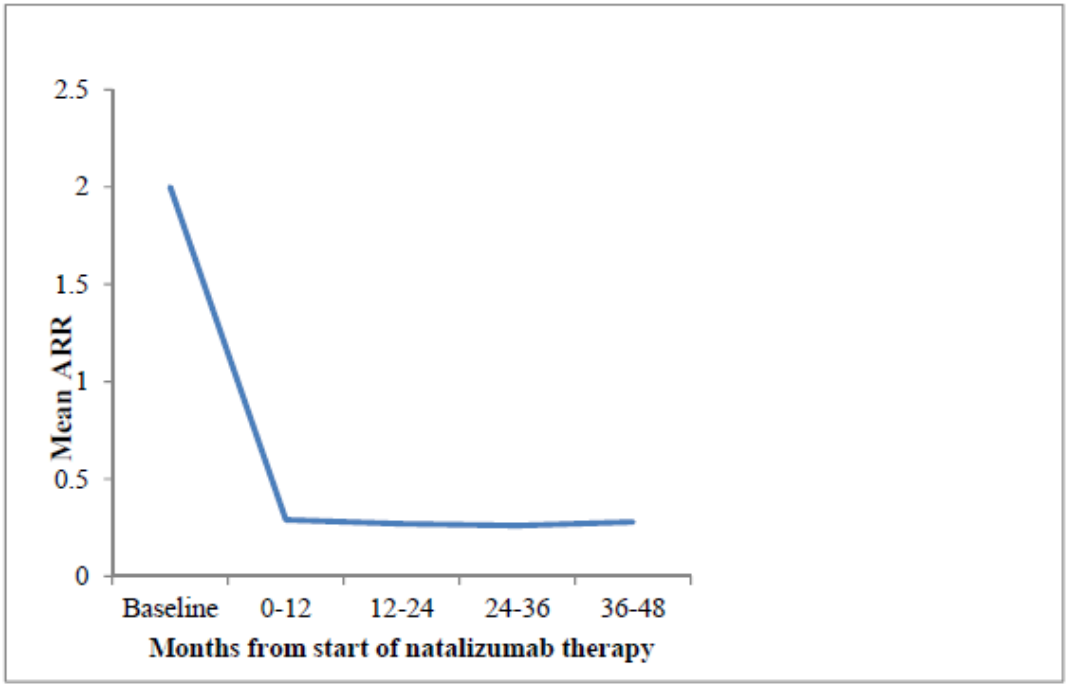
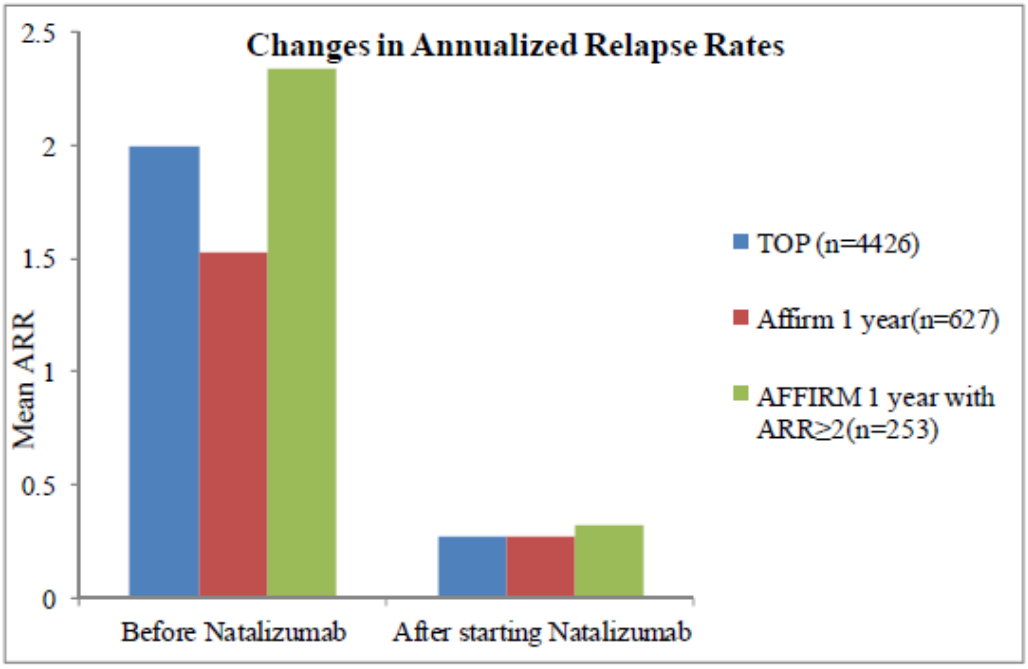


Figure 2. Overall ARR in TOP compared to AFFIRM



Source: Table 11 and Polman et al (2006)

Overall, the subjects dosed in this study at the time of the analysis had received a mean of 20.4 infusions of Tysabri (Standard Deviation or SD: 13.8) and a median of 19 infusions of Tysabri (range 1 to 63).

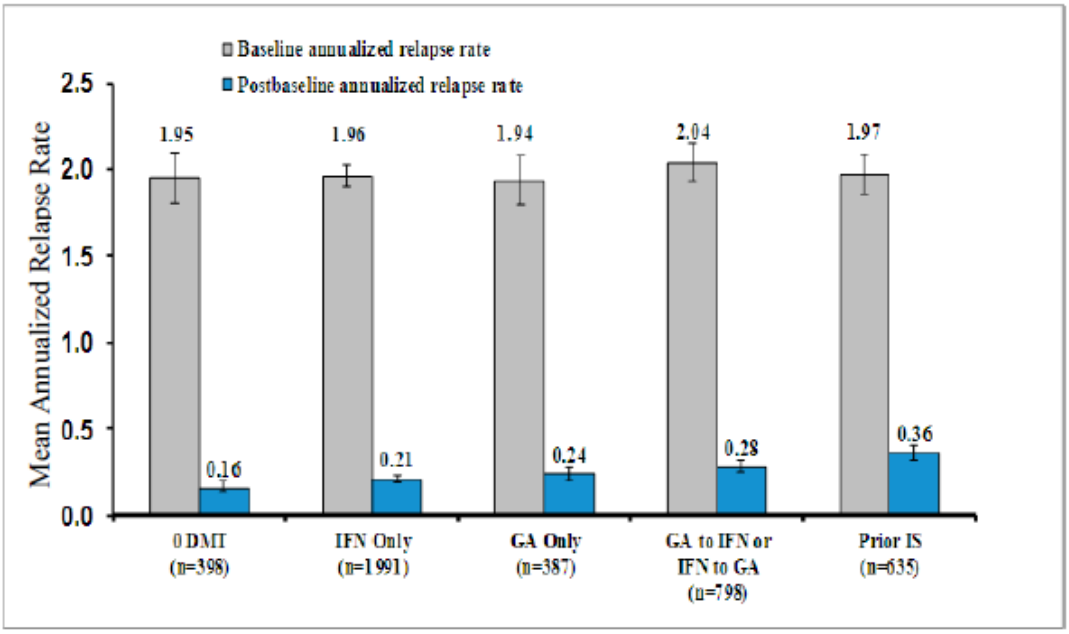
The efficacy outcome of ARR is summarised in Table 4 and Figure 3. The term DMT covers approved disease modifying treatments excluding Tysabri i.e. IFN-beta or GA.

Table 1 Comparison of ARR pre-and post-Tysabri treatment

Subject Population Prior to Switch to Tysabri	Pre-Tysabri Mean ARR	Post-Tysabri Mean ARR
Overall TOP population (n=4426)	2.00	0.27*
No previous DMT (n=398)	1.95	0.16
IFN-beta was the only previous DMT (n=1991)	1.96	0.21*
GA was the only previous DMT (n= 387)	1.94	0.24*
GA to IFN or IFN to GA (n=798)	2.04	0.28*

*P<0.0001, p-value was for mean ARR change from pre-treatment using Wilcoxon signed rank test.

Figure 3. Baseline and post-baseline annualised relapse rates by baseline treatment history



Tysabri was associated with significant reductions in the ARR in all subsets of subjects, irrespective of a history of GA only use or IFN-beta only use or switching between these DMTs prior to Tysabri. The magnitude of the response was similar across populations.

2) The Swedish Tysabri Registry (IMSE)

Of the 1152 MS patients for whom information was available as of May 2012, the last DMT used prior to Tysabri was Avonex in 408 patients (22.7%), Betaferon in 143 patients (8%), Rebif in 230 patients (12.8 %), GA in 234 patients (13%) and other therapies in the remaining patients. The number of patients who received GA as the last MS therapy prior to starting Tysabri was similar in those patients who continued on Tysabri treatment and those who discontinued Tysabri.

RRMS patients (n=901) improved significantly in several parameters and the major changes occurred in the 12 month interval (see Figure 4).

Figure 4

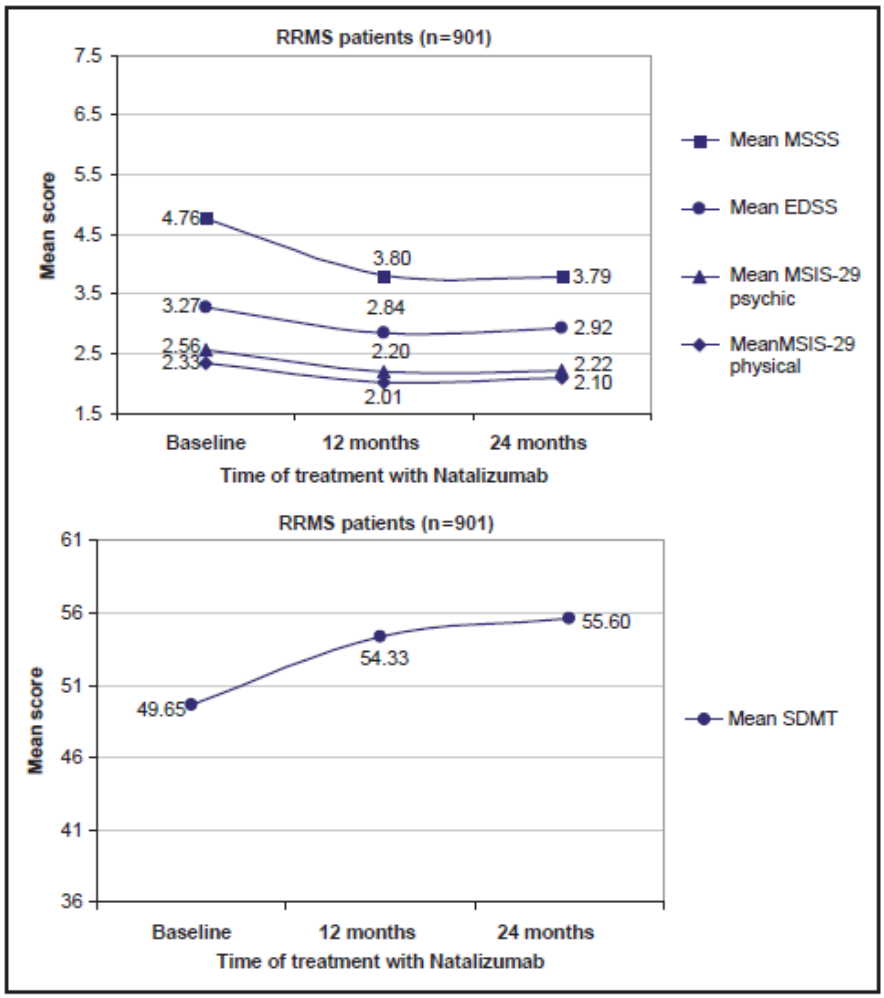


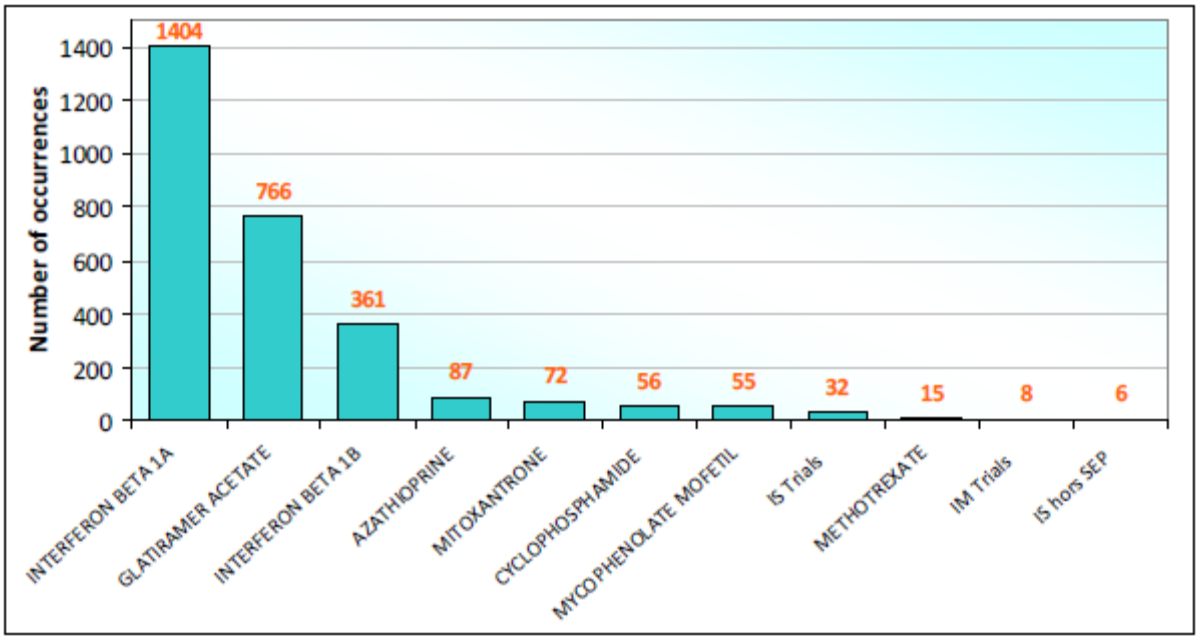
Figure 1. Clinical data of mean EDSS, MSSS, MSIS-29 and SDMT over time in patients with RRMS ($n = 901$). From baseline until 24 months of treatment with natalizumab, mean EDSS (−10.7%), MSSS (−20.4%), MSIS-29 physical (−9.9%) and MSIS-29 psychological score (−13.3%) all decreased significantly (p-values ≤ 0.05). Mean SDMT also showed significant increase with +10.7% from baseline until 24 months of treatment with natalizumab (p-values ≤ 0.05).

EDSS was on average 0.43 steps lower (decrease with 13.1%) at the end of the first year of treatment (p≤0.05). In those patients where EDSS data was complete at baseline, 12 months and 24 months, the proportions of patients free from EDSS progression were 89% at 12 months and 84% at 24 months. Accordingly, average Multiple Sclerosis Severity Score (MSSS) decreased from 4.76 to 3.80 (decrease of 20.2%) in the first 12 months (p≤0.05). The patient-reported outcomes in the Multiple Sclerosis Impact Scale (MSIS-29) decreased both in the physical and psychological domains (p≤0.05). The performance on Symbol Digit Modalities Test (SDMT), included to assess cognitive aspects, showed a consistent improvement from 49.65 to 54.33 (8.6%) during 12 months (p≤0.05). The improvement in EDSS and MSSS did not continue during the second year of treatment (Holmen et al. 2011, Multiple Sclerosis Journal 17: 708-719). The analyses were not designed to differentiate between different types of prior disease modifying treatments.

3) The French Tysabri Registry (TYSEDMUS)

The study was launched in November 2007. An interim analysis of data (as of November 3, 2011) from TYSEDMUS showed that of 3178 MS patients prescribed Tysabri in France, 766 patients (27%) received GA as their last treatment for MS just prior to starting Tysabri; many of these patients had also received other MS therapies in the past. See Figure 5.

Figure 5. Last disease modifying treatment prior to Tysabri (natalizumab)



The number of relapses in the year before inclusion and in the first year of follow-up was known for 2245 patients out of 2324. The annual relapse rate in the first year of follow-up was 0.34 (+/- 0.68), versus 1.97 (+/- 1.17) in the year before inclusion, i.e. a significant reduction by 83% ($p<0.0001$, paired t-test). One thousand seven hundred and sixty-one patients out of 2324 (76%) had no relapse during the first year of follow-up.

The number of relapses in the year before inclusion and in the first two years of follow-up was known for 1507 patients out of 1560. The ARR was 0.31 (+/- 0.52) in the overall two-year period, versus 2.03 (+/- 1,16) in the year before inclusion, i.e. a reduction of 85% ($p<0.0001$, paired t-test). The annual relapse rate was 0.34 (+/-0.68) in the first year and remained low in the second year (0.27 +/-0.60). One thousand two hundred and thirty three out of 1560 (65%) had no relapse during the first two years of follow-up.

The initial EDSS score (at inclusion) and at one year (+/- 3 months) was known for 1553 patients among the 2324 treated at least one year. The mean EDSS significantly decreased between inclusion and the first year (3.7 ± 1.8, versus 3.3 ±1.9, $p<0.0001$, paired t-test). The median EDSS score after one year was significantly lower from the median initial EDSS score (4.0 versus 3.5; $p<0.0001$, Wilcoxon signed-rank test). Five hundred and seventy six patients (37%) were stable after 1 year, 656 (42%) improved by at least 0.5 point, and 321 (21%) worsened by at least 0.5 point.

The initial EDSS score (at inclusion) and at three years (+/- 3 months) was known for 504 patients among the 815 treated at least 3 years. The mean EDSS between inclusion and the third year was significantly different (3.8 ± 1.8 versus 3.4 ± 2.0 ($p<0.0001$, paired t-test). The median EDSS score after three years was significantly different from the median initial EDSS score (4.0 vs. 3.5, $p<0.0001$, Wilcoxon signed-rank test). One hundred and thirty patients (26%) were stable, 228 (45%) patients improved by at least 0.5 point, and 146 (29%) worsened by at least 0.5 point.

Among the 2324 patients followed for at least 1 year, both baseline and one year (+/- 3 months) MRI with gadolinium were available in 682 patients. This small proportion could in part be explained by the initial absence of recommendations regarding a systematic MRI follow-up of patients treated with Tysabri. Since January 2010, a yearly MRI has been recommended both by the EMA and the AFSSAPS. Thirty-seven patients (5 %) presented an active lesion (gadolinium-enhancing) after one year, versus

380 (56 %) at the time of inclusion, i.e. a reduction of 90% of the number of active scans (p<0.0001, Mc Nemar test).

Among the 1560 patients followed for at least 2 years, both baseline and two years (+/- 3 months) MRI with gadolinium were available in 419 patients. Twenty four patients (6 %) presented an active lesion (gadolinium-enhancing) after two years versus 236 (56 %) at the time of inclusion, i.e. a reduction of 90% of the number of active scans (p<0.0001, Mc Nemar test).

Overall, preliminary data confirmed the effectiveness of Tysabri in the TYSEDMUS population as a whole. Although no sub-group efficacy analyses were available of last MS therapy received before starting Tysabri, the report did not suggest that the effectiveness of Tysabri differed depending on the last MS therapy received prior to Tysabri.

4) GLANCE

Based on data from monthly MRIs, the mean rate of development of new active lesions (the primary study outcome) was 0.03 with combination therapy versus 0.11 with GA alone (p = 0.031). Combination therapy resulted in lower mean numbers of new gadolinium-enhancing lesions (0.6 versus 2.3 for GA alone, p = 0.020) and new/newly enlarging T2-hyperintense lesions (0.5 versus 1.3, p = 0.029). In addition, approximately 43% fewer patients reported MS relapses in the Tysabri plus GA group as compared to GA alone. Similarly when the relapse rates were annualized, there was a 40% reduction in relapse rate on the Tysabri/GA combination versus GA alone. ARR in the GA group was 0.669 (95% CI: 0.338, 1.324) compared to 0.403 (95% CI: 0.195, 0.830) for the group that received GA in combination with Tysabri.

5) Patient cohort studies

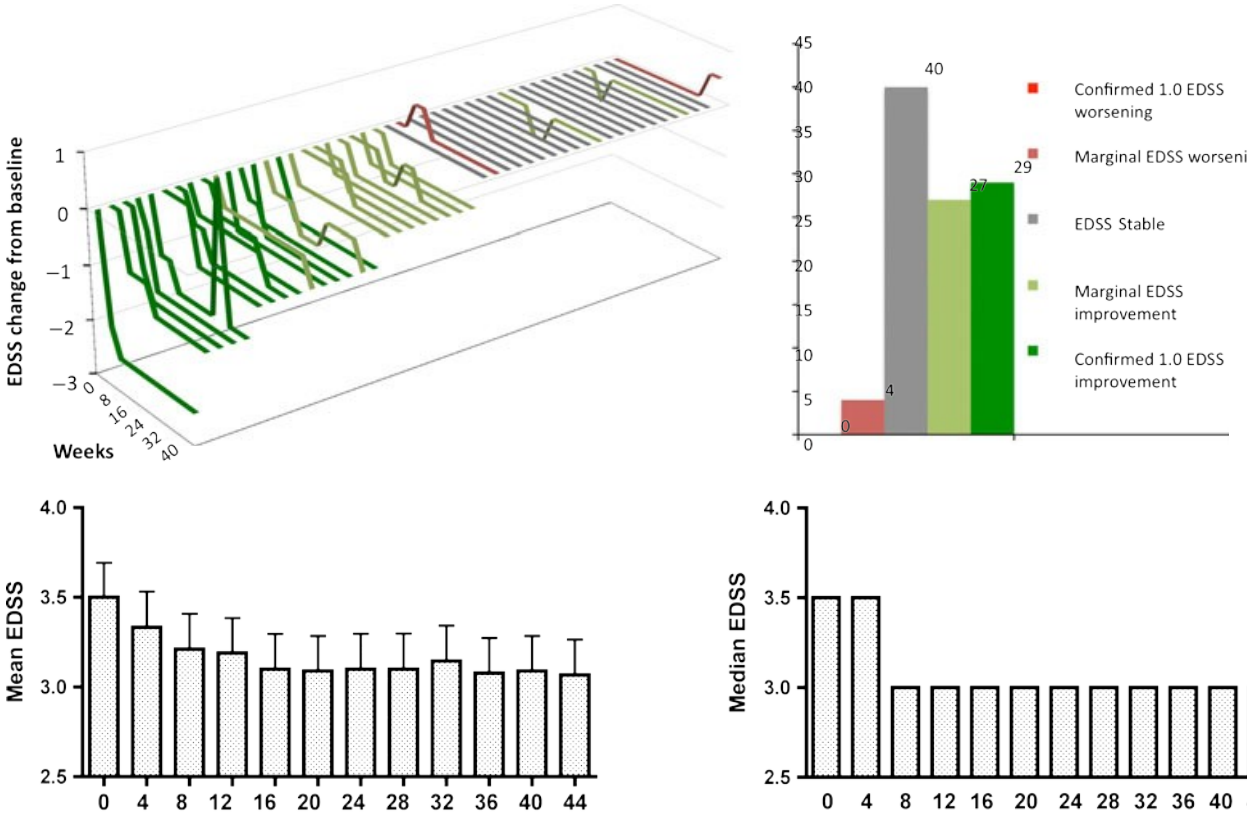
- The results from the retrospective cohort study at the MS Centre, Wayne State University School of Medicine, Detroit, USA showed that there was no improvement in efficacy conferred following a switch from IFN-beta to GA, or from GA to IFN-beta; substantial efficacy was observed after switching from either DMT directly to Tysabri, as summarized in Table 2:

Table 2. Comparison of ARR after switching between DMTs and Tysabri

DMT	ARR 2 years before switch	ARR on last 1 year before switch	ARR after switching between DMTs	ARR after switching to Tysabri
Copaxone (n=25)	0.8	1.2	1.04	0.08 (p<0.0001)
IFN-beta (n=21)	0.8	1.24	1.14	0.09 (p<0.0001)

- The Belgian observational study showed that Tysabri was prescribed following first line treatment failure where the last DMT used was Avonex (42%), GA (27%), Rebif (16%), Betaferon (16%). Sixty-two percent of patients showed no clinical and no radiological signs of disease activity and 29% showed a rapid and confirmed EDSS improvement over 44 weeks of Tysabri therapy. Approximately 30% showed improvement in ambulation after switching to Tysabri. The analyses were not designed to differentiate between different types of prior disease modifying treatments (Vokaer et al. 2010; Belachew et al. 2010). See Figures 6-9.

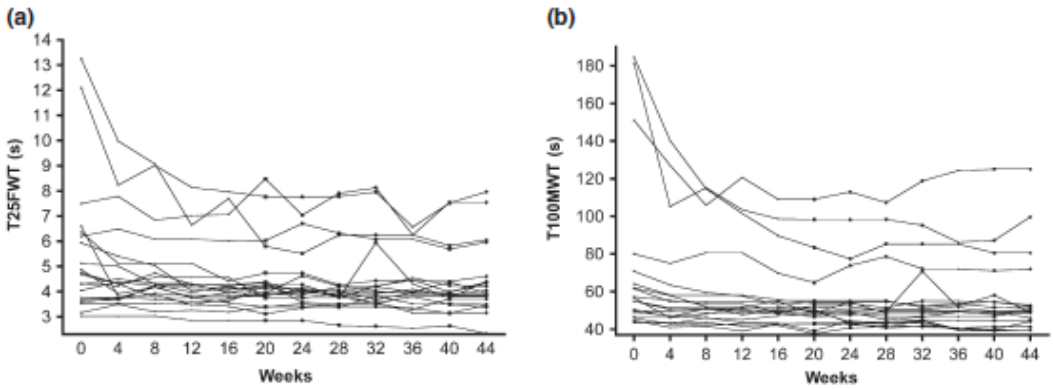
Figures 6-9. Results from the Belgian observational study



Figures 6-9 Individual EDSS changes from baseline over 44 weeks of follow-up. Colour codes are consistent with the different subgroups described in panel b, with grey lines representing EDSS-stable patients; light green lines for patients experiencing a marginal EDSS improvement; dark green lines for patients experiencing a confirmed EDSS improvement; light red lines for patients experiencing a marginal EDSS worsening; dark red lines for patients experiencing a confirmed EDSS worsening (b) Distribution of EDSS evolution in our population after 44 weeks of natalizumab therapy (c) EDSS evolution (mean ± SD) over 44 weeks of natalizumab therapy (d) EDSS evolution (median) over 44 weeks of natalizumab therapy.

Analyses of ambulation parameters also revealed significant improvement in most patients during the 44 weeks of natalizumab treatment. See Figures 10-11.

Figures 10-11



(a) Individual Timed 25- Foot Walk Test (T25FWT) evolution over 44 weeks of natalizumab therapy (b) Individual Timed 100 Metre Walk Test (T100MWT) evolution over 44 weeks of natalizumab therapy.

- The cohort study conducted in German speaking countries showed that Tysabri was prescribed following first line treatment failure where the last DMT used was IFN-beta in 73 patients (75%), GA in 10 patients (10%) and other therapies in 14 patients (15%). Tysabri was associated with a reduction in mean ARR from 2.3 to 0.2 ± 0.1 after 12 months (P < 0.001), and 80% of patients remained relapse free during the observation period. The analyses were not designed to differentiate between different types of prior disease modifying treatments (Putzki et al. 2009). See Figures 12-13.

Figure 12

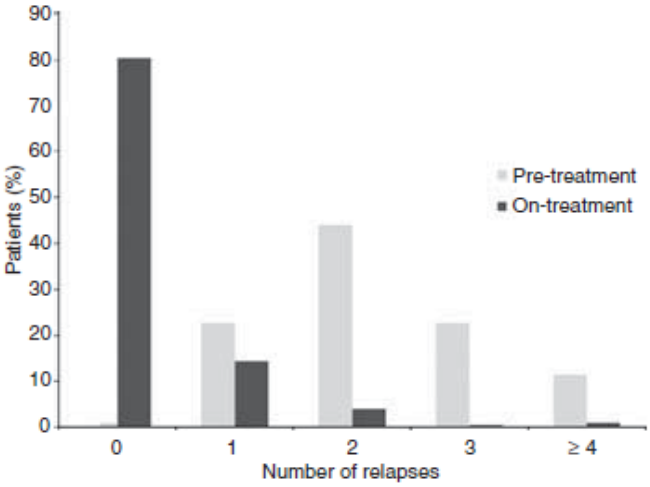
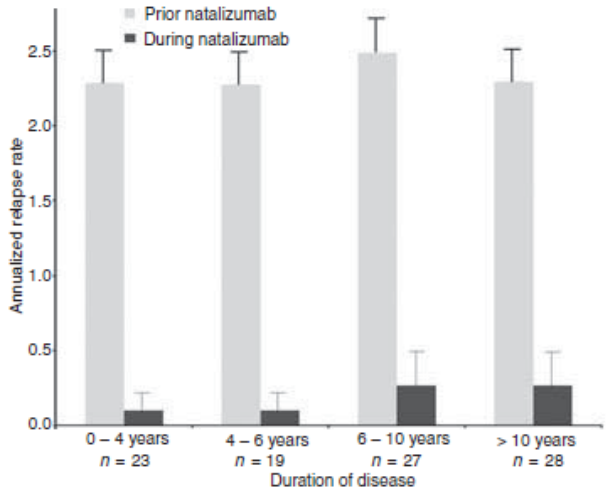


Figure 1 Distribution of number of relapses before and during treatment with natalizumab. After treatment initiation with natalizumab ('on treatment': mean treatment duration 19.3 ± 3.1), relapse activity was reduced in patients with high and low previous relapse activity. Eighty per cent of patients were relapse free after introduction of natalizumab during the observational period.

Distribution of number of relapses before and during treatment with natalizumab. After treatment initiation with natalizumab ('on treatment': mean treatment duration 19.3 ± 3.1), relapse activity was reduced in patients with high and low previous relapse activity. Eighty per cent of patients were relapse free after introduction of natalizumab during the observational period.

Figure 13



Stratified analyses of ARR in categories of disease duration. Mean ARR were equally high in patients with different disease duration and decreased after introduction of natalizumab in all groups. ARR tended to be lower for patients with disease duration ≤6 years compared with > 6 years (p=0.04)

- Some of the patients included in the retrospective multicentre cohort in Switzerland were also included in the cohort study conducted in the German speaking countries described above. The last DMT used was IFN-beta in 57 patients (67%), GA in 11 patients (13%) and other therapies in 18 patients (20%). Tysabri was associated with a reduction in ARR from 2.0 to 0.27, and 93% of patients were free of disability progression after 12 months (Putzki et al. 2009).

2.4.1.2. Discussion

In clinical practice both IFN-beta and glatiramer acetate (GA) are used as first line treatment in RRMS, with patients being changed from an IFN-beta to GA or vice versa if they are unable to tolerate or if they fail treatment. More recently, two randomized studies have supported this practice as they confirmed that GA has comparable efficacy to IFN-beta (REGARD and BEYOND studies) with ARR reductions to approximately 0.3.

Data from patients who have had an inadequate response to GA and switched directly to Tysabri have been presented from several observational studies including TOP, patient cohort data from MS treatment centers, the Swedish Tysabri Registry (IMSE), the French Tysabri Registry (TYSEDMUS), and the phase 2 study GLANCE. Overall, data indicated that Tysabri was effective as measured by relapses, EDSS, cognitive function, and other Quality of Life scales.

Interim data from TOP showed that in 25% of MS patients, the last MS therapy used immediately prior to the start of Tysabri treatment was GA. This was comparable to the usage of IFN-beta 1-b (18%), subcutaneous IFN-beta 1-a (23%) and intramuscular IFN-beta 1-a (18%). Tysabri was associated with significant reductions in the ARR in all subsets of subjects, irrespective of a history of GA only use or IFN-beta only use or switching between these DMTs prior to Tysabri. The magnitude of the response was similar across populations. The TOP data further indicated that patients who have not responded to a currently available first line treatment (IFN-beta or GA), rarely respond to the other second first-line treatment. However, switching to Tysabri in these patients was associated with significant clinical response.

Similar findings were reported from patient cohort studies, patient registries and GLANCE, although these programs were not designed to differentiate between different types of prior disease modifying treatments, as they did not include sub-group efficacy analyses based on the last MS therapy received before starting Tysabri. However, results did not suggest that the effectiveness of Tysabri differed depending on the last MS therapy received prior to Tysabri.

Overall, these data indicate that Tysabri as a second line treatment is efficacious in patients that did not respond to a full and adequate course of GA.

The benefit-risk profile of Tysabri has not been established for (future) alternative first-line immunomodulatory treatments. The CHMP therefore recommended revision of the initial proposed wording for section 4.1 since the MAH proposal would not only have introduced glatiramer acetate as an additional example of treatment failure, but would have broaden the indication statement to patients who have failed alternative immunomodulatory therapies (see 2.7).

2.4.1.3. Conclusions

On the basis of the available data, the CHMP concluded that the efficacy of Tysabri is demonstrated in the RRMS population with high disease activity who have failed to respond to a full and adequate course (normally at least one year of treatment) of glatiramer acetate.

2.5. Clinical safety

The safety results from the TOP study which have been summarized in prior PSURs. A recent analysis of TOP was performed using data as of June 1, 2012.

2.5.1.1. Results

The TOP interim report provided with the following safety summary information:

Overall 6.9% patients experienced an Serious Adverse Event (SAE) and 2.3% experienced an SAE that was considered related to Tysabri. No new safety concerns were identified. Apart from infections (1.5%), no single SAE occurred in more than 1% of study patients. See Table 3.

Table 3

Table 16-1 Incidence of Serious Adverse Events

	Number of patients dosed (n= 2311)
Patients with at least 1 SAE	308 (6.9 %)
Patients with at least 1 treatment–related SAE	100 (2.3%)
Deaths	8 (0.2%)
Patients diagnosed with PML	12 (0.3%)
Patients hospitalized for an Opportunistic Infection	1 (0.0%)
Patients hospitalized for other Infections	43 (1.0%)
Patients diagnosed with a malignancy	20 (0.5%)

Source: Table 16

There was a lower overall incidence of SAEs in therapy-naïve patients as compared with patients who received either ≥1 DMT (without prior immunosuppressant (IS) use) or IS therapy previously (naïve: 5.8%; ≥1 DMTs: 6.9%; IS: 7.8%). This was also true for infection SAEs (naïve:1.3%; ≥1 DMTs :1.5%; IS : 1.6%) and progressive multifocal leukoencephalopathy (PML) SAEs (naïv: 0; ≥1 DMTs :0.3%; IS : 0.5%), although differences were not significant

Twelve patients were diagnosed with PML. The overall PML incidence rate was 2.71/1000 (95% CI: 1.2, 4.2). Median number of Tysabri infusion prior to the diagnosis of PML was 27 with doses ranging from 11-44. Three PML patients previously used IS (mitoxantrone in all cases).

The distribution of the type of malignancies in Tysabri-treated TOP patients is similar to that observed in a similarly aged general population. There were 20 patients diagnosed with 10 types of malignancies. The most frequently reported malignancies were breast cancer (n=5) and papillary thyroid cancer (n=3).

Eight deaths occurred during the study. Three were attributed to suicide, one each to sepsis (patient also had PML, which was ongoing at time of death due to urosepsis), pulmonary embolism, pathological fracture, drowning and lastly cause of death was unknown in one patient.

2.5.1.2. Discussion

Safety findings in TOP were generally consistent with previous studies of Tysabri. Safety results were not stratified for prior disease modifying treatment. However, previous experience with use of Tysabri does not indicate that the choice of prior disease modifying treatment, GA or beta INF, respectively, may influence the safety profile of Tysabri treatment.

2.5.1.3. Conclusions

On the basis of the available data, the CHMP concluded that the safety profile was sufficiently characterised in the RRMS population with high disease activity who have failed to respond to a full and adequate course (normally at least one year of treatment) of glatiramer acetate and is consistent to the known safety profile in the approved indication.

2.5.2. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan. This advice follows the withdrawal of the variation related to RRMS population without high disease activity, for those patients who are negative for anti-JCV antibodies.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 16.1, the PRAC considers by consensus that the risk management system for natalizumab (TYSABRI) could be acceptable for the currently approved indication with the introduction of glatiramer acetate as an additional example of treatment failure provided an updated risk management plan is submitted and all references to the withdrawn indication are removed.

The currently approved indication is:

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

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

  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. 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.

Advice on conditions of the marketing authorisation

The PRAC do not advise any changes to the current conditions of the Marketing Authorisation.

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 Progressive Multifocal Leukoencephalopathy (PML) 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 Long term exposure data in anti-JCV antibody negative RRMS patients without high disease activity.

The PRAC agreed.

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 (US, Canada) Study 101MS403 (ROW) **Category 3**	To obtain long-term safety data on subjects with MS treated with Tysabri in a clinical practice setting	PML and Other Infections Malignancies Anti-Natalizumab Antibody Formation Hypersensitivity Reactions	Started	2014
Epidemiology of	Epidemiology of	PML and Other	Started	2013

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**
JCV Antibody Seroprevalence in Multiple Sclerosis Patients **(JEMS)** Study 100JC401	JCV antibodies as risk factor for PML	Infections		
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)** Study 101JC401 **Category 3**	To define the prevalence of anti-JCV antibodies in serum and plasma and to confirm the false negative rate of the anti-JCV antibody assay.	PML and Other Infections	Started	2012
JCV Antibody Program in Patients with	To evaluate whether the incidence of PML	• PML and Other Infections • Long term	Started	2015

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
Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri® **(STRATIFY-2)** Study 101JC402 **Category 3**	in Tysabri-treated patients who are anti-JCV antibody negative is lower than in patients who are anti-JCV antibody positive.	exposure data in anti-JCV antibody negative RRMS patients without high disease activity.		
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 protocol : Study 101-MS-321 **Category 3**	To evaluate the risk of hypersensitivity and immunogenicity upon redosing with natalizumab, and to confirm the safety of switching treatment from other MS therapies to natalizumab	PML and Other Infections Anti-Natalizumab Antibody Formation Hypersensitivity Reactions	Started	2018

*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 proposed indication.

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

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.	Physician Education via a Physician Information and Management Guidelines (see

	Contraindication in section 4.3 of the SmPC. Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC.	above).
Anti-natalizumab antibody formation	Recommendation that therapy be carefully reconsidered in patients showing no evidence of therapeutic benefit beyond 6-months and check of antibody status if infusion events occur and before re-dosing in section 4.2 of the SPC. Warning in Section 4.4 of SmPC. Listed as ADR in Section 4.8 of SmPC.	None.
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.
Long term exposure data in anti-JCV antibody negative RRMS patients without high disease activity.	Recommendation for anti-JCV antibody testing prior to starting Tysabri treatment and strong recommendation for 6-monthly testing in patients who are anti-JCV antibody negative in section 4.4 of the SmPC.	None.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The PRAC also considered that all references to risk minimisation activities for the withdrawn variation should be removed from the risk minimisation plan which should be submitted in the new format within a month of the Commission Decision.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

The MAH initially proposed the following changes to the Product Information (new text= underlined, deleted text= strikethrough):

Section 4.1

TYSABRI is indicated as single disease modifying therapy in adult patients aged 18 years and over with ~~highly active~~ relapsing remitting multiple sclerosis ~~for~~in the following patient groups:

● ~~Adult p~~Patients ~~aged 18 years and~~ who are negative for anti-JCV antibodies (see section 4.4) ~~over~~ with or without high disease activity~~despite treatment with a beta interferon.~~

● 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:

●P~~These p~~atients ~~may be defined as those~~ 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

● ~~Adult p~~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.

Section 4.4

~~Anti-JCV antibody testing provides supportive information for risk stratification of TYSABRI treatment.~~ Patients who are anti-JCV antibody negative have a significantly lower risk of PML compared with anti-JCV antibody positive patients. Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients receiving TYSABRI with an unknown antibody status is recommended. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Patients whose antibody status changes to anti-JCV antibody positive while on Tysabri should consider the benefit of continuing treatment in relation to the increase in risk of PML.

Section 5.1

The European Medicines Agency has deferred the obligation to submit the results of studies with Tysabri in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

Following the withdrawal of the variation related to RRMS population without high disease activity, for those patients who are negative for anti-JCV antibodies, the CHMP considered that the initial proposed wording for section 4.1 would not only have introduced glatiramer acetate as an additional example of treatment failure, but would have broaden the indication statement to patients who have failed alternative immunomodulatory therapies. However, the benefit-risk profile of Tysabri has not been

established for (future) alternative first-line immunomodulatory treatments. The CHMP therefore recommended a different wording to be implemented in section 4.1, which was accepted by the MAH. The final recommended wording of the indication is as follows:

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

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

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

or

- Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

In addition, the paediatric deferral statement has been included in the SmPC in accordance with QRD template version 8 (as shown above) and the list of local representatives in the PL has been revised to add the contact details for the representative of Croatia.

Regarding the initial proposed changes in section 4.4, the CHMP noted that following the withdrawal of the variation related to RRMS population without high disease activity, for those patients who are negative for anti-JCV antibodies, the MAH submitted an update regarding the risk of PML for anti-JCV antibody negative patients in the context of the ongoing PSUR assessment (EMEA/H/C/000603/ PSU-057).

3. Benefit-Risk Balance

3.1.1. Beneficial effects

In clinical practice both therapies, IFN-beta and GA, are used as first line treatment in RRMS. Recent data indicate that both treatments have comparable efficacy with ARR reductions to approximately 0.3 (REGARD and BEYOND studies). This reflects modest efficacy in slowing disease progression. Patients are changed from an IFN-beta to GA or vice versa if they are unable to tolerate or if they fail treatment.

Data from patients who have had an inadequate response to either IFN-beta or GA and switched to Tysabri indicate that Tysabri is equally efficacious is these two patient populations as measured by relapses, EDSS, cognitive function, and other Quality of Life scales.

Moreover, TOP data indicate that patients who have not responded to a currently available first line treatment (IFN-beta or GA), rarely respond to the other second first-line treatment, while switching to Tysabri was associated with significant clinical response in these patients.

3.1.2. Uncertainty in the knowledge about the beneficial effects

A limitation of single-arm observational studies like TOP and data from patient registries versus randomized clinical trials is the lack of control groups and randomized treatment assignment.

However, the data form observational studies and registries presented here in support of extending the indication to RRMS patients who have failed on GA therapy are in line with previous data from controlled clinical trials. Although most analyses were not designed to discriminate between different prior disease modifying therapies, data do not indicate that the choice of prior disease modifying treatment, GA or beta INF, may influence the efficacy profile of Tysabri treatment.

3.2. Risks

3.2.1. Unfavourable effects

In TOP, safety findings were generally consistent with previous studies of Tysabri. No new safety concerns were identified.

3.2.2. Uncertainty in the knowledge about the unfavourable effects

Safety results in TOP were not stratified for prior disease modifying treatment. However, the safety profile of Tysabri has been well characterized with over 6 years of marketing experience. Current data do not indicate new safety concerns.

3.3. Benefit-risk balance

3.3.1. Importance of favourable and unfavourable effects

Current data do not indicate new safety concerns. Therefore, the benefit-risk balance is considered to be similar in patients being switched from either of the two first line therapies, INF-beta or GA, with the same risk stratification algorithm applying to both patient groups.

3.3.2. Benefit-risk balance

IFN-beta and GA are both considered to confer moderate efficacy based upon the reduction in ARRs observed in randomized clinical studies. Although IFN beta therapy has been the standard of care for the early treatment of MS since the mid-nineties, two recent randomized studies have confirmed that GA has comparable efficacy to IFN-beta (REGARD and BEYOND studies) with ARR reductions to approximately 0.3. As such, these therapies are used as first line therapy in many patients and patients are only changed from an IFN-beta to GA or vice versa if they are unable to tolerate treatment or if they fail treatment. The various subgroup analyses in TOP indicate that Tysabri confers a substantial treatment benefit to patients after failure with either an IFN beta or GA, irrespective of whether one of these DMTs has been used alone or sequentially.

Data on safety did not indicate new concerns in patients switching from GA to Tysabri. Therefore, the benefit-risk balance is considered to be equal in patients being switched from either of the two first line therapies, INF-beta or GA, with the same risk stratification algorithm applying to both patient groups.

4. Recommendations

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

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

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

In addition, the paediatric deferral statement has been included in the SmPC in accordance with QRD template version 8 and the list of local representatives was updated in the Package Leaflet to include Croatia.

The requested variation proposed amendments to the SmPC and Package Leaflet.