Laquinimod in Relapsing–Remitting Multiple Sclerosis

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Abstract

Laquinimod is a novel oral immunomodulatory agent in development for the treatment of relapsing–remitting multiple sclerosis (RRMS). It is a derivative of roquinimex that was structurally altered to maximize safety and efficacy. In animal models laquinimod was far more potent than its parent compound with no apparent propensity to induce inflammatory reactions. Laquinimod is a broad-spectrum immunomodulatory agent with a multitude of effects on the immune system but no effect on the ability of animals to mount a cellular or humoral immune response. In phase II trials selected for highly active RRMS patients, laquinimod reduced the frequency of gadolinium-enhancing lesions by 55%, significantly reduced the number of new T_2 lesions, and had a trend toward an effect on reducing brain volume loss. Laquinimod was well tolerated in phase II trials and had a favorable safety profile with a paucity of adverse events. It is metabolized by the cytochrome P-450 system (CYP-3A4) and may interact with some compounds used in symptomatic therapy. With a favorable efficacy and safety profile, laquinimod is a potential first-line agent in the future treatment of RRMS.

Keywords

Multiple sclerosis, laquinimod, immunomodulatory, safety, efficacy

Disclosure: Douglas R Jeffery, MD, PhD, has received honoraria for speaking and consulting from Teva, Bayer, Biogen-Idec, Novartis, Serono, Pfizer, Acorda, and GSK, and has received research support from Teva, Bayer, Biogen-Idec, Serono, Novartis, and Pfizer. The remaining authors have no conflicts of interest to declare.
Received: June 23, 2010 **Accepted:** July 26, 2010 **Citation:** *US Neurology*, 2010;6(2):70–5 *DOI: 10.17925/USN.2010.06.02.70*
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Support: The publication of this article was funded by Teva Neuroscience. The views and opinions expressed are those of the authors and not necessarily those of Teva Neuroscience.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that affects at least 400,000 people in the US alone. Estimates of the prevalence of MS were made in the early 1990s and may vastly underestimate the true prevalence of the disease.[1,2] The cause of MS remains unknown, but it is clear that inflammatory demyelination and axonal damage lead to considerable disability in both early- and late-stage disease. The rate and extent of disability progression are highly variable.

The mainstay of MS treatment over the past 17 years has primarily been treatment with interferons (IFNs) and glatiramer acetate. IFNβ-1b (Betaseron) was introduced in 1993 and was the first US Food and Drug Administration (FDA)-approved treatment indicated to reduce the frequency of relapses. Intramuscular (IM) IFNβ-1b was approved in 1996 to reduce the frequency of relapses and to decrease magnetic resonance imaging (MRI) activity in relapsing–remitting MS (RRMS). Glatiramer acetate (Copaxone), a non-IFN immunomodulatory therapy, was introduced in 1996 and approved to reduce relapse frequency. Subcutaneous (SC) IFNβ-1b (Rebif) was approved in the US in 2003 to reduce relapse rates and to decrease MRI activity. Since their introduction, all of the IFNs have been studied in secondary progressive MS (SPMS) and are now approved for patients with relapsing forms of MS.

The availability of the IFNs and glatiramer acetate in the treatment of MS revolutionized treatment strategies for MS and improved the outlook for patients with MS. The knowledge gained from conducting clinical trials with these agents and a multitude of smaller studies led to real advances in the understanding and treatment of MS. Although effective, these injectable medications have troublesome side effects and are inconvenient. Thus, there is a significant unmet need for effective oral agents with good tolerability and safety profiles.

Laquinimod

Laquinimod is a new oral immunomodulatory therapy in development for the treatment of MS. The parent compound of laquinimod was an agent known as roquinimex that showed potent anti-inflammatory effects in acute and chronic experimental autoimmune encephalomyelitis (EAE) and in phase II trials in MS. Unfortunately, in phase III trials roquinimex caused a number of inflammatory toxicities. Specifically, it induced

pericarditis, pleuritis, pancreatitis, and vasculitis of the coronary arteries, resulting in several myocardial infarctions.[3] Its development was subsequently stopped.

Research on the structure and activity relationships of the parent compound led to the development of laquinimod. Laquinimod is a quinoline 3-carboxamide derivative that was selected from over 60 quinoline carboxamide derivatives on the basis of structure and activity relationships that were maximized to achieve superior safety and efficacy in EAE.[4] Numerous compounds from this class were systematically evaluated to obtain a compound with maximal efficacy in EAE and an absence of proinflammatory effects in beagle dogs. The type and position of the quinoline ring was the major determinant of efficacy, whereas the N-carboxyamide substitution appeared to be the major factor determining safety. Laquinimod proved to have the best safety and efficacy profile of all the compounds tested.

Laquinimod ameliorated neurologic deficits in both acute and chronic EAE.[5–7] In acute EAE in SJL/N mice, disease severity was decreased in a dose-dependent fashion and laquinimod was 20 times more potent than roquinimex.[8] In a Lewis rat model of EAE, laquinimod was more potent at inhibiting disease than roquinmex and was again dose-dependent, suggesting that it affected a biologically relevant target in inflammatory disease of the CNS. Its administration resulted in a decrease in the infiltration of CD^+ T cells and macrophages into CNS tissue, and this effect was more robust than that seen with the parent compound, roquinimex.[6] There was an associated downregulation of tumor necrosis factor-alpha (TNF-α) and interleukin-12 (IL-12) and an upregulation of transforming growth factor-beta (TGF-β), IL-4, and IL-10, consistent with the hypothesis that an effect on cytokine profiles in an inflammatory environment could be partly responsible for the anti-inflammatory effects of laquinimod.

In myelin oligodendrocyte (MOG)-protein-induced EAE in C57BL/6 mice, laquinimod reduced macrophage and T-cell infiltration into spinal cord tissue and significantly reduced demyelination and axonal loss. These effects were apparent when laquinimod was given both as pre-treatment and after the start of clinical disease.[9] These effects were accompanied by a downregulation of pro-inflammatory cytokines.

Laquinimod was also effective in other forms of EAE. In EAE induced with myelin basic protein (MBP) fragment 89–101, there was a reduction in EAE disease severity. This effect was also dose-dependent.[6] Once again, there was a marked reduction of macrophage and T-cell infiltration into the CNS and a decrease in demyelination and axonal loss compared with vehicle-treated animals. Of interest is that laquinimod had potent effects on reducing disease severity in animal models of other autoimmune disease, including experimental allergic neuritis (EAN).[10]

Mechanism of Action

Our understanding of the mechanism of action of laquinimod is far from complete, but some information has been derived from its evaluation in EAE and from other basic immunologic investigation. Laquinimod appears to act as a broad-spectrum immunomodulatory agent with varied effects on the immune system. The administration of laquinimod to C57BL/6 mice with MOG-induced EAE and with depleted $CD4^+$ and $CD25^+$ T cells inhibited disease severity. This indicated that laquinimod does not require this regulatory pathway for the inhibition of MOG-induced EAE.[11] Moreover, there was no effect on cardiac allograft rejection in rats, suggesting that laquinimod has no effect on the ability of an animal to mount a cellular or humoral immune response. In other words, it is not immunosuppressive, which has important implications for safety in human use.

In the Lewis rat model of EAE, laquinimod induced a shift in the cytokine profile from a Th1 to a Th2 pattern.[6] Following the administration of laquinimod there was an upregulation of MBP-specific IL-4-, IL-10-, and TGF-β-expressing cells. Similar results have been obtained in other types of EAE. In MBP-induced EAE there was an upregulation of Th2/Th3 cells and a downregulation of MBP Th1 cells consistent with a shift in the cytokine profile to an anti-inflammatory milieu.[6] In another EAE study in mice, laquinimod produced a profound effect on the steady-state distribution of monocyte subsets that the authors thought might be due to its impact on the myeloid precursor compartment.[12]

In addition to the downregulation of inflammatory cytokines, laquinimod brought about a decrease in the expression of major histocompatibility complex (MHC) class II antigens required for antigen presentation.[13] This will also contribute to the downregulation of CNS inflammation. In EAE, laquinimod decreased the production of TNF-α and IFN-γ and increased IL-4 mRNA expression.[6] It also brought about a reduction in the disease-specific T-cell response. Since laquinimod has effects in both EAE and EAN, it may affect a pivotal pathway involved in autoimmunity. While little is known about its mechanism of action at this point in time, it appears to be a broad-spectrum immunomodulator that has no immunosuppressive effects.

In studies on peripheral blood mononuclear cells from patients with RRMS and from healthy controls, laquinimod reduced the expression of MHC class II antigen-presenting molecules, chemokine signaling molecules, integrin, and adhesion-related molecules.[14] Laquinimod also brought about a profound downregulation of the dendritic cell compartment in murine EAE, suggesting that it could also be acting through this mechanism.[15] These effects are also consistent with a suppression of inflammatory disease activity.

In purified human B cells derived from healthy controls stimulated with CpG oligonucleotid, culture of cells with 1μM laquinimod decreased the percentages of $CD5^+$ and $CD27^+$ cells ($p<0.004$ and $p<0.03$, respectively compared with no laquinimod). $CD86^+$ and $CD25^+$ cells, however, were increased ($p<0.04$ and $p<0.0$, respectively) and the subpopulation overexpressing IL-10 was significantly increased by laquinimod.[16]

In studies on cell cultures from patients with RRMS, laquinimod affected $CD4^+$ cells by activating the IL-4 gene, suppressing the ALOX5 gene and there was an over-expression of TNFRSF4 receptor genes consistent with anti-inflammatory Th2 response.[17] In $CD8^+$ cells, laquinimod suppressed cell proliferation, which the study authors suggested could be explained by suppression of the cell cycle transcription factor genes E2F3 and CDK3 and may reverse the autoimmune pathogenic effects of $CD8^+$ T cells in MS. Similar effects were noted in B cells. This study also

showed that the addition of laquinimod resulted in a suppression of the genes known to be involved in NK signaling of effector T cells (Th1) that cause cytoxic activity upon antigen presentation.[17]

In MOG-immunized mice, laquinimod inhibited the ability of chemokine C-C motif ligand (CCL) 21 to stimulate very late antigen 4 (VLA-4) adhesiveness to vascular cell adhesion molecule 1 (VCAM-1). This is consistent with the idea that laquinimod may also decrease T-cell trafficking from the periphery into the CNS.[18]

Another factor that might contribute to the immunomodulatory effects of laquinimod is its ability to downregulate cytokine release from activated microglia.[19] In cultured microglia, laquinimod decreased the release of TNFα, IL-10, and matrix metalloproteinase 9 (MMP-9). In addition, laquinimod reduced the elevation in microglial activity that was stimulated by lipolysacharide. In humans participating in a clinical trial of laquinimod in RRMS, laquinimod significantly increased plasma concentrations of brain-derived neurotrophic factor (BDNF).[20] Three months after treatment, levels of BDNF were increased by as much as 11-fold compared with the placebo-treated group. This suggests that laquinimod might also possess neuroprotective effects.

In short, laquinimod appears to have a wide array of immuno-modulatory effects. It downregulates pro-inflammatory cytokines while at the same time upregulating anti-inflammatory cytokines, promotes a Th1 to Th2/Th3 shift, downregulates MHC class II functions, inhibits microglial activation, and stimulates the production of BDNF. This is consistent with a broad-spectrum immunomodulatory effect and suggests that this agent could prove highly effective in MS.

Pharmacokinetics

Laquinimod is rapidly absorbed following oral administration and has a bioavailability of about 82–95%. The half-life is 80 hours and peak plasma concentration is within one hour.[21] A high proportion of the drug in circulation is protein-bound; in plasma only 1.4% is unbound. The volume of distribution is approximately 10 liters. At steady state there are only small fluctuations between minimum and maximum concentration (C_{min} and C_{max}, respectively). There is no accumulation of the drug in tissues, and brain penetration is low with a blood to brain ratio of 0.01:0.08.

Laquinimod is extensively metabolized prior to elimination, with only 10% of the parent compound excreted unchanged. The primary metabolic pathway is glucuronidation of the parent compound and its hydroxylated metabolites. Metabolism of laquinimod occurs in the liver by the cytochrome P-450 enzyme system. The CYP3A4 isoenzyme is the predominant enzyme active in the metabolism of laquinimod.[22] While there may be a small contribution from other P-450 iso-enzymes, CYP3A4 is predominant. As a result, laquinimod may interact with other agents metabolized by CYP3A4. This may be clinically important as many patients with MS are treated with symptomatic therapies metabolized by the CYP3A4 isoenzyme. Significant interactions may occur with fluoxetine, fluvoxamine, sertraline, floxin antibiotics, erythromycin, and antifungal agents such as fluconazole. Interactions may also occur with some calcium blockers and amiodarone. Drug-interaction studies with these agents will help determine whether these potential interactions are clinically relevant and whether dose adjustments may be needed.

Phase II Trials in Relapsing–Remitting Multiple Sclerosis

There have been two phase II trials of laquinimod in relapsing forms of MS. The first phase II trial of laquinimod compared doses of 0.1 and 0.3mg versus placebo in 209 patients.[23] The primary outcome measure in this trial was the total number of gadolinium (Gd)-enhancing lesions and the number of new non-Gd-enhancing T_2 lesions over a 24-week treatment period. This trial used MRI every eight weeks with triple-dose contrast to improve lesion detection. In order to enrich the patient population by including those with more active inflammatory disease, the inclusion criteria stipulated that patients had to be 18–65 years of age and must have had at least one relapse in the year prior to study entry. In this study relapse was defined differently from previous definitions i.e. the presence of at least one Gd-enhancing lesion or a new T_2 lesion demonstrated on two consecutive MRI scans, one exacerbation in the last year or two exacerbations in the last two years (one could be subclinical) or Gd-enhancement on the screening MRI scan. Patients were also required to have at least nine T_2 lesions or three T_2 lesions and one gadolinium-enhancing lesion. After the 24-week treatment period laquinimod was stopped and patients were monitored for an additional eight weeks.

Laquinimod at 0.3mg brought about a 44% reduction in the cumulative number of active lesions over the 24-week treatment period (p=0.0498). The 0.1mg dose did not appreciably decrease the number of new active lesions. The effects were more robust in patients with active disease. In those with Gd-enhancing lesions on their baseline MRI, there was a 52% reduction in active lesions (p=0.005) and a 64% decrease in lesion volume over the treatment period. After cessation of dosing, lesion frequency increased, suggesting a therapeutic effect at the 0.3mg dose. While these results were encouraging, it was felt that a higher dose might prove superior since the drug was well tolerated and there were few adverse events (AEs).[23]

The second phase II trial used doses of 0.3 and 0.6mg and employed a different strategy to enrich the patient population for disease activity.[24] This trial enrolled 306 patients and stipulated that patients had to have had at least one relapse in the year prior to study entry and to have an active Gd-enhancing lesion on their baseline MRI in order to enter into the study. The use of these criteria resulted in a study population with far more active disease since Gd-enhancing lesions predict higher relapse rates, a higher frequency of new lesions, and a greater progression of cerebral atrophy;[24] however, it also resulted in the inclusion of patients with more aggressive disease, which may have led to an under-estimation of the efficacy of the agent under study.

MRI scans were carried out at baseline and then at four-week intervals beginning at week 12. The primary outcome measure was the cumulative number of Gd-enhancing lesions from week 24 to week 36. A number of secondary outcomes were also evaluated, including relapse rates, cumulative number of Gd-enhancing lesions at each time-point, and cumulative number of new T_2 lesions at weeks 24, 28, 32, and 36. The study was not powered to detect an effect on relapse rate.

In the group treated with laquinimod 0.6mg there was a 55% decrease in the median cumulative number of Gd-enhancing lesions between weeks 24 and 36 and a 40.4% reduction in the mean cumulative number of Gd-enhancing lesions during the same period (p=0.0048). The cumulative number of new T_2 lesions decreased by 44% (p=0.0013) and the cumulative number of new T_1 hypointense lesions decreased by 51% (p=0.0064). There was also a trend toward a slowing of the rate of cerebral volume loss (p=0.07). Relapse rates were reduced by 33%, but this did not reach statistical significance because of the small sample size employed. The study was not powered to detect an effect on relapse rates. In the group treated with laquinimod 0.3mg there was no significant effect on any outcome measure.[24]

An extension of this trial was carried out in which the placebo group was randomized to either the 0.3 or the 0.6mg dose and followed prospectively for an additional 36 weeks.[25] There were 119 patients in the 0.3mg group and 138 in the 0.6mg group. Patient retention in the study was quite good, with more than 90% completing the study. The effects of laquinimod in the main trial were duplicated in the extension. In placebo patients switched to laquinimod, the mean number of Gd-enhancing lesions decreased by 52% (p<0.0007); this was significant for both the 0.6mg and 0.3mg doses. In the group initially randomized to 0.6mg at the start of the phase II trial, Gd-enhancing lesions continued to be suppressed, indicating that there was no loss of effect over time.[25] At the end of the extension, all patients were placed on the 0.6mg dose and continue to be followed. Two hundred and fifty-seven patients entered the extension phase, of whom 209 completed. At the last follow-up, 50% of 0.6mg laquinimod-treated, 44% of 0.3mg laquinimod-treated and 47% of placebo-treated patients were free of Gd-enhancing lesions.[25]

These two phase II trials suggest that laquinimod has potent anti-inflammatory effects in MS. There was a significant reduction in the frequency of enhancing lesions, new T_2 lesions, and new T_1 hypointense lesions and a trend toward an effect on cerebral volume loss. In the extension, these effects were confirmed. Relapse rates were reduced by 33% and, while not significant, this magnitude of effect is similar to that achieved with IFNs and glatiramer acetate. Of note is that these effects were brought to bear in a group of patients with quite active disease. The placebo relapse rate in the second phase II trial was 0.78. This is much higher than observed in the most recent clinical trial, in which placebo relapse rates were in the range of 0.3–0.4.[26]

Safety and Tolerability

Laquinimod was well tolerated in both phase II trials, having few side effects and a paucity of AEs. There was no difference in the number of AEs and serious AEs (SAEs) between the placebo and the treated groups. In the initial phase II trial there was one SAE in the placebo group, one in the 0.1mg group, and four in the 0.3mg group. One patient developed iritis in the 0.3mg group. Erythrocyte sedimentation rate (ESR) was increased on at least one assessment in 6% of the placebo group, 13.2% of the 0.1mg group, and 17.6% of the 0.3mg group. C-reactive protein (CRP) was elevated on at least one assessment in 34% of the placebo group, 25% of the 0.1mg group, and 34% of the 0.3mg group. Liver function tests were elevated on at least one occasion in 34% of the placebo group, 34% of the 0.1mg group, and 47% of the 0.6mg group. There were no associated elevations of bilirubin, and elevations of liver function enzymes were generally mild and transient and not considered to be clinically significant.[23]

Laquinimod was also well tolerated in the second phase II trial. There was a higher early termination rate due to AEs in the placebo group. There were four SAEs in the placebo group, five in the 0.3mg group, and two in the 0.6mg group. One of each was assessed as being possibly study-drug-related. In the 0.3mg group there were two early terminations due to liver function test abnormalities. In the 0.6mg group there was an early termination because of an elevated CRP in the setting of a throat infection that was felt not to be drug-related. A second patient developed fever and eosinophilia accompanied by an elevation of liver enzymes, and was diagnosed with Budd-Chiari syndrome (hepatic vein thrombosis); this patient was treated with anticoagulants and recovered fully. This patient had a factor V Leiden deficiency that may have caused a predisposition to thrombotic events. Some elevations of liver function tests were noted. Elevations of alanine transaminase (ALT) were noted, but most normalized while on therapy. There were no associated increases in bilirubin, suggesting an absence of hepatocellular injury. CRP was elevated to a greater extent in the placebo than in the laquinimod 0.6mg group (17.6 versus 13.2%). Transient elevations of fibrinogen occurred in 29.4% of the placebo group, 32.6% of the 0.3mg group, and 44.4% of the 0.6mg group. All elevations of fibrinogen were reversible. Some patients developed mild arthralgias, arthritis, and edema, but all resolved spontaneously without intervention. There were no instances of leukopenia or life-threatening infections.[24]

Another study evaluated the safety and tolerability of laquinimod at a dose of 0.9mg in an open-label design.[27] This study enrolled 22 patients with RRMS or SPMS who were treated for 48 weeks. Three patients withdrew and two patients required a reduction in dose to 0.6mg; the 17 remaining patients completed the study. Two patients were treated at the reduced dose level of 0.6mg/day and three discontinued treatment during the course of the study. Transient elevations of liver function tests were observed but were mild and found to be reversible.

In summary, laquinimod had a good safety profile in phase II trials. The initial concerns regarding the safety of this agent centered on elevation of liver function tests and pro-inflammatory effects. There was no indication of either toxicity in the phase II trials.

Phase III Trials

There are two phase III trials of laquinimod in RRMS currently under way. The first is the ALLEGRO Trial. This is a randomized, double-blind, placebo-controlled trial of laquinimod in RRMS. Inclusion criteria for this trial required patients to have had at least one relapse in the year prior to study entry, two relapses in the two years preceding study entry, or one relapse between months 12 and 24 preceding study entry and one enhancing lesion in the year prior to study entry. The primary outcome measure is relapse rate reduction and the main secondary outcome measure is disability progression as measured by the expanded disability status scale (EDSS). It is a two-year study involving 1,100 MS patients. Results are expected in late 2010.[28]

The second trial under way is the BRAVO trial. This is a global, randomized, rater-blinded three-arm trial that will compare placebo, laquinimod 0.6mg, and IFNβ-1a 30mcg once weekly. The inclusion criteria for this trial are the same as those for the ALLEGRO trial, and the trial is fully enrolled. The primary outcome measure is relapse rate reduction at two years.[29]

Other Agents in Development for Multiple Sclerosis

In addition to laquinimod, a number of other agents are currently in phase II and III trials in RRMS.[30] These developing agents include oral fumarate, teriflunomide, and oral VLA-4 inhibitors. Oral fumarate and teriflunomide are in phase III trials that have not yet been completed, but both agents showed efficacy in phase II trials. Oral VLA-4 antagonists continue at various stages of evaluation, but phase II trials have not been uniformly successful. Two other notable oral treatments, fingolimod and cladribine, have now completed phase III trials. Fingolimod was approved for use in RRMS by the FDA in September 2010. Cladribine was approved for use in RRMS by the TGA in Australia in September 2010 and is currently under consideration for the same indication at the FDA. Both fingolimod and cladribine showed good efficacy in the phase III trials, but may have safety considerations that could affect their use.

Parenteral agents in development include ocreluzumab, daclizumab, alemtuzumab, and ofetumubab. Ocreluzumab and ofetumubab are monoclonal antibodies against CD20 (B cells). The prototypic agent in this group is rituximab, which showed quite good efficacy in phase II trials but will not be further developed for MS. Alemtuzumab was compared with Rebif in a phase II trial, and decreased relapse rates by 74% and rates of disability progression by 71% in comparison with Rebif.[31] Despite the appearance of superior efficacy, alemtuzumab was associated with potentially serious autoimmune adverse events including immune thrombotytopenic purpura (ITP), autoimmune thyroiditis, and Goodpasture's syndrome. Daclizumab is currently being evaluated in phase II and III clinical trials, but efficacy results in a monotherapy setting are not yet available.

Clearly, the therapeutic environment in MS will become far more complicated in the coming years. All of the newer agents have potential advantages, but safety and tolerability could have a major impact on their use. One effect of this could be that many more MS patients are cared for in an MS center where there is an in-depth knowledge of the newer agents and their potential risks and benefits. An oral agent such as laquinimod with a good safety and tolerability profile, convenient once-daily dosing, and good efficacy could become a first-line agent in the new environment.

Another aspect of the new therapeutic environment that deserves consideration is the potential use of combination therapy. Agents such as laquinimod could be combined with the currently available parenteral therapies or with other agents. Initial studies using teriflunomide in conjunction with IFN-β and glatiramer acetate have taken place, and the results suggest that the combination is more effective than either agent alone. The use of a combination therapy might be preferred to the use of a highly effective monotherapy with the potential for serious or life-threatening side effects.

Summary

Laquinimod is a novel oral immunomodulatory agent with once-daily dosing. It has potent anti-inflammatory effects in animal models of MS and in humans. In phase II trials in patients with active disease, median enhancing lesion frequency was decreased by 55% with a trend toward an effect on decreasing brain atrophy. Laquinimod appears to act as a broad-spectrum immunomodulator that has no immunosuppressive effects. Unlike its parent compound roquinimex, laquinimod has not shown a tendency to induce inflammatory reactions.

In phase II trials laquinimod has shown a highly favorable safety profile. It is metabolized by CYP-3A4 and could interact with some agents used in symptomatic treatment of MS symptoms. Results from two phase III trials, ALLEGRO and BRAVO, are expected in 2011. Laquinimod has an excellent safety profile and, if the efficacy results are reproduced in the phase III trial program, laquinimod could become a first-line agent in the treatment of MS. ■

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