

# Natalizumab for the treatment of relapsing multiple sclerosis

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**Abstract:** Natalizumab is an  $\alpha$ 4-integrin antagonist approved as monotherapy for patients with relapsing multiple sclerosis (MS), based on demonstrated efficacy in the pivotal AFFIRM study (N = 942). Natalizumab monotherapy reduced risk of disability progression by 42%–54% and annualized relapse rate by 68% during a period of 2 years. Natalizumab was also associated with significant reductions in number of T2-hyperintense, gadolinium-enhancing, and T1-hypointense lesions and in volume of T2-hyperintense lesions (all  $p < 0.001$ ) on magnetic resonance imaging. Furthermore, natalizumab-treated patients in AFFIRM experienced significant improvements from baseline in the physical and mental components of the Short Form-36 ( $p \leq 0.01$ ) and a 35% reduction in risk of clinically significant vision loss ( $p = 0.008$  vs placebo). Natalizumab was well tolerated in phase 3 studies. Common adverse events were generally mild and included headache, fatigue, urinary tract infections, and arthralgia. Serious adverse events were similar between treatment groups. The incidence of serious hypersensitivity reactions associated with natalizumab was  $<1\%$ . Progressive multifocal leukoencephalopathy was a rare complication of treatment, observed in 2 patients with MS who received natalizumab plus interferon  $\beta$ -1a. The robust clinical benefits of natalizumab, including benefits on patient-reported quality of life, make it an important addition to disease-modifying therapies available to patients with relapsing MS.

**Keywords:** multiple sclerosis, natalizumab,  $\alpha$ 4-integrin antagonist

## Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS). The disease is characterized by focal areas of demyelination and axonal loss that may be manifested as sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, clumsiness, gait ataxia, neuropsychological impairment, sexual and bladder dysfunction, pain, fatigue, and spasticity (Noseworthy et al 2000). Although the pathogenesis of MS is not completely understood, it is believed that interactions between adhesion molecules on activated leukocytes and their receptors on endothelial cells of the vessel wall promote leukocyte migration across the blood-brain barrier. Once in the CNS, leukocytes may reactivate and promote recruitment of a second wave of leukocytes into the CNS. This reaction in turn promotes an inflammatory cascade that causes demyelination and axonal loss (French-Constant 1994).

Natalizumab (Tysabri<sup>®</sup>; Biogen Idec, Inc., Cambridge, MA, USA and Elan Pharmaceuticals, Inc., San Francisco, CA, USA), a humanized monoclonal antibody to the  $\alpha$ 4-subunit of  $\alpha$ 4 $\beta$ 1-integrin (expressed on the surface of all leukocytes except neutrophils), is the first selective adhesion molecule inhibitor available for the treatment of MS. By binding to  $\alpha$ 4-integrin, natalizumab inhibits the  $\alpha$ 4-mediated adhesion of leukocytes to the vascular cell adhesion molecule-1 receptor expressed on vascular endothelial cells, preventing leukocyte recruitment into the CNS and subsequent inflammatory activity. Natalizumab has also been postulated to inhibit leukocyte priming

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and lymphocyte apoptosis by inhibiting interactions between  $\alpha 4$ -integrin and its ligands (Rudick and Sandrock 2004).

Two randomized, double-blind, placebo-controlled studies, AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) and SENTINEL (Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing-Remitting Multiple Sclerosis), were conducted to evaluate the efficacy and safety of natalizumab alone (AFFIRM) or in combination with interferon  $\beta$ -1a (SENTINEL) in patients with relapsing MS (Polman et al 2006; Rudick et al 2006). The primary endpoints in both studies were the rate of clinical relapses at 1 year and the cumulative probability of disability progression sustained for 12 weeks at 2 years. Predefined secondary and tertiary endpoints included the effect of natalizumab on magnetic resonance imaging (MRI) outcomes, health-related quality of life (HRQoL), and visual function. This article reviews the available data describing the effects of natalizumab on these clinical parameters. In addition, the safety and tolerability profile of natalizumab is discussed.

## Efficacy of natalizumab in pivotal studies

The efficacy of natalizumab monotherapy was evaluated in the AFFIRM study (Polman et al 2006). Key inclusion criteria were similar to pivotal studies of disease-modifying therapies (DMTs) for MS (IFNB Study Group 1993; Jacobs et al 1996; Johnson et al 1995; PRISMS Study Group 1998) and included a diagnosis of relapsing MS according to McDonald criteria (McDonald et al 2001), Expanded Disability Status Scale (EDSS) scores from 0 to 5.0, MRI lesions consistent with MS, and at least 1 medically documented relapse within the 12 months before randomization. Patients were excluded from the study if they had progressive forms of MS (Lublin and Reingold 1996); had a relapse within 50 days of study drug administration; or were treated with interferon  $\beta$ , glatiramer acetate, or both for more than 6 months. Enrolled patients were randomized in a 2:1 ratio to receive an intravenous infusion of natalizumab 300 mg or placebo every 4 weeks for up to 116 weeks (Polman et al 2006).

The SENTINEL study evaluated the efficacy of natalizumab added to intramuscular interferon  $\beta$ -1a (Avonex<sup>®</sup>; Biogen Idec, Inc., Cambridge, MA, USA). In addition to the key inclusion criteria in the AFFIRM study, patients entering the SENTINEL study had received treatment with intramuscular interferon  $\beta$ -1a for at least 12 months before randomization and had at least 1 relapse in the prior year despite interferon therapy. Patients with progressive forms

of MS (Lublin and Reingold 1996), those who experienced a relapse within 50 days before study drug administration, or those who received treatment with an approved DMT other than intramuscular interferon  $\beta$ -1a once weekly within the 12 months before randomization were excluded from the study. Enrolled patients were randomized to receive an intravenous infusion of natalizumab 300 mg or placebo every 4 weeks in addition to an intramuscular injection of interferon  $\beta$ -1a (30  $\mu$ g) once weekly for up to 116 weeks (Rudick et al 2006).

Primary endpoints in both studies were the rate of clinical relapses at 1 year and the cumulative probability of disability progression sustained for at least 12 weeks during the 2-year study period. Relapses were defined as any new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurologic findings upon examination. Disability progression was defined as at least a 1.0-point increase in EDSS score from a baseline score  $\geq 1.0$  or a 1.5-point increase from a baseline score of 0, sustained for at least 12 weeks. Secondary 1-year endpoints in both studies were the proportion of relapse-free patients, the number of new or enlarging T2-hyperintense lesions, and the number of gadolinium-enhancing (Gd+) lesions. Secondary 2-year endpoints in both studies were the rate of clinical relapses, disease progression as measured by the Multiple Sclerosis Functional Composite (MSFC) (Rudick et al 1997), the number of new T1-hypointense lesions, and the volume of T2-hyperintense lesions. Tertiary endpoints in both studies included the effects of natalizumab on brain atrophy, HRQoL, and visual function.

A total of 942 patients ( $n = 627$  natalizumab;  $n = 315$  placebo) were enrolled in the AFFIRM study. Baseline demographics of these patients were similar to those of patients with MS who participated in pivotal studies of DMTs (IFNB Study Group 1993; Jacobs et al 1996; Johnson et al 1996; PRISMS Study Group 1998). The mean age of patients was 36 years, and the mean number of relapses within the 12 months before randomization was 1.52. The mean EDSS score was 2.3, and the median disease duration was 5 years. Patients in the SENTINEL study had similar baseline demographics and disease characteristics. Of the 1171 patients enrolled in SENTINEL ( $n = 589$  natalizumab + interferon  $\beta$ -1a;  $n = 582$  placebo + interferon  $\beta$ -1a), the mean age of patients was 39 years and the mean number of relapses within the 12 months before randomization was 1.47. Mean EDSS score was 2.4, and the median disease duration was 7 years (Polman et al 2006; Rudick et al 2006).

## Clinical outcomes

In the AFFIRM study, natalizumab monotherapy reduced the risk of disability progression sustained for 12 weeks over 2 years by 42% compared with placebo; 17% of patients treated with natalizumab experienced disease progression compared with 29% of those treated with placebo (hazard ratio [HR] = 0.58; 95% confidence interval [CI] = 0.43–0.77;  $p < 0.001$ ). In a sensitivity analysis, natalizumab reduced the risk of progression of disability sustained for 24 weeks over 2 years by 54% compared with placebo (HR = 0.46; 95% CI = 0.33–0.64;  $p < 0.001$ ) (Polman et al 2006). Moreover, natalizumab significantly reduced disability progression as measured by the MSFC compared with placebo. A significant difference between the groups in change from baseline in MSFC z-score was apparent 12 weeks after start of treatment ( $p < 0.001$ ), an effect that was maintained over the 2-year study (Balcer et al 2005; Phillips et al 2006).

Natalizumab monotherapy was also associated with significant improvements in relapse-related outcomes. At 1 year, natalizumab reduced the annualized relapse rate by 68% compared with placebo (0.26 natalizumab vs 0.81 placebo;  $p < 0.001$ ), and this reduction was maintained at 2 years (0.23 natalizumab vs 0.73 placebo;  $p < 0.001$ ). This result suggests that the effect of natalizumab on relapses is substantially greater than that of other MS treatments, which have been shown to reduce MS relapses over 2 years by up to 34% (IFNB Study Group 1993; Jacobs et al 1996; Johnson et al 1996; Polman et al 2006; PRISMS Study Group 1998; US FDA PCNS Advisory Committee 2006). The proportion of relapse-free patients was also significantly greater in the natalizumab group compared with the placebo group at 1 year (77% vs 56%;  $p < 0.001$ ). A similar effect was observed at 2 years (67% natalizumab vs 41% placebo;  $p < 0.001$ ) (Polman et al 2006), which was maintained for up to 3 years in an open-label extension study (O'Connor et al 2007).

In the SENTINEL study, natalizumab added to interferon  $\beta$ -1a reduced the risk of disability progression sustained for 12 weeks over 2 years by 24% compared with interferon  $\beta$ -1a alone (HR = 0.76; 95% CI = 0.61–0.96;  $p = 0.02$ ). In a sensitivity analysis of the risk of disability progression sustained for 24 weeks, no significant differences were found between the treatment groups (15% for combination therapy vs 18% for interferon  $\beta$ -1a alone; HR = 0.82; 95% CI = 0.61–1.09;  $p = 0.17$ ). The addition of natalizumab to interferon  $\beta$ -1a significantly reduced disability progression as measured by the MSFC compared with interferon  $\beta$ -1a alone. A significant difference between the groups in change from baseline in MSFC z-score was apparent 48 weeks after beginning

treatment ( $p \leq 0.005$ ), and this effect was maintained over the 2-year study (Data on file, Biogen Idec, Inc. 2007).

As in AFFIRM, natalizumab was also associated with significant reductions in relapse-related outcomes in SENTINEL. The addition of natalizumab to interferon  $\beta$ -1a resulted in a 54% reduction in annualized relapse rate at 1 year (0.38 for interferon  $\beta$ -1a + natalizumab vs 0.82 interferon  $\beta$ -1a alone;  $p < 0.001$ ); at 2 years, the relative reduction was 55% (0.34 for interferon  $\beta$ -1a + natalizumab vs 0.75 interferon  $\beta$ -1a alone;  $p < 0.001$ ). Furthermore, the proportion of relapse-free patients at 2 years was 54% in the combination therapy group compared with 32% in the interferon  $\beta$ -1a alone group ( $p < 0.001$ ) (Rudick et al 2006).

## MRI outcomes

In AFFIRM, natalizumab monotherapy caused marked reductions in the number and volume of MRI lesions. At 1 year, the mean number of new or enlarging T2-hyperintense lesions was 1.2 in natalizumab-treated patients compared with 6.1 in placebo-treated patients ( $p < 0.001$ ). Furthermore, natalizumab reduced the mean number of new or enlarging T2-hyperintense lesions by 83% over 2 years compared with placebo (1.9 vs 11.0;  $p < 0.001$ ). Natalizumab also reduced the mean number of Gd+ lesions by 92% at 1 and 2 years compared with placebo ( $p < 0.001$ ) (Polman et al 2006) and the mean number of new T1-hypointense lesions by 76% over 2 years compared with placebo (1.1 vs 4.6;  $p < 0.001$ ) (Miller et al 2007). Median T2-hyperintense lesion volume was significantly lower in natalizumab-treated patients compared with placebo-treated patients at 2 years (9175 mm<sup>3</sup> vs 11,137 mm<sup>3</sup>;  $p < 0.001$ ) (Miller et al 2007).

Brain atrophy can be reliably assessed in patients with MS by measuring the brain parenchymal fraction (BPF), which is the ratio of brain parenchymal volume to the total volume within a smoothed surface contour around the brain (Rudick et al 1999). During 2 years of treatment in AFFIRM, the change from baseline BPF was similar in natalizumab- and placebo-treated patients (mean percent change in BPF = -0.80% vs -0.82%;  $p = 0.822$ ). Although both groups exhibited a decrease in BPF from baseline to 1 year, a relatively greater reduction was observed in the natalizumab group compared with the placebo group (-0.56% vs -0.40%;  $p = 0.002$ ). In the second year, the mean percent change in BPF was significantly less in the natalizumab group compared with the placebo group (-0.24% vs -0.43%;  $p = 0.004$ ), indicating a significant slowing of atrophy compared with placebo (Miller et al 2007). It is speculated that the greater decrease in BPF observed in natalizumab-treated patients

during the first year of treatment may have been attributable to a reduction in inflammation and edema, which can cause an acute shrinkage of brain tissue known as pseudoatrophy (Fisher et al 2006).

In the SENTINEL study, the addition of natalizumab to interferon  $\beta$ -1a resulted in significant reductions in the number of MRI lesions. At 1 year, the mean number of new or enlarging T2-hyperintense lesions was 0.5 in patients treated with natalizumab plus interferon  $\beta$ -1a compared with 2.4 in patients treated with interferon  $\beta$ -1a alone ( $p < 0.001$ ). Furthermore, the mean number of new or enlarging T2-hyperintense lesions was reduced by 83% over 2 years (0.9 interferon  $\beta$ -1a + natalizumab vs 5.4 interferon  $\beta$ -1a alone;  $p < 0.001$ ). In addition, natalizumab added to interferon  $\beta$ -1a reduced the mean number of Gd+ lesions by 88% at 1 year (0.1 interferon  $\beta$ -1a + natalizumab vs 0.8 interferon  $\beta$ -1a alone;  $p < 0.001$ ) and by 89% at 2 years (0.1 interferon  $\beta$ -1a + natalizumab vs 0.9 interferon  $\beta$ -1a alone;  $p < 0.001$ ) compared with interferon  $\beta$ -1a alone (Rudick et al 2006). The mean number of new T1-hypointense lesions was reduced by 44% over 2 years (2.3 interferon  $\beta$ -1a + natalizumab vs 4.1 interferon  $\beta$ -1a alone;  $p < 0.001$ ). Median T2-hyperintense lesion volume was significantly lower in patients receiving interferon  $\beta$ -1a plus natalizumab compared with patients receiving interferon  $\beta$ -1a alone at 2 years (5848 mm<sup>3</sup> vs 7260 mm<sup>3</sup>;  $p < 0.001$ ) (Data on file, Biogen Idec, Inc. 2007).

Measurements of changes in BPF at 1 and 2 years in the SENTINEL study revealed patterns of reduction in the interferon  $\beta$ -1a plus natalizumab and interferon  $\beta$ -1a alone treatment groups that were similar to those observed in the placebo and natalizumab monotherapy groups, respectively, in AFFIRM. During 2 years of treatment in SENTINEL, the changes in BPF from baseline were similar in the natalizumab plus interferon  $\beta$ -1a and interferon  $\beta$ -1a alone treatment groups (−0.81% vs −0.82%,  $p = 0.926$ ). In the first year, however, there was a greater reduction in BPF in the natalizumab plus interferon  $\beta$ -1a group (−0.5% vs −0.42%,  $p = 0.058$ ), whereas the reduction in the second year was greater in the interferon  $\beta$ -1a alone group (−0.40% vs −0.31%,  $p = 0.020$ ) (Data on file, Biogen Idec, Inc. 2007).

### Clinical and MRI efficacy in AFFIRM

Post hoc analyses were conducted in patients from the AFFIRM study to determine the ability of natalizumab to achieve a complete clinical and MRI response. Absence of clinical disease activity was defined as no relapses and no disability progression, sustained for 12 weeks. Absence of MRI disease activity was defined as no Gd+ lesions at 1 and

2 years and no new or enlarging T2-hyperintense lesions during the 2 years. The proportions of patients who were free of clinical activity, MRI activity, and a more stringent definition of clinical and MRI disease activity over 2 years were determined. Significantly more natalizumab-treated patients were free of clinical disease activity (64.3% vs 38.9%;  $p < 0.0001$ ), MRI disease activity (57.7% vs 14.2%;  $p < 0.0001$ ), and both clinical and MRI disease activity (36.7% vs 7.2%;  $p < 0.0001$ ) compared with placebo-treated patients over the 2 years of the study (Havrdova et al 2007).

### Clinical and MRI efficacy in patients with highly active MS

Post hoc analyses of patients with highly active relapsing MS ( $\geq 2$  relapses in the year prior to study entry and  $\geq 1$  Gd+ lesion on T1-weighted MRI at study entry) were performed for AFFIRM and SENTINEL. In AFFIRM patients with highly active disease ( $n = 148$  natalizumab;  $n = 61$  placebo), natalizumab monotherapy reduced the risk of disability progression sustained for 12 weeks by 53% (HR = 0.47; 95% CI = 0.24–0.93;  $p = 0.029$ ) and progression sustained for 24 weeks by 64% (HR = 0.36; 95% CI = 0.17–0.76;  $p = 0.008$ ) compared with placebo. In addition, natalizumab reduced the 2-year annualized relapse rate by 81% compared with placebo (0.28 vs 1.46, respectively;  $p < 0.001$ ) in these patients. Furthermore, significant improvements on all MRI outcomes were observed with natalizumab compared with placebo in patients with highly active disease (Data on file, Biogen Idec, Inc. 2007; European Union TYSABRI SmPC 2006).

In SENTINEL patients with highly active disease ( $n = 74$  interferon  $\beta$ -1a + natalizumab;  $n = 95$  interferon  $\beta$ -1a alone), the addition of natalizumab to interferon  $\beta$ -1a reduced the risk of disability progression sustained for 12 weeks by 61% (HR = 0.39; 95% CI = 0.21, 0.74;  $p = 0.004$ ) and sustained for 24 weeks by 58% (HR = 0.42, CI = 0.19, 0.95;  $p = 0.038$ ) compared with interferon  $\beta$ -1a alone. The addition of natalizumab to interferon  $\beta$ -1a also led to a 76% reduction in the 2-year annualized relapse rate compared with interferon  $\beta$ -1a alone (0.28 vs 1.16;  $p < 0.001$ ). Furthermore, significant improvements on all MRI outcomes were observed in the interferon  $\beta$ -1a plus natalizumab group compared with the interferon  $\beta$ -1a group in highly active patients (Data on file, Biogen Idec, Inc. 2007).

### HRQoL

The chronic symptoms of MS interfere with activities of daily living, resulting in significantly reduced HRQoL. In contrast to the clinical and MRI outcomes that are measured by physicians,

HRQoL endpoints provide an assessment of a therapy on domains regarded by patients as key factors in determining their overall health status. The majority of phase 3 studies in patients with MS lack HRQoL measures; thus, a rigorous assessment of HRQoL was performed in AFFIRM and SENTINEL. HRQoL was evaluated using the Short Form-36 (SF-36) (Ware et al 1992) and the visual analog scale (VAS), a subjective global assessment of well-being. To date, the SF-36 has not been used to assess HRQoL in pivotal trials of other MS treatments. In AFFIRM and SENTINEL it was administered as a part of the Multiple Sclerosis Quality of Life Inventory (Consortium of Multiple Sclerosis Centers 1997). Two summary scores from the SF-36 were calculated: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The SF-36 and the VAS were administered to patients enrolled in both AFFIRM and SENTINEL at baseline and at weeks 24, 52, and 104 (Rudick et al 2007).

Data from AFFIRM and SENTINEL (N = 2113) were combined to evaluate the burden of MS on HRQoL. The baseline mean PCS and MCS scores were  $43.2 \pm 0.4$  and  $47.0 \pm 0.5$ , respectively, and were significantly lower than the mean scores for the general US population (50.0) (Rudick et al 2007). Furthermore, at study entry, the PCS scores for patients with an EDSS score  $\geq 2.0$  were significantly lower than for those patients with an EDSS score of 0 ( $p < 0.005$ ) (Rudick et al 2007). Similarly, VAS scores for patients with EDSS scores  $\geq 1.5$  were significantly lower compared with those for patients with an EDSS score of 0 ( $p < 0.05$ ). Taken together, these data provide evidence that HRQoL is significantly reduced in patients with relapsing MS.

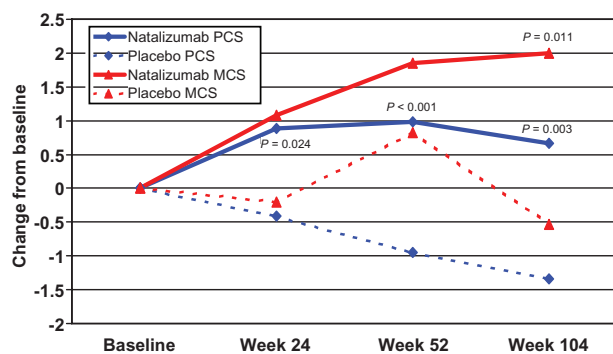
In AFFIRM, natalizumab monotherapy was associated with significant improvements in PCS ( $p = 0.003$ ) and MCS

( $p = 0.011$ ) scores at week 104 (Figure 1). In fact, changes from baseline in PCS scores were significantly higher at weeks 24, 52, and 104 compared with placebo. In SENTINEL, changes from baseline in PCS scores for patients treated with interferon  $\beta$ -1a plus natalizumab were significantly higher at weeks 52 ( $p = 0.014$ ) and 104 ( $p < 0.001$ ) compared with scores for patients treated with interferon  $\beta$ -1a alone (Rudick et al 2007). Additionally, a greater percentage of natalizumab-treated patients improved and a lower percentage worsened by a clinically important amount (defined as a  $\geq 0.5$  standard deviation change from baseline to week 104 in PCS and MCS scores) compared with placebo- or interferon  $\beta$ -1a-treated patients in both studies (Rudick et al 2007). Findings from the subject global assessment of well-being were similar to those from the SF-36. Changes from baseline in VAS scores for patients treated with natalizumab monotherapy were greater than those for patients treated with placebo at weeks 52 ( $p = 0.042$ ) and 104 ( $p = 0.007$ ) (Rudick et al 2007).

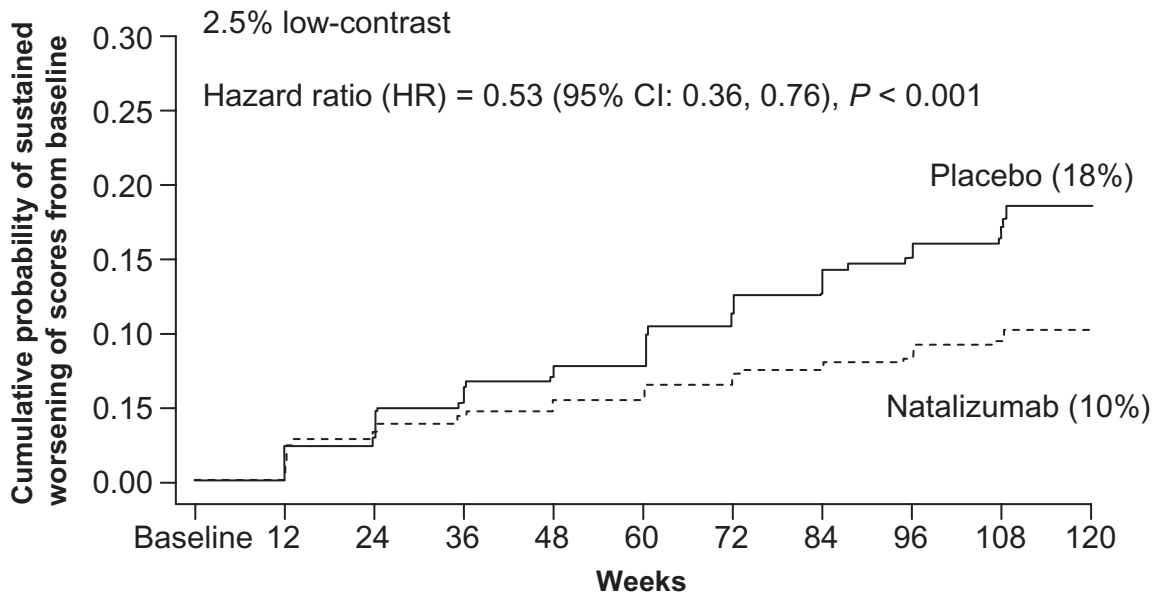
## Visual function

Visual function is an important measure of neurologic impairment in patients with relapsing MS. For example, remitting episodes of acute optic neuritis can influence the overall visual function of a patient. Thus, prespecified analyses were performed in AFFIRM and SENTINEL to determine the effect of natalizumab on visual function (Balcer et al 2007). Visual acuity was measured using the Sloan letter chart at 3 contrast levels: 100% (high-contrast), 2.5% (low-contrast), and 1.25% (low-contrast). Visual function testing was performed every 12 weeks using a standardized protocol based on visual acuity testing methods from the Early Treatment Diabetic Retinopathy Study (Balcer et al 2007). Sloan chart scores for each contrast level were calculated based on the number of letters correctly identified by the patient. The cumulative probability of clinically significant worsening of visual function, defined as 2-line (10-letter) reductions in Sloan chart scores persisting over 12 weeks, was determined using Kaplan-Meier analysis (Balcer et al 2007).

When low-contrast Sloan charts were used, patients treated with natalizumab had lower cumulative probabilities of sustained clinically significant worsening of visual function compared with placebo or interferon  $\beta$ -1a alone. In AFFIRM, natalizumab reduced the risk of sustained clinically significant worsening of visual function by 47% (HR = 0.53; 95% CI = 0.36–0.76;  $p < 0.001$ ) at the 2.5% contrast level and by 35% (HR = 0.65; 95% CI = 0.47–0.90;  $p = 0.008$ ) at the 1.25% contrast level compared with placebo (Figure 2) (Balcer et al 2007).

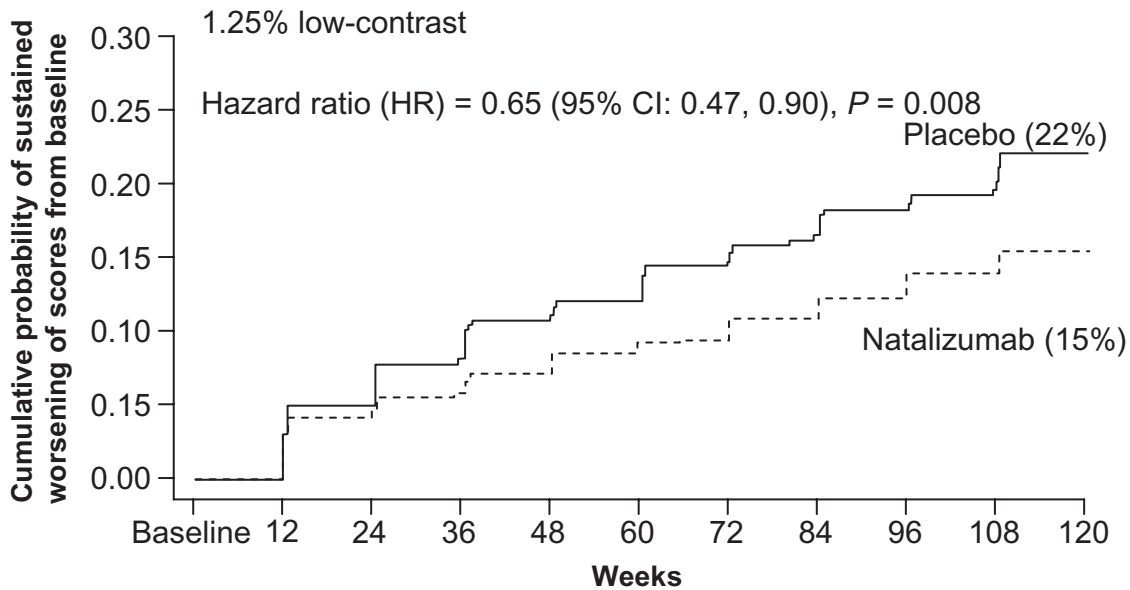


**Figure 1** Mean changes from baseline in Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the Short Form-36 in patients from the AFFIRM study. Reprinted from Rudick RA, Miller D, Hass S, et al. 2007. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol*, 62:335–46. Copyright © 2007 (American Neurological Association), with permission of John Wiley & sons, Inc.



No. at risk

Placebo	307	301	287	278	272	266	255	247	242	233
Natalizumab	619	609	590	582	573	561	553	546	531	519



No. at risk

Placebo	307	296	278	267	261	254	245	235	232	222
Natalizumab	619	598	580	569	556	544	534	520	504	491

**Figure 2** Kaplan-Meier plots of the time to sustained worsening of vision scores from baseline during the AFFIRM study. The cumulative probability of sustained worsening of visual function was defined as 2-line (10-letter) reductions in Sloan chart scores persisting over 12 weeks. Reprinted from Balcer LJ, Galetta SL, Calabresi PA, et al. 2007. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology*, 68:1299–304. Copyright © 2007, with permission from Lippincott, Williams & Wilkins.

In SENTINEL, the cumulative probability of sustained clinically significant worsening of visual function was lower for both low-contrast Sloan charts in patients treated with interferon  $\beta$ -1a plus natalizumab compared with patients treated with interferon  $\beta$ -1a alone. However, clinically significant differences were demonstrated only at the 1.25% contrast level (HR = 0.72; 95% CI = 0.54–0.98;  $p = 0.038$ ). In addition, differences between treatment groups occurred later over the 2-year treatment period. These findings were attributed to the use of an active-comparator treatment arm, which may require longer follow-up periods and more sensitive treatment measures to detect treatment effects (Balcer et al 2007).

## Immunogenicity of natalizumab

Antibody formation is an expected response to treatment with therapeutic proteins, and the formation of such antibodies has been demonstrated to reduce the efficacy of the product (Schellekens and Casadevall 2004). In the AFFIRM and SENTINEL studies, patients were tested for the development of anti-natalizumab antibodies every 12 weeks throughout the study. Serum concentrations of anti-natalizumab antibodies were determined by an enzyme-linked immunosorbent assay, and patients were defined as being antibody negative ( $< 0.5 \mu\text{g/mL}$  at all time points), transiently positive ( $\geq 0.5 \mu\text{g/mL}$  at a single time point), or persistently positive ( $\geq 0.5 \mu\text{g/mL}$  at 2 or more time points at least 6 weeks apart) (Calabresi et al 2007).

In AFFIRM, 57 natalizumab patients (9%) developed anti-natalizumab antibodies; 3% ( $n = 20$ ) were transiently positive, and 6% ( $n = 37$ ) were persistently positive. During SENTINEL, 12% of patients ( $n = 70$ ) developed anti-natalizumab antibodies; 5% ( $n = 32$ ) were transiently positive, and 6% ( $n = 38$ ) were persistently positive (Calabresi et al 2007). Most patients who developed anti-natalizumab antibodies did so within 12 weeks of starting natalizumab treatment (88% AFFIRM; 96% SENTINEL) (Calabresi et al 2007). Notably, the presence of anti-natalizumab antibodies was associated with a reduction in trough serum natalizumab concentrations (Calabresi et al 2007). Persistent antibodies were associated with a loss of efficacy as measured by clinical and MRI outcomes. In contrast, transiently positive patients experienced delayed therapeutic effects of natalizumab, but full efficacy was eventually achieved with continued treatment (Calabresi et al 2007).

## Tolerability and safety

Overall, natalizumab was well tolerated in the AFFIRM and SENTINEL studies. In AFFIRM, infusion reactions, defined

as any event occurring within 2 hours of the start of infusion, occurred in 24% of natalizumab-treated patients compared with 18% of placebo patients ( $p = 0.04$ ) (Polman et al 2006). Similarly, in SENTINEL, the incidence of infusion reactions was 24% in the interferon  $\beta$ -1a plus natalizumab group and 20% in the interferon  $\beta$ -1a alone group ( $p = 0.11$ ). The most common of these reactions was headache, which did not usually result in discontinuation of natalizumab treatment. Hypersensitivity reactions were defined as reports of hypersensitivity, allergic reaction, or anaphylactic/anaphylactoid reactions and any reports of urticaria, allergic dermatitis, or hives. In AFFIRM, the incidence of hypersensitivity reactions associated with natalizumab was 4% and the incidence of anaphylactic/anaphylactoid reactions was 0.8% (Polman et al 2006). In SENTINEL, 11 patients (1.9%) receiving combination therapy experienced a hypersensitivity reaction, and there were no reports of anaphylactic or anaphylactoid reactions associated with natalizumab (Rudick et al 2006). An evaluation of hypersensitivity reactions according to anti-natalizumab antibody status revealed that 46% of 37 persistently positive patients and 15% of 20 transiently positive patients in AFFIRM experienced a hypersensitivity reaction. The corresponding values for patients in SENTINEL were 21% of 38 persistently positive patients and none of 32 transiently positive patients (Calabresi et al 2007). Patients who experienced hypersensitivity reactions while receiving natalizumab during the studies discontinued treatment.

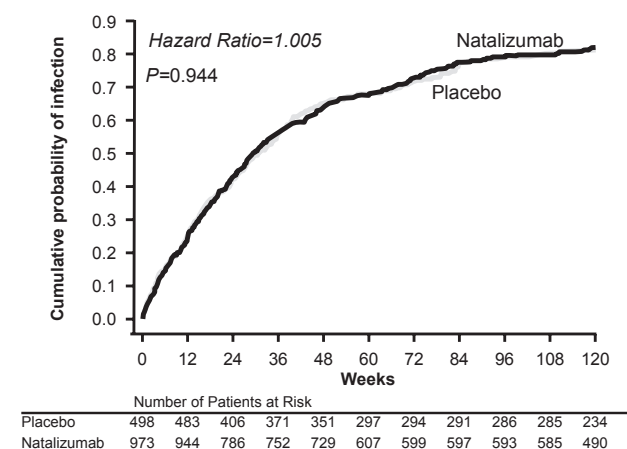
As previously stated, non-hypersensitivity-mediated infusion reactions did not necessitate discontinuation of natalizumab therapy in AFFIRM or SENTINEL. However, infusion reactions that occurred over multiple natalizumab infusions were associated with persistent positivity for anti-natalizumab antibodies. Therefore, testing for anti-natalizumab antibodies should be considered in the setting of recurrent infusion-related symptoms. Two consecutive positive blood samples separated by 2–3 months after at least 6 months' treatment confirm persistent antibody-positive status. Discontinuation of natalizumab should be strongly considered once persistent positivity is confirmed.

Generally, few differences in adverse event profiles were observed between natalizumab and placebo or interferon  $\beta$ -1a groups in AFFIRM and SENTINEL. Common adverse events were generally mild and included headache, fatigue, urinary tract infections, and arthralgia (Tysabri<sup>®</sup> package insert 2007). In AFFIRM, patients treated with natalizumab monotherapy experienced more fatigue (27% vs 21%;  $p = 0.048$ ) and allergic reactions (9% vs 4%;  $p = 0.012$ ) compared with those who received placebo (Polman et al 2006). During the

SENTINEL study, patients treated with natalizumab plus interferon  $\beta$ -1a experienced significantly more pharyngitis (7% vs 4%;  $p \leq 0.05$ ), anxiety (12% vs 8%;  $p \leq 0.01$ ), sinus congestion (6% vs 3%;  $p \leq 0.01$ ), and peripheral edema (5% vs 1%;  $p \leq 0.001$ ) compared with patients who received interferon  $\beta$ -1a alone (Rudick et al 2006). In both studies, the incidence of infection was similar between the treatment groups (AFFIRM, 79% in natalizumab and placebo groups [Figure 3]; SENTINEL, 83% in the interferon  $\beta$ -1a + natalizumab group vs 81% in interferon  $\beta$ -1a alone) (Polman et al 2006; Rudick et al 2006).

Laboratory testing has shown that natalizumab causes reversible elevations in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells (but not neutrophils). Moreover, rare cases of clinically significant hepatotoxicity have been reported in the postmarketing setting (Tysabri<sup>®</sup> package insert 2007). Regular laboratory monitoring during natalizumab treatment is not considered necessary.

In February 2005, commercial and clinical trial dosing of natalizumab was voluntarily suspended after 2 reports of progressive multifocal leukoencephalopathy (PML), a serious, sometimes fatal, demyelinating disease of the CNS that results from reactivation of the latent JC virus and that usually occurs in immunocompromised patients (Major et al 1992). Both patients had received natalizumab plus interferon  $\beta$ -1a in SENTINEL (Kleinschmidt-DeMasters and Tyler 2005; Langer-Gould et al 2005). A third case of PML was retrospectively identified in a patient who was treated with natalizumab for Crohn's disease in a clinical study (Van Assche et al 2005). Subsequent to these reports of PML, an extensive safety evaluation revealed no additional cases of PML among 3116 patients who received natalizumab in clinical studies.



**Figure 3** Cumulative probability of infection in the AFFIRM study (unpublished data on file, Biogen Idec).

The risk of developing PML associated with natalizumab use was determined to be 1 in 1000 patients (95% CI = 0.2, 2.8 in 1000 patients) over 17.9 months of treatment (Yousry et al 2006). Natalizumab was reintroduced in the United States and approved in the European Union in June 2006.

To better assess the safety profile of natalizumab, a comprehensive risk management plan that includes the Tysabri<sup>®</sup> Outreach: Unified Commitment to Health (TOUCH<sup>™</sup>) Prescribing Program and the Tysabri<sup>®</sup> Global Observation Program in Safety (TYGRIS) observational cohort study was developed. The TOUCH<sup>™</sup> Prescribing Program is a mandatory prescribing program in the United States. All physicians, infusion sites, and patients are required to enroll before natalizumab treatment is initiated, and reauthorization is required every 6 months. The objectives of TOUCH<sup>™</sup> are to ensure appropriate and informed use of natalizumab, assess the incidence of serious opportunistic infections, including PML, in patients treated with natalizumab, and monitor natalizumab-treated patients for signs and symptoms of PML. TYGRIS is a voluntary global observational study designed to investigate the long-term safety of natalizumab in the clinical practice setting. A recent update of safety data collected from the TOUCH<sup>™</sup> and TYGRIS programs showed that the safety profile of natalizumab was consistent with that seen in earlier clinical studies (Panzara et al 2007). Global utilization data released in January, 2008, indicate that approximately 30,900 patients have been treated with natalizumab in the combined clinical trial and postmarketing settings, and of these patients, approximately 6,300 have received natalizumab for at least 1 year (unpublished data on file, Biogen Idec). In addition to TOUCH<sup>™</sup> and TYGRIS, the Tysabri<sup>®</sup> Observational Program in Europe will provide further insight into the long-term effects of natalizumab. Currently, several initiatives to better understand PML and its management in the context of natalizumab therapy are being planned or conducted.

## Patient selection and PML diagnostic algorithm

A recent publication by a panel of experts in neurology, neuroradiology, and PML provides guidelines to help with the selection of appropriate candidates for natalizumab therapy and with the diagnosis of suspected PML (Kappos et al 2007). The article recommends that patients who have received prior treatment with immunosuppressants or antineoplastic agents should be carefully assessed for ongoing immunosuppression before initiating natalizumab. Recommendations based on clinical and laboratory markers to help identify



immunocompetence in patients who have been exposed to immunosuppressive therapy have been published separately by Gold and colleagues (Gold et al 2007). A pretreatment cranial MRI scan is also recommended for all patients within 3 months of commencing natalizumab therapy to help in the assessment of subsequent new or worsening neurologic symptoms that may develop during treatment.

It is further recommended in the article that new or worsening neurological symptoms should lead to immediate suspension of natalizumab dosing and completion of a thorough neurologic assessment (Figure 4). Continued suspicion of PML after the neurologic assessment warrants a cranial MRI scan with gadolinium enhancement for comparison with the baseline pretreatment MRI scan and, if PML is still a concern, cerebrospinal fluid (CSF) testing for JC virus (JCV) DNA is recommended. However, CSF is usually negative for JCV DNA in the early stages of PML. Therefore, if the disease is still suspected after a negative CSF test, diagnostic work up should continue and natalizumab treatment should not be restarted. Clinical and MRI characteristics that may help to distinguish between PML and MS are presented in Table 1 (Kappos et al 2007).

At present, there is no proven treatment for PML. However, experience with PML in organ transplant recipients and patients with HIV strongly suggests that reconstitution of the immune system is associated with a better prognosis (Clifford et al 1999; Crowder et al 2005; Shitrit et al 2005). A recent study by Khatri et al provided preliminary evidence

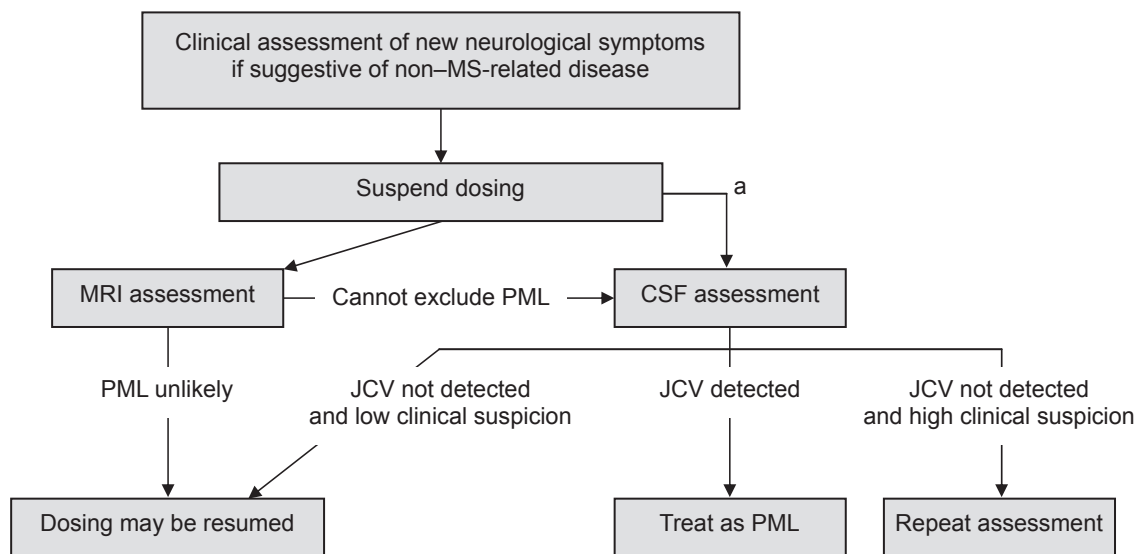
that accelerated removal of natalizumab from circulation via plasma exchange may be a method to reconstitute the immune system in natalizumab-treated patients who develop PML (Khatri et al 2007). However, because plasma exchange has not been specifically tested in natalizumab-treated patients with PML, the true efficacy of the procedure remains unknown.

## Prescribing considerations

Natalizumab is indicated as monotherapy for the treatment of relapsing MS and is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies. However, prescribing information in the United States does not preclude the use of natalizumab as a first-line agent for the treatment of relapsing MS (Tysabri® package insert 2007). In the European Union, natalizumab is approved as a first-line agent for patients with highly active disease ( $\geq 2$  disabling relapses in the previous year and  $\geq 1$  Gd+ lesion on MRI) and as a second-line therapy in patients who have experienced  $\geq 1$  relapse in the previous year and  $\geq 9$  T2 lesions or  $\geq 1$  Gd+ lesion while receiving interferon  $\beta$  (European Agency for the Evaluation of Medicinal Products 2006).

## Summary

Natalizumab is the first  $\alpha 4$ -integrin receptor antagonist available for the treatment of relapsing MS. Through its proposed mechanism of action, natalizumab provides evidence for



**Figure 4** Diagnostic algorithm for patients with suspected progressive multifocal leukoencephalopathy (PML). Reprinted from Kappos L, Bates D, Hartung H-P, et al. 2007. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol*, 6:431–41. Copyright © 2007, with permission from Elsevier.

<sup>a</sup>If PML is suspected on the basis of clinical presentation and MRI is not readily available, CSF assessment to exclude PML should be considered before MRI.

**Abbreviations:** CSF, cerebrospinal fluid; JCV, polyomavirus JC virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

**Table 1** Clinical and MRI characteristics of MS and PML

	MS	PML
Clinical characteristics <sup>a</sup>		
Onset	Acute	Subacute
Evolution	Hours to days	Weeks
	Normally stabilizes	Progressive
	Resolves spontaneously or with treatment	
Clinical presentation	Diplopia	Cortical signs and symptoms
	Optic neuritis	Behavioral and neuropsychological alterations
	Incomplete myelopathy or partial myelitis	Retrochiasmal visual deficits Hemiparesis
MRI characteristics		
Location	Mostly focal	Diffuse, mainly subcortical
	Widespread in brain and spinal cord	White matter tracts, sparing cortex
	Periventricular	
	Posterior fossa lesions often seen early	
Borders	Sharp edges, round or finger-like	Ill-defined, irregular shape,
	Confluent with other lesions	infiltrating
	U-fibers may be involved	U-fibers destroyed
Mode of extension	Lesions initially focal	Diffuse, asymmetric, homogenous lesions
	Enlarge within days or weeks	No confluence with other lesions
	Eventually decrease in size over months	Continuous progression
Mass effect	May be seen in acute lesions	Rare, even in large lesions

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<sup>a</sup>Pertaining to relapse in MS.

**Abbreviations:** MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

the role of circulating mononuclear leukocytes in disease pathogenesis. Natalizumab has demonstrated significant clinical and MRI efficacy in patients with relapsing MS. Natalizumab monotherapy was associated with significant reductions in annualized relapse rate, the risk of sustained disability progression, and the number and volume of MRI lesions. Additional data have shown that natalizumab reduces the risk of developing sustained visual loss and is associated with improvements in HRQoL. Natalizumab demonstrated a favorable tolerability profile in phase 3 studies; a low incidence of persistent anti-natalizumab antibody development and hypersensitivity reactions was observed, and most natalizumab-associated adverse events were generally mild. The risk of PML with natalizumab use is small, but appropriate patient selection requires an individual assessment of benefit-risk and careful monitoring.

With its demonstrated efficacy on a number of physician- and patient-measured outcomes, natalizumab represents a major advance in the treatment of relapsing MS. The available data support a favorable benefit-risk profile of natalizumab. Ongoing research and clinical experience

will expand current knowledge regarding long-term efficacy and safety.

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