(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 April 2013 (18.04.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/055907 A1

(51) **International Patent Classification**:
A61K 31/47 (2006.01) *A61K 31/135* (2006.01)

(21) **International Application Number**:
PCT/US2012/059733

(22) **International Filing Date**:
11 October 2012 (11.10.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/546,102 12 October 2011 (12.10.2011) US

(71) **Applicant** *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petach Tikva (IL).

(71) **Applicant** *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, North Wales, PA 19454 (US).

(72) **Inventors; and**
(71) **Applicants** *(for US only)*: **HALLAK, Hussein** [IL/IL]; P.O. Box 19541, 91194 East Jerusalem (IL). **TARCIC, Nora** [IL/IL]; Migdal David St. 29/1, Modiin (IL). **FLAXMAN KAYE, Joel** [IL/IL]; 14/5 Hazamir St., 42752 Netanya (IL).

(74) **Agent**: **WHITE, John, P.**; Cooper & Dunham LLP, 30 Rockefeller Plaza, New York, NY 10112 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/055907 A1

(54) **Title**: TREATMENT OF MULTIPLE SCLEROSIS WITH COMBINATION OF LAQUINIMOD AND FINGOLIMOD

(57) **Abstract**: This invention provides a method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising administering to the subject laquinimod as an add-on therapy to or in combination with fingolimod. This invention also provides a package and a pharmaceutical composition comprising laquinimod and fingolimod for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome. This invention also provides laquinimod for use as an add-on therapy or in combination with fingolimod in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome. This invention further provides use of laquinimod and fingolimod in the preparation of a combination for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

Treatment Of Multiple Sclerosis With Combination Of Laquinimod And Fingolimod

This application claims priority of U.S. Provisional Application No. 61/546,102, filed October 12, 2011, the entire content of which is hereby incorporated by reference herein.

Throughout this application, various publications are referred to by first author and year of publication. Full citations for these publications are presented in a References section immediately before the claims. Disclosures of the documents and publications referred to herein are hereby incorporated in their entireties by reference into this application.

Background

Multiple Sclerosis (MS) is a neurological disease affecting more than 1 million people worldwide. It is the most common cause of neurological disability in young and middle-aged adults and has a major physical, psychological, social and financial impact on subjects and their families, friends and bodies responsible for health care (EMEA Guideline, 2006).

It is generally assumed that MS is mediated by some kind of autoimmune process possibly triggered by infection and superimposed upon a genetic predisposition. It is a chronic inflammatory condition that damages the myelin of the Central Nervous System (CNS). The pathogenesis of MS is characterized by the infiltration of autoreactive T-cells from the circulation directed against myelin antigens into the CNS (Bjartmar, 2002). In addition to the inflammatory phase in MS, axonal loss occurs early in the course of the disease and can be extensive over time, leading to the subsequent development of progressive, permanent, neurologic impairment and, frequently, severe disability (Neuhaus, 2003). Symptoms associated with the disease include fatigue, spasticity, ataxia, weakness, bladder and bowel disturbances, sexual dysfunction, pain, tremor, paroxysmal manifestations, visual impairment, psychological problems and cognitive dysfunction (EMEA Guideline, 2006).

MS disease activity can be monitored by cranial scans, including magnetic resonance imaging (MRI) of the brain, accumulation of disability, as well as rate and severity of relapses. The diagnosis of clinically definite MS as determined by the Poser criteria (Poser, 1983) requires at least two neurological events suggesting demyelination in the CNS separated in time and in location. A clinically isolated syndrome (CIS) is a single monosymptomatic attack suggestive of MS, such as optic neuritis, brain stem symptoms, and partial myelitis. Patients with CIS that experience a second clinical attack are generally considered to have clinically definite multiple sclerosis (CDMS). Over 80 percent of patients with a CIS and MRI lesion go on to develop MS, while approximately 20 percent have a self-limited process (Brex, 2002; Frohman, 2003).

Various MS disease stages and/or types are described in Multiple Sclerosis Therapeutics (Duntiz, 1999). Among them, relapsing-remitting multiple sclerosis (RRMS) is the most common form at the time of initial diagnosis. Many subjects with RRMS have an initial relapsing-remitting course for 5-15 years, which then advances into the secondary progressive MS (SPMS) disease course. Relapses result from inflammation and demyelination, whereas restoration of nerve conduction and remission is accompanied by resolution of inflammation, redistribution of sodium channels on demyelinated axons and remyelination (Neuhaus, 2003; Noseworthy, 2000).

In April 2001, an international panel in association with the National MS Society of America recommended diagnostic criteria for multiple sclerosis. These criteria became known as the McDonald Criteria: The McDonald Criteria make use of MRI techniques and are intended to replace the Poser Criteria and the older Schumacher Criteria (McDonald, 2001). The McDonald Criteria was revised in March 2005 by an international panel (Polman, 2005) and updated again in 2010 (Polman, 2011).

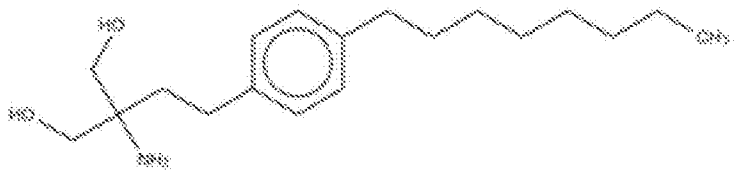
Intervention with disease-modifying therapy at relapsing stages of MS is suggested to reduce and/or prevent accumulating neurodegeneration (Hohlfeld, 2000; De Stefano, 1999). There are currently a number of disease-modifying medications approved for use in relapsing MS (RMS), which includes RRMS and SPMS (The Disease Modifying Drug Brochure, 2006). These include interferon beta 1-a (Avonex® and Rebif®), interferon beta 1-b (Betaseron®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), natalizumab (Tysabri®) and Fingolimod (Gilenya®). Most of them are believed to act as immunomodulators. Mitoxantrone and natalizumab are believed to act as immunesuppressants. However, the mechanisms of action of each have been only partly elucidated. Immunosuppressants or cytotoxic agents are used in some subjects after failure of conventional therapies. However, the relationship between changes of the immune response induced by these agents and the clinical efficacy in MS is far from settled (EMEA Guideline, 2006).

Other therapeutic approaches include symptomatic treatment which refers to all therapies applied to improve the symptoms caused by the disease (EMEA Guideline, 2006) and treatment of acute relapses with corticosteroids. While steroids do not affect the course of MS over time, they can reduce the duration and severity of attacks in some subjects.

Fingolimod

Fingolimod (Fingolimod, Gilenya™) is a new class of drugs called sphingosine 1-phosphate (S1P) receptor modulators. These medicines reduce inflammation and may also have a direct beneficial effect on cells in the central nervous system (CNS). Upon administration, fingolimod is

phosphorylated by sphingosine kinase to form the the active metabolite fingolimod-phosphate - Fingolimod is therefore a prodrug. Fingolimod-phosphate binds the sphingosine 1-phosphate receptors S1PR-1, S1PR3, S1PR4 and S1PR5 with high affinity and thereby blocks the capacity of leukocytes to migrate from lymph nodes into the peripheral blood. These receptors are also known as EDG receptors, and are all members of the rhodospin-like GPCR family, the largest single historical successful family of drug targets (GPCR SARfari: S1PR-1 (aka. EDG1)). The curative mechanism underlying fingolimod's therapeutic effect is unknown but may involve a reduced migration of lymphocytes into the CNS. The chemical structure of fingolimod was derived from the myriocin (ISP-1) metabolite of the fungus *Isaria sinclairii*. It is a structural analogue of sphingosine and gets phosphorylated by sphingosine kinases in the cell (most importantly sphingosine kinase 2) (Paugh SW 2003; Billich A, 2003; Sanchez, T, 2003). The molecular biology of phospho-fingolimod is thought to lie in its activity at one of the five sphingosine-1-phosphate receptors, S1PR1(Hla T,2001). It can sequester lymphocytes in lymph nodes, preventing them from moving to the central nervous system for auto-immune responses in multiple sclerosis and was originally proposed as a anti-rejection medication indicated post-transplantation. It has been reported to stimulate the repair process of glial cells and precursor cells after injury (Alejandro Horga, 2008). Fingolimod has also been reported to be a cannabinoid receptor antagonist (Paugh SW, 2006), a cPLA2 inhibitor (Payne SG, 2007) and a ceramide synthase inhibitor (Berdyshev EV, 2009).



IUPAC: 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol

The approved medication Gilenya is an oral capsule containing 0.56mg of the hydrochloride salt of fingolimod which is equivalent to 0.5mg of fingolimod.

Laquinimod

Laquinimod is a novel synthetic compound with high oral bioavailability which has been suggested as an oral formulation for the treatment of Multiple Sclerosis (MS) (Polman, 2005; Sandberg-Wollheim, 2005; Comi et al 2008). Laquinimod and its sodium salt form are described, for example, in U.S. Patent No. 6,077,851. The mechanism of action of laquinimod is not fully understood.

Animal studies show it causes a Th1 (T helper 1 cell, produces pro-inflammatory cytokines) to Th2 (T helper 2 cell, produces anti-inflammatory cytokines) shift with an anti-inflammatory profile (Yang, 2004; Brück, 2011). Another study demonstrated (mainly via the NFkB pathway) that laquinimod induced suppression of genes related to antigen presentation and corresponding inflammatory pathways (Gurevich, 2010). Other suggested potential mechanisms of action include inhibition of leukocyte migration into the CNS, increase of axonal integrity, modulation of cytokine production, and increase in levels of brain-derived neurotrophic factor (BDNF) (Runström, 2006; Brück, 2011).

Laquinimod showed a favorable safety and tolerability profile in two phase III trials (Results of Phase III BRAVO Trial Reinforce Unique Profile of Laquinimod for Multiple Sclerosis Treatment; Teva Pharma, Active Biotech Post Positive Laquinimod Phase 3 ALLEGRO Results).

Combination Therapy

The administration of two drugs to treat a given condition, such as multiple sclerosis, raises a number of potential problems. *In vivo* interactions between two drugs are complex. The effects of any single drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit, activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug (Guidance for Industry, 1999). In one example, combined administration of fingolimod and interferon (IFN) has been experimentally shown to abrogate the clinical effectiveness of either therapy. (Brod 2000) In another experiment, it was reported that the addition of prednisone in combination therapy with IFN-β antagonized its up-regulator effect. Thus, when two drugs are administered to treat the same condition, it is unpredictable whether each will complement, have no effect on, or interfere with, the therapeutic activity of the other in a human subject.

Not only may the interaction between two drugs affect the intended therapeutic activity of each drug, but the interaction may increase the levels of toxic metabolites (Guidance for Industry, 1999). The interaction may also heighten or lessen the side effects of each drug. Hence, upon administration of two drugs to treat a disease, it is unpredictable what change will occur in the negative side profile of each drug. In one example, the combination of natalizumab and interferon β-1a was observed to increase the risk of unanticipated side effects. (Vollmer, 2008; Rudick 2006; Kleinschmidt-DeMasters, 2005; Langer-Gould 2005)

Additionally, it is difficult to accurately predict when the effects of the interaction between the two drugs will become manifest. For example, metabolic interactions between drugs may become

apparent upon the initial administration of the second drug, after the two have reached a steady-state concentration or upon discontinuation of one of the drugs (Guidance for Industry, 1999).

Therefore, the state of the art at the time of filing is that the effects of combination therapy of two drugs, in particular laquinimod and fingolimod, cannot be predicted until the results of a combination study are available.

Brief Description of the Drawings

Figure 1 is a graphical representation of the experimental results from Example 1. The graph shows the clinical score for the EAE rodents in each group (on the y-axis) against the days after induction of the disease (on the x-axis).

5

Summary of the Invention

This invention provides a method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising periodically administering to the subject an amount of laquinimod, and an amount of fingolimod, wherein the amounts when taken together are effective to treat the subject.

This invention also provides a method of treating a human patient afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising periodically administering to the patient an amount of laquinimod and an amount of fingolimod, wherein the amounts when taken together is more effective to treat the human patient than when each agent is administered alone.

This invention also provides a method of treating a human patient afflicted with an immune disease, comprising periodically administering to the patient an amount of laquinimod and an amount of fingolimod, wherein the amounts when taken together are effective to treat the human patient, and wherein the immune disease is an autoimmune disease, an arthritic condition, a demyelinating disease, an inflammatory disease, multiple sclerosis, relapsing-remitting multiple sclerosis, diabetes mellitus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or systemic lupus erythematosus.

This invention also provides a package comprising: a) a first pharmaceutical composition comprising an amount of laquinimod and a pharmaceutically acceptable carrier; b) a second pharmaceutical composition comprising an amount of fingolimod and a pharmaceutically acceptable carrier; and c) instructions for use of the first and second pharmaceutical compositions together to treat a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

This invention also provides laquinimod for use as an add-on therapy or in combination with fingolimod in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the laquinimod and the fingolimod are administered simultaneously, contemporaneously or concomitantly.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod for use in treating a human patient afflicted with an immune disease, wherein the laquinimod and the fingolimod are administered simultaneously, contemporaneously,

or concomitantly and wherein the immune disease is an autoimmune disease, an arthritic condition, a demyelinating disease, an inflammatory disease, multiple sclerosis, relapsing-remitting multiple sclerosis, diabetes mellitus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or systemic lupus erythematosus.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod.

This invention also provides use of an amount of laquinimod and an amount of fingolimod in the preparation of a combination for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome wherein the laquinimod and the fingolimod are administered simultaneously, contemporaneously or concomitantly.

This invention also provides pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome as an add-on therapy or in combination with fingolimod by periodically administering the pharmaceutical composition and the fingolimod to the subject.

This invention also provides a pharmaceutical composition comprising an amount of fingolimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome as an add-on therapy or in combination with laquinimod by periodically administering the pharmaceutical composition and the laquinimod to the subject.

This invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) one or more unit doses, each such unit dose comprising: i) an amount of laquinimod and ii) an amount of fingolimod wherein the respective amounts of said laquinimod and said fingolimod in said unit dose are effective, upon concomitant administration to said subject, to treat the subject, and b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

This invention further provides a pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) an amount of laquinimod; b) an amount of fingolimod, wherein the respective amounts of said laquinimod and said fingolimod in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject.

Detailed Description of the Invention

This invention provides a method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising periodically administering to the subject an amount of laquinimod and an amount of fingolimod, wherein the amounts when taken together are effective to treat the subject.

This invention also provides a method of treating a human patient afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising periodically administering to the patient an amount of laquinimod and an amount of fingolimod, wherein the amounts when taken together is more effective to treat the human patient than when each agent is administered alone.

This invention also provides a method of treating a human patient afflicted with an immune disease, comprising periodically administering to the patient an amount of laquinimod and an amount of fingolimod, wherein the amounts when taken together are effective to treat the human patient, and wherein the immune disease is an autoimmune disease, an arthritic condition, a demyelinating disease, an inflammatory disease, multiple sclerosis, relapsing-remitting multiple sclerosis, diabetes mellitus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or systemic lupus erythematosus.

In an embodiment, the amount of laquinimod and the amount of fingolimod when administered together is more effective to treat the subject than when each agent at the same amount is administered alone.

In one embodiment, the multiple sclerosis is relapsing multiple sclerosis. In another embodiment, the relapsing multiple sclerosis is relapsing-remitting multiple sclerosis.

In an embodiment, the amount of laquinimod and the amount of fingolimod when taken together is effective to reduce a symptom of multiple sclerosis in the subject. In one embodiment, the symptom is a MRI-monitored multiple sclerosis disease activity, relapse rate, accumulation of physical disability, frequency of relapses, decreased time to confirmed disease progression, decreased time to confirmed relapse, frequency of clinical exacerbation, brain atrophy, neuronal dysfunction, neuronal injury, neuronal degeneration, neuronal apoptosis, risk for confirmed progression, deterioration of visual function, fatigue, impaired mobility, cognitive impairment, reduction of brain volume, abnormalities observed in whole Brain MTR histogram, deterioration in general health status, functional status, quality of life, and/or symptom severity on work.

In one embodiment, the amount of laquinimod and the amount of fingolimod when taken together is effective to decrease or inhibit reduction of brain volume. In another embodiment, brain volume is measured by percent brain volume change (PBVC).

In one embodiment, the amount of laquinimod and the amount of fingolimod when taken together is effective to increase time to confirmed disease progression. In another embodiment, time to confirmed disease progression is increased by 20-60%. In another embodiment, time to confirmed disease progression is increased by at least 50%.

In one embodiment, the amount of laquinimod and the amount of fingolimod when taken together is effective to decrease abnormalities observed in whole Brain MTR histogram. In another embodiment, the accumulation of physical disability is measured by Kurtzke Expanded Disability Status Scale (EDSS) score. In another embodiment, the accumulation of physical disability is assessed by the time to confirmed disease progression as measured by Kurtzke Expanded Disability Status Scale (EDSS) score.

In one embodiment, the subject had an EDSS score of 0-5.5 at baseline. In another embodiment, the subject had an EDSS score of 1.5-4.5 at baseline. In another embodiment, the subject had an EDSS score of 5.5 or greater at baseline. In another embodiment, confirmed disease progression is a 1 point increase of the EDSS score. In another embodiment, confirmed disease progression is a 0.5 point increase of the EDSS score.

In one embodiment, impaired mobility is assessed by the Timed-25 Foot Walk test. In another embodiment, impaired mobility is assessed by the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) self-report questionnaire. In another embodiment, impaired mobility is assessed by the Ambulation Index (AI). In another embodiment, impaired mobility is assessed by the Six-Minute Walk (6MW) Test. In another embodiment, impaired mobility is assessed by the Lower Extremity Manual Muscle Test (LEMMT) Test.

In an embodiment, the amount of laquinimod and the amount of fingolimod when taken together is effective to reduce cognitive impairment. In another embodiment, cognitive impairment is assessed by the Symbol Digit Modalities Test (SDMT) score.

In an embodiment, general health status is assessed by the EuroQoL (EQ5D) questionnaire, Subject Global Impression (SGI) or Clinician Global Impression of Change (CGIC). In another embodiment, functional status is measured by the subject's Short-Form General Health survey (SF-36) Subject Reported Questionnaire score. In another embodiment, quality of life is assessed by SF-36, EQ5D, Subject Global Impression (SGI) or Clinician Global Impression of Change (CGIC). In another embodiment, the subject's SF-36 mental component summary score (MSC) is

improved. In another embodiment, the subject's SF-36 physical component summary sore (PSC) is improved. In another embodiment, fatigue is assessed by the EQ5D, the subject's Modified Fatigue Impact Scale (MFIS) score or the French valid versions of the Fatigue Impact Scale (EMIF-SEP) score. In another embodiment, symptom severity on work is measured by the work productivity and activities impairment General Health (WPAI-GH) questionnaire.

In one embodiment, laquinimod is laquinimod sodium. In another embodiment, fingolimod is fingolimod hydrochloride.

In one embodiment, the laquinimod and/or the fingolimod is administered via oral administration. In another embodiment, the laquinimod and/or the fingolimod is administered daily. In another embodiment, the laquinimod and/or the fingolimod is administered more often than once daily. In another embodiment, the laquinimod and/or the fingolimod is administered less often than once daily.

In one embodiment, the amount laquinimod administered is less than 0.6 mg/day. In another embodiment, the amount laquinimod administered is 0.1-40.0 mg/day. In another embodiment, the amount laquinimod administered is 0.1-2.5 mg/day. In another embodiment, the amount laquinimod administered is 0.25-2.0 mg/day. In another embodiment, the amount laquinimod administered is 0.5-1.2 mg/day. In another embodiment, the amount laquinimod administered is 0.25 mg/day. In another embodiment, the amount laquinimod administered is 0.3 mg/day. In another embodiment, the amount laquinimod administered is 0.5 mg/day. In another embodiment, the amount laquinimod administered is 0.6 mg/day. In another embodiment, the amount laquinimod administered is 1.0 mg/day. In another embodiment, the amount laquinimod administered is 1.2 mg/day. In another embodiment, the amount laquinimod administered is 1.5 mg/day. In another embodiment, the amount laquinimod administered is 2.0 mg/day.

In one embodiment, the amount of fingolimod administered is less than 0.5 mg/day. In another embodiment, the amount of fingolimod administered is 0.01-2.5 mg/day. In another embodiment, the amount of fingolimod administered is 2.5 mg/day. In another embodiment, the amount of fingolimod administered is 0.01-1 mg/day. In another embodiment, the amount of fingolimod administered is 0.1 mg/day. In another embodiment, the amount of fingolimod administered is 0.25 mg/day. In another embodiment, the amount of fingolimod administered is 0.5 mg/day.

In one embodiment, the amount of laquinimod and the amount of fingolimod when taken together is effective to alleviate a symptom of multiple sclerosis in the subject. In another embodiment, the symptom is a MRI-monitored multiple sclerosis disease activity, relapse rate, accumulation of

physical disability, frequency of relapses, frequency of clinical exacerbation, brain atrophy, risk for confirmed progression, or time to confirmed disease progression.

In one embodiment, a loading dose of an amount different form the intended dose is administered for a period of time at the start of the periodic administration. In another embodiment, the loading dose is double the amount of the intended dose.

In one embodiment, the subject is receiving laquinimod therapy prior to initiating fingolimod therapy. In another embodiment, the administration of laquinimod substantially precedes the administration of fingolimod.

In one embodiment, the subject is receiving fingolimod therapy prior to initiating laquinimod therapy. In another embodiment, the administration of fingolimod substantially precedes the administration of laquinimod. In another embodiment, the subject is receiving fingolimod therapy for at least 24 weeks prior to initiating laquinimod therapy. In another embodiment, the subject is receiving fingolimod therapy for at least 28 weeks prior to initiating laquinimod therapy. In another embodiment, the subject is receiving fingolimod therapy for at least 48 weeks prior to initiating laquinimod therapy. In yet another embodiment, the subject is receiving fingolimod therapy for at least 52 weeks prior to initiating laquinimod therapy.

In one embodiment, the method further comprises administration of nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, slow-acting drugs, gold compounds, hydroxychloroquine, sulfasalazine, combinations of slow-acting drugs, corticosteroids, cytotoxic drugs, immunosuppressive drugs and/or antibodies.

In one embodiment, the periodic administration of laquinimod o and fingolimod continues for at least 3 days. In another embodiment, the periodic administration of laquinimod and fingolimod continues for more than 30 days. In another embodiment, the periodic administration of laquinimod and fingolimod continues for more than 42 days. In another embodiment, the periodic administration of laquinimod and fingolimod continues for 8 weeks or more. In another embodiment, the periodic administration of laquinimod and fingolimod continues for at least 12 weeks. In another embodiment, the periodic administration of laquinimod and fingolimod continues for at least 24 weeks. In another embodiment, the periodic administration of laquinimod and fingolimod continues for more than 24 weeks. In yet another embodiment, the periodic administration of laquinimod and fingolimod continues for 6 months or more.

In one embodiment, the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 20%. In another embodiment, the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 30%. In another

embodiment, the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 50%. In another embodiment, the administration of laquinimod and fingolimod or inhibits a symptom of relapsing multiple sclerosis by at least 70%. In another embodiment, the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by more than 100%. In another embodiment, the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by more than 300%. In another embodiment, the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by more than 1000%.

In one embodiment, each of the amount of laquinimod when taken alone, and the amount of fingolimod or when taken alone is effective to treat the subject. In another embodiment, either the amount of laquinimod when taken alone, the amount of fingolimod or when taken alone, or each such amount when taken alone is not effective to treat the subject. In yet another embodiment, the subject is a human patient.

This invention also provides a package comprising: a) a first pharmaceutical composition comprising an amount of laquinimod and a pharmaceutically acceptable carrier; b) a second pharmaceutical composition comprising an amount of fingolimod and a pharmaceutically acceptable carrier; and c) instructions for use of the first and second pharmaceutical compositions together to treat a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

In one embodiment, the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in an aerosol, an inhalable powder, an injectable a liquid, a solid, a capsule or a tablet form. In one embodiment, the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in liquid form. In another embodiment, the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in solid form. In another embodiment, the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in capsule form. In another embodiment, the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in tablet form. In another embodiment, the tablets are coated with a coating which inhibits oxygen from contacting the core. In another embodiment, the coating comprises a cellulosic polymer, a detackifier, a gloss enhancer, or pigment.

In one embodiment, the first pharmaceutical composition further comprises mannitol. In another embodiment, the first pharmaceutical composition further comprises an alkalinizing agent. In another embodiment, the alkalinizing agent is meglumine.

In one embodiment, the first pharmaceutical composition further comprises an oxidation reducing agent. In another embodiment, the first pharmaceutical composition is stable and free of an alkalinizing agent or an oxidation reducing agent. In another embodiment, the first pharmaceutical composition is free of an alkalinizing agent and free of an oxidation reducing agent. In another embodiment, the first pharmaceutical composition is stable and free of disintegrant.

In one embodiment, the first pharmaceutical composition further comprises a lubricant. In another embodiment, the lubricant is present in the composition as solid particles. In another embodiment, the lubricant is sodium stearyl fumarate or magnesium stearate.

In one embodiment, the first pharmaceutical composition further comprises a filler. In another embodiment, the filler is present in the composition as solid particles. In another embodiment, the filler is lactose, lactose monohydrate, starch, isomalt, mannitol, sodium starch glycolate, sorbitol, lactose spray dried, lactose anhydrouse, or a combination thereof. In yet another embodiment, the filler is mannitol or lactose monohydrate.

In an embodiment, the package further comprises a desiccant. In another embodiment, the desiccant is silica gel.

In one embodiment, the first pharmaceutical composition is stable and has a moisture content of no more than 4%. In another embodiment, laquinimod is present in the composition as solid particles. In another embodiment, the package is a sealed packaging having a moisture permeability of not more than 15 mg/day per liter. In another embodiment, the sealed package is a blister pack in which the maximum moisture permeability is no more than 0.005 mg/day. In another embodiment, the sealed package is a bottle. In another embodiment, the bottle is closed with a heat induction liner. In another embodiment, the sealed package comprises an HDPE bottle. In another embodiment, the sealed package comprises an oxygen absorbing agent. In yet another embodiment, the oxygen absorbing agent is iron.

In an embodiment of the present invention, the amount of laquinimod in the first composition is less than 0.6 mg. In another embodiment, the amount of laquinimod in the first composition is 0.1-40.0 mg. In another embodiment, the amount of laquinimod in the first composition is 0.1-2.5 mg. In another embodiment, the amount of laquinimod in the first composition is 0.25-2.0 mg. In another embodiment, the amount of laquinimod in the first composition is 0.5-1.2 mg. In another embodiment, the amount of laquinimod in the first composition is 0.25 mg. In another embodiment,

the amount of laquinimod in the first composition is 0.3 mg. In another embodiment, the amount of laquinimod in the first composition is 0.5 mg. In another embodiment, the amount of laquinimod in the first composition is 0.6 mg. In another embodiment, the amount of laquinimod in the first composition is 1.0 mg. In another embodiment, the amount of laquinimod in the first composition is 1.2 mg. In another embodiment, the amount of laquinimod in the first composition is 1.5 mg. In another embodiment, the amount of laquinimod in the first composition is 2.0 mg.

In an embodiment of the present invention, the amount of fingolimod in the second composition is less than 0.5 mg. In another embodiment of the present invention, the amount of fingolimod in the second composition is 0.01-2.5 mg. In another embodiment, the amount of fingolimod in the second composition is 2.5 mg. In another embodiment, the amount of fingolimod in the second composition is 0.01-1 mg. In another embodiment, the amount of fingolimod in the second composition is 0.1 mg. In another embodiment, the amount of fingolimod in the second composition is 0.25 mg. In another embodiment, the amount of fingolimod in the second composition is 0.5 mg.

This invention also provides laquinimod for use as an add-on therapy or in combination with fingolimod or in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the laquinimod and the fingolimod f are administered simultaneously, contemporaneously or concomitantly.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod for use in treating a human patient afflicted with an immune disease, wherein the laquinimod and the fingolimod are administered simultaneously, contemporaneously, or concomitantly and wherein the immune disease is an autoimmune disease, an arthritic condition, a demyelinating disease, an inflammatory disease, multiple sclerosis, relapsing-remitting multiple sclerosis, diabetes mellitus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or systemic lupus erythematosus.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod.

In one embodiment, laquinimod is laquinimod sodium. In another embodiment, fingolimod is fingolimod hydrochloride.

In one embodiment, the composition is in an aerosol, an inhalable powder, an injectable, a liquid, a solid, a capsule or a tablet form. In another embodiment, the composition is in liquid form. In another embodiment, the composition is in solid form. In another embodiment, the composition is in capsule form. In another embodiment, the composition is in tablet form.

In one embodiment, the tablets are coated with a coating which inhibits oxygen from contacting the core. In another embodiment, the coating comprises a cellulosic polymer, a detackifier, a gloss enhancer, or pigment.

In one embodiment, the pharmaceutical composition further comprises mannitol. In another embodiment, the pharmaceutical composition further comprises an alkalinizing agent. In another embodiment, the alkalinizing agent is meglumine. In an embodiment, the pharmaceutical composition comprises an oxidation reducing agent.

In an embodiment the pharmaceutical composition is free of an alkalinizing agent or an oxidation reducing agent. In another embodiment, the pharmaceutical composition is free of an alkalinizing agent and free of an oxidation reducing agent.

In one embodiment, the pharmaceutical composition is stable and free of disintegrant. In another embodiment, the pharmaceutical composition further comprises a lubricant. In another embodiment, the lubricant is present in the composition as solid particles. In another embodiment, the lubricant is sodium stearyl fumarate or magnesium stearate.

In an embodiment, the pharmaceutical composition further comprises a filler. In another embodiment, the filler is present in the composition as solid particles. In another embodiment, the filler is lactose, lactose monohydrate, starch, isomalt, mannitol, sodium starch glycolate, sorbitol, lactose spray dried, lactose anhydrouse, or a combination thereof. In another embodiment, the filler is mannitol or lactose monohydrate.

In one embodiment, the amount of laquinimod in the composition is less than 0.6 mg. In another embodiment, the amount of laquinimod in the composition is 0.1-40.0 mg. In another embodiment, the amount of laquinimod in the composition is 0.1-2.5 mg. In another embodiment, the amount of laquinimod in the composition is 0.25-2.0 mg. In another embodiment, the amount of laquinimod in the composition is 0.1-2.5 mg. In another embodiment, the amount of laquinimod in the composition is 0.25 mg. In another embodiment, the amount of laquinimod in the composition is 0.3 mg. In another embodiment, the amount of laquinimod in the composition is 0.5 mg. In another embodiment, the amount of laquinimod in the composition is 0.6 mg. In another embodiment, the amount of laquinimod in the composition is 1.0 mg. In another embodiment, the amount of laquinimod in the composition is 1.2 mg. In another embodiment, the amount of laquinimod in the

composition is 1.5 mg. In another embodiment, the amount of laquinimod in the composition is 2.0 mg.

In one embodiment, the amount of fingolimod in the composition is less than 0.5 mg. In another embodiment, the amount of fingolimod in the composition is 0.01-2.5 mg. In another embodiment, the amount of fingolimod in the composition is 2.5 mg. In another embodiment, the amount of fingolimod in the composition is 0.01-1 mg. In another embodiment, the amount of fingolimod in the composition is 0.1 mg. In another embodiment, the amount of fingolimod in the composition is 0.25 mg. In another embodiment, the amount of fingolimod in the composition is 0.5 mg.

This invention also provides use ofan amount of laquinimod and an amount of fingolimod in the preparation of a combination for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome wherein the laquinimod or pharmaceutically acceptable salt thereof and the fingolimod or pharmaceutically acceptable salt thereof are administered simultaneously, contemporaneously or concomitantly.

In one embodiment, the multiple sclerosis is relapsing multiple sclerosis. In another embodiment, the relapsing multiple sclerosis is relapsing-remitting multiple sclerosis.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome as an add-on therapy or in combination with fingolimod by periodically administering the pharmaceutical composition and the fingolimod to the subject.

This invention also provides a pharmaceutical composition comprising an amount of fingolimod for use treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome as an add-on therapy or in combination with laquinimod by periodically administering the pharmaceutical composition and the laquinimod to the subject.

This invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) one or more unit doses, each such unit dose comprising: i) an amount of laquinimod and ii) an amount of fingolimod wherein the respective amounts of said laquinimod and said fingolimod in said unit dose are effective, upon concomitant administration to said subject, to treat the subject, and b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject. In an embodiment, the respective amounts of said laquinimod and said fingolimod in said unit dose when taken together is more effective to

treat the subject than when compared to the administration of said laquinimod in the absence of said fingolimod or the administration of said fingolimod in the absence of said laquinimod.

This invention further provides a pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises: a) an amount of laquinimod; b) an amount of fingolimod, wherein the respective amounts of said laquinimod and said fingolimod in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject. In an embodiment, the respective amounts of said laquinimod and said fingolimod in said unit dose when taken together is more effective to treat the subject than when compared to the administration of said laquinimod in the absence of said fingolimod or the administration of said fingolimod in the absence of said laquinimod.

For the foregoing embodiments, each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments.

Fingolimod

Fingolimod mixtures, compositions, the process for the manufacture thereof, the use thereof for treatment of various conditions, and the corresponding dosages and regimens are described in, e.g., U.S. Patent Application Publication Nos. 2012-0184617, 2009-0176744, 2009-0082347, and 2011-0152380, U.S. Patent No. 5,719,176, and Pelletier and Hafler (2012) "Fingolimod for Multiple Sclerosis" New England Journal of Medicine, 366(4):339-347, each of which is hereby incorporated by reference in its entireties into this application.

Laquinimod

Laquinimod mixtures, compositions, and the process for the manufacture thereof are described in, e.g., U.S. Patent No. 6,077,851, U.S. Patent No. 7,884,208, U.S. Patent No. 7,989,473, U.S. Patent No. 8,178,127, U.S. Application Publication No. 2010-0055072, U.S. Application Publication No. 2012-0010238, and U.S. Application Publication No. 2012-0010239, each of which is hereby incorporated by reference in its entireties into this application.

Use of laquinimod for treatment of various conditions, and the corresponding dosages and regimens, are described in U.S. Patent No. 6,077,851 (multiple sclerosis, insulin-dependent diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, psoriasis, inflammatory respiratory disorder, atherosclerosis, stroke, and Alzheimer's disease), U.S. Application Publication No. 2011-0027219 (Crohn's disease), U.S. Application Publication No. 2010-0322900 (Relapsing-remitting multiple sclerosis), U.S. Application

Publication No. 2011-0034508 (brain-derived neurotrophic factor (BDNF)-related diseases), U.S. Application Publication No. 2011-0218179 (active lupus nephritis), U.S. Application Publication No. 2011-0218203 (rheumatoid arthritis), U.S. Application Publication No. 2011-0217295 (active lupus arthritis), and U.S. Application Publication No. 2012-0142730 (reducing fatigue, improving quality of life, and providing neuroprotection in MS patients), each of which is hereby incorporated by reference in its entireties into this application.

A pharmaceutically acceptable salt of laquinimod as used in this application includes lithium, sodium, potassium, magnesium, calcium, manganese, copper, zinc, aluminum and iron. Salt formulations of laquinimod and the process for preparing the same are described, e.g., in U.S. Patent No. 7,589,208 and PCT International Application Publication No. WO 2005/074899, which are hereby incorporated by reference into this application.

Laquinimod can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit can be in a form suitable for oral administration. Laquinimod can be administered alone but is generally mixed with a pharmaceutically acceptable carrier, and co-administered in the form of a tablet or capsule, liposome, or as an agglomerated powder. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders.

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, dicalcium phosphate, calcium sulfate, mannitol, sorbitol, microcrystalline cellulose and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn starch, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, povidone, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, sodium benzoate, sodium acetate, sodium chloride, stearic acid, sodium stearyl fumarate, talc and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, croscarmellose sodium, sodium starch glycolate and the like.

Specific examples of the techniques, pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described, e.g., in U.S. Patent

No. 7,589,208, PCT International Application Publication Nos. WO 2005/074899, WO 2007/047863, and 2007/146248.

General techniques and compositions for making dosage forms useful in the present invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds).; Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol. 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds). These references in their entireties are hereby incorporated by reference into this application.

Disclosed is a method for treating a subject, e.g., human patient, afflicted with relapsing multiple sclerosis or presenting a CIS using laquinimod with fingolimod which provides a more efficacious treatment than each agent alone. The use of laquinimod for relapsing multiple sclerosis had been previously suggested in, e.g., U.S. Patent No. 6,077,851. However, the inventors have surprisingly found that the combination of laquinimod and fingolimod is particularly effective for the treatment of a subject afflicted with MS or presenting a CIS as compared to each agent alone.

Terms

As used herein, and unless stated otherwise, each of the following terms shall have the definition set forth below.

As used herein, “laquinimod” means laquinimod acid or a pharmaceutically acceptable salt thereof.

As used herein, “fingolimod” means fingolimod acid or a pharmaceutically acceptable salt thereof.

As used herein, an “amount” or “dose” of laquinimod or fingolimod as measured in milligrams refers to the milligrams of laquinimod or fingolimod acid present in a preparation, regardless of the form of the preparation. A “dose of 0.6 mg laquinimod” means the amount of laquinimod acid in a preparation is 0.6 mg, regardless of the form of the preparation. Thus, when in the form of a

salt, e.g. a laquinimod sodium salt, the weight of the salt form necessary to provide a dose of 0.6 mg laquinimod would be greater than 0.6 mg (e.g., 0.64 mg) due to the presence of the additional salt ion. Similarly, when in the form of a salt, e.g. fingolimod hydrochloride, the weight of the salt form necessary to provide a dose of 0.5 mg fingolimod would be greater than 0.5 mg (e.g., 0.56 mg) due to the presence of the additional salt ion.

As used herein, a "unit dose", "unit doses" and "unit dosage form(s)" mean a single drug administration entity/entities.

As used herein, "about" in the context of a numerical value or range means ±10% of the numerical value or range recited or claimed.

As used herein, a composition that is "free" of a chemical entity means that the composition contains, if at all, an amount of the chemical entity which cannot be avoided although the chemical entity is not part of the formulation and was not affirmatively added during any part of the manufacturing process. For example, a composition which is "free" of an alkalizing agent means that the alkalizing agent, if present at all, is a minority component of the composition by weight. Preferably, when a composition is "free" of a component, the composition comprises less than 0.1 wt%, 0.05 wt%, 0.02 wt%, or 0.01 wt% of the component.

As used herein, "alkalizing agent" is used interchangeably with the term "alkaline-reacting component" or "alkaline agent" and refers to any pharmaceutically acceptable excipient which neutralizes protons in, and raises the pH of, the pharmaceutical composition in which it is used.

As used herein, "oxidation reducing agent" refers to a group of chemicals which includes an "antioxidant", a "reduction agent" and a "chelating agent".

As used herein, "antioxidant" refers to a compound selected from the group consisting of tocopherol, methionine, glutathione, tocotrienol, dimethyl glycine, betaine, butylated hydroxyanisole, butylated hydroxytoluene, turmerin, vitamin E, ascorbyl palmitate, tocopherol, deteroxime mesylate, methyl paraben, ethyl paraben, butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, sodium or potassium metabisulfite, sodium or potassium sulfite, alpha tocopherol or derivatives thereof, sodium ascorbate, disodium edentate, BHA (butylated hydroxyanisole), a pharmaceutically acceptable salt or ester of the mentioned compounds, and mixtures thereof.

The term "antioxidant" as used herein also refers to Flavonoids such as those selected from the group of quercetin, morin, naringenin and hesperetin, taxifolin, afzelin, quercitrin, myricitrin, genistein, apigenin and biochanin A, flavone, flavopiridol, isoflavonoids such as the soy

isoflavonoid, genistein, catechins such as the tea catechin epigallocatechin gallate, flavonol, epicatechin, hesperetin, chrysin, diosmin, hesperidin, luteolin, and rutin.

As used herein, "reduction agent" refers to a compound selected from the group consisting of thiol-containing compound, thioglycerol, mercaptoethanol, thioglycol, thiodiglycol, cysteine, thioglucose, dithiothreitol (DTT), dithio-bis-maleimidoethane (DTME), 2,6-di-tert-butyl-4-methylphenol (BHT), sodium dithionite, sodium bisulphite, formamidine sodium metabisulphite, and ammonium bisulphite."

As used herein, "chelating agent" refers to a compound selected from the group consisting of penicillamine, trientine, N,N'-diethyldithiocarbamate (DDC), 2,3,2'-tetraamine (2,3,2'-tet), neocuproine, N,N,N',N'-tetrakis(2-pyridylmethyl)ethylenediamine (TPEN), 1,10-phenanthroline (PHE), tetraethylenepentamine, triethylenetetraamine and tris(2-carboxyethyl) phosphine (TCEP), ferrioxamine, CP94, EDTA, deferoxainine B (DFO) as the methanesulfonate salt (also known as desferrioxanilne B mesylate (DFOM)), desferal from Novartis (previously Ciba-Giegy), and apoferritin.

As used herein, a pharmaceutical composition is "stable" when the composition preserves the physical stability/integrity and/or chemical stability/integrity of the active pharmaceutical ingredient during storage. Furthermore, "stable pharmaceutical composition" is characterized by its level of degradation products not exceeding 5% at 40°C/75%RH after 6 months or 3% at 55°C/75% RH after two weeks, compared to their level in time zero.

As used herein, "combination" means an assemblage of reagents for use in therapy either by simultaneous or contemporaneous administration. Simultaneous administration refers to administration of an admixture (whether a true mixture, a suspension, an emulsion or other physical combination) of the laquinimod and the fingolimod. In this case, the combination may be the admixture or separate containers of the laquinimod and the fingolimod that are combined just prior to administration. Contemporaneous administration refers to the separate administration of the laquinimod and the fingolimod at the same time, or at times sufficiently close together that a synergistic activity relative to the activity of either the laquinimod or the fingolimod alone is observed.

As used herein, "concomitant administration" or administering "concomitantly" means the administration of two agents given in close enough temporal proximately to allow the individual therapeutic effects of each agent to overlap.

As used herein, "add-on" or "add-on therapy" means an assemblage of reagents for use in therapy, wherein the subject receiving the therapy begins a first treatment regimen of one or more reagents

prior to beginning a second treatment regimen of one or more different reagents in addition to the first treatment regimen, so that not all of the reagents used in the therapy are started at the same time. For example, adding laquinimod therapy to a patient already receiving fingolimod therapy.

As used herein, "effective" when referring to an amount of laquinimod and/or fingolimod refers to the quantity of laquinimod and/or fingolimod that is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention.

"Administering to the subject" or "administering to the (human) patient" means the giving of, dispensing of, or application of medicines, drugs, or remedies to a subject/patient to relieve, cure, or reduce the symptoms associated with a condition, e.g., a pathological condition.

"Treating" as used herein encompasses, e.g., inducing inhibition, regression, or stasis of a disease or disorder, e.g., RMS, or alleviating, lessening, suppressing, inhibiting, reducing the severity of, eliminating or substantially eliminating, or ameliorating a symptom of the disease or disorder. "Treating" as applied to patients presenting CIS can mean delaying the onset of clinically definite multiple sclerosis (CDMS), delaying the progression to CDMS, reducing the risk of conversion to CDMS, or reducing the frequency of relapse in a patient who experienced a first clinical episode consistent with multiple sclerosis and who has a high risk of developing CDMS.

"Inhibition" of disease progression or disease complication in a subject means preventing or reducing the disease progression and/or disease complication in the subject.

A "symptom" associated with RMS includes any clinical or laboratory manifestation associated with RMS and is not limited to what the subject can feel or observe.

As used herein, "a subject afflicted with multiple sclerosis" or "a subject afflicted with relapsing multiple sclerosis" means a subject who has been clinically diagnosed to have multiple sclerosis or relapsing multiple sclerosis (RMS), which includes relapsing-remitting multiple sclerosis (RRMS) and Secondary Progressive multiple sclerosis (SPMS).

As used herein, a subject at "baseline" is as subject prior to administration of laquinimod.

A "patient at risk of developing MS" (i.e. clinically definite MS) as used herein is a patient presenting any of the known risk factors for MS. The known risk factors for MS include any one of a clinically isolated syndrome (CIS), a single attack suggestive of MS without a lesion, the presence of a lesion (in any of the CNS, PNS, or myelin sheath) without a clinical attack, environmental factors (geographical location, climate, diet, toxins, sunlight), genetics (variation of genes encoding HLA-DRB1, IL7R-alpha and IL2R-alpha), and immunological components

(viral infection such as by Epstein-Barr virus, high avidity $CD4^+$ T cells, $CD8^+$ T cells, anti-NF-L, anti-CSF 114(Glc)).

"Clinically isolated syndrome (CIS)" as used herein refers to 1) a single clinical attack (used interchangeably herein with "first clinical event" and "first demyelinating event") suggestive of MS, which, for example, presents as an episode of optic neuritis, blurring of vision, diplopia, involuntary rapid eye movement, blindness, loss of balance, tremors, ataxia, vertigo, clumsiness of a limb, lack of co-ordination, weakness of one or more extremity, altered muscle tone, muscle stiffness, spasms, tingling, paraesthesia, burning sensations, muscle pains, facial pain, trigeminal neuralgia, stabbing sharp pains, burning tingling pain, slowing of speech, slurring of words, changes in rhythm of speech, dysphagia, fatigue, bladder problems (including urgency, frequency, incomplete emptying and incontinence), bowel problems (including constipation and loss of bowel control), impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning, and 2) at least one lesion suggestive of MS. In a specific example, CIS diagnosis would be based on a single clinical attack and at least 2 lesions suggestive of MS measuring 6 mm or more in diameter.

"Relapse Rate" is the number of confirmed relapses per unit time. "Annualized relapse rate" is the mean value of the number of confirmed relapses of each patient multiplied by 365 and divided by the number of days that patient is on the study drug.

"Expanded Disability Status Scale" or "EDSS" is a rating system that is frequently used for classifying and standardizing the condition of people with multiple sclerosis. The score ranges from 0.0 representing a normal neurological exam to 10.0 representing death due to MS. The score is based upon neurological testing and examination of functional systems (FS), which are areas of the central nervous system which control bodily functions. The functional systems are: Pyramidal (ability to walk), Cerebellar (coordination), Brain stem (speech and swallowing), Sensory (touch and pain), Bowel and bladder functions, Visual, Mental, and Other (includes any other neurological findings due to MS) (Kurtzke JF, 1983).

A "confirmed progression" of EDSS, or "confirmed disease progression" as measured by EDSS score is defined as a 1 point increase from baseline EDSS if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5. In order to be considered a confirmed progression, the change (either 1 point or 0.5 points) must be sustained for at least 3 months. In addition, confirmation of progression cannot be made during a relapse.

"Adverse event" or "AE" means any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not have a causal relationship with the

treatment. An adverse event can therefore be any unfavorable and unintended sign including an abnormal laboratory finding, symptom, or diseases temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

"Gd-enhancing lesion" refers to lesions that result from a breakdown of the blood-brain barrier, which appear in contrast studies using gandolinium contrast agents. Gandolinium enhancement provides information as to the age of a lesion, as Gd-enhancing lesions typically occur within a six week period of lesion formation.

"Magnetization Transfer Imaging" or "MTI" is based on the magnetization interaction (through dipolar and/or chemical exchange) between bulk water protons and macromolecular protons. By applying an off resonance radio frequency pulse to the macromolecular protons, the saturation of these protons is then transferred to the bulk water protons. The result is a decrease in signal (the net magnetization of visible protons is reduced), depending on the magnitude of MT between tissue macromolecules and bulk water. "MT" or "Magnetization Transfer" refers to the transfer of longitudinal magnetization from the hydrogen nuclei of water that have restricted motion to the hydrogen nuclei of water that moves with many degrees of freedom. With MTI, the presence or absence of macromolecules (e.g. in membranes or brain tissue) can be seen (Mehta, 1996; Grossman, 1994).

"Magnetization Resonance Spectroscopy" or "MRS" is a specialized technique associated with magnetic resonance imaging (MRI). MRS is used to measure the levels of different metabolites in body tissues. The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain, (Rosen, 2007) as well as to provide information on tumor metabolism (Golder, 2007).

As used herein "mobility" refers to any ability relating to walking, walking speed, gait, strength of leg muscles, leg function and the ability to move with or without assistance. Mobility can be evaluated by one or more of several tests including but not limited to Ambulation Index, Time 25 foot walk, Six-Minute Walk (6MW), Lower Extremity Manual Muscle Test (LEMMT) and EDSS. Mobility can also be reported by the subject, for example by questionnaires, including but not limited to 12-Item Multiple Sclerosis Walking Scale (MSWS-12). Impaired Mobility refers to any impairment, difficulty or disability relating to mobility.

"T1-weighted MRI image" refers to an MR-image that emphasizes T1 contrast by which lesions may be visualized. Abnormal areas in a T1-weighted MRI image are "hypointense" and appear as dark spots. These spots are generally older lesions.

"T2-weighted MRI image" refers to an MR-image that emphasizes T2 contrast by which lesions may be visualized. T2 lesions represent new inflammatory activity.

The "Six-Minute Walk (6MW) Test" is a commonly used test developed to assess exercise capacity in patients with COPD (Guyatt, 1985). It has been used also to measure mobility in multiple sclerosis patients (Clinical Trials Website).

The "Timed-25 Foot Walk" or "T25-FW" is a quantitative mobility and leg function performance test based on a timed 25-walk. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the patient has reached the 25-foot mark. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. The score for the T25-FW is the average of the two completed trials. This score can be used individually or used as part of the MSFC composite score (National MS Society Website).

One of the central symptoms of multiple sclerosis is fatigue. Fatigue can be measured by several tests including but not limited to decrease of French valid versions of the Fatigue Impact Scale (EMIF-SEP) score, and European Quality of Life (EuroQoL) Questionnaire (EQ5D). Other tests, including but not limited to Clinician Global Impression of Change (CGIC) and Subject Global Impression (SGI), as well as EQ-5D, can be used to evaluate the general health status and quality of life of MS patients.

"Ambulation Index" or "AI" is a rating scale developed by Hauser et al. to assess mobility by evaluating the time and degree of assistance required to walk 25 feet. Scores range from 0 (asymptomatic and fully active) to 10 (bedridden). The patient is asked to walk a marked 25-foot course as quickly and safely as possible. The examiner records the time and type of assistance (e.g., cane, walker, crutches) needed. (Hauser, 1983)

"EQ-5D" is a standardized questionnaire instrument for use as a measure of health outcome applicable to a range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. EQ-5D was developed by the "EuroQoL" Group which comprises a network of international, multilingual, multidisciplinary researchers,

originally from seven centers in England, Finland, the Netherlands, Norway and Sweden. The EQ-5D questionnaire is in the public domain and can be obtained from EuroQoL.

"SF-36" is a multi-purpose, short-form health survey with 36 questions which yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The survey is developed by and can be obtained from QualityMetric, Inc. of Providence, RI.

A "pharmaceutically acceptable carrier" refers to a carrier or excipient that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio. It can be a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the instant compounds to the subject.

It is understood that where a parameter range is provided, all integers within that range, and tenths thereof, are also provided by the invention. For example, "0.1-2.5mg/day" includes 0.1 mg/day, 0.2 mg/day, 0.3 mg/day, etc. up to 2.5 mg/day.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details

EXAMPLE 1: Assessment of Efficacy of Laquinimod Alone or In-Combination With Fingolimod In MOG-induced EAE

In this experiment, MOG-induced EAE Mice were treated with a sub-optimal dose of laquinimod (10mg/kg) alone or with add on fingolimod (0.3mg/kg) to assess the efficacy of laquinimod alone or in combination with fingolimod. MOG-induced Experimental Autoimmune Encephalomyelitis (EAE) in the C57Bl strain of mice is an established EAE model to test the efficacy of candidate molecules for MS treatment.

The dosages were chosen based on known effective dose amounts for laquinimod (0.6 mg/day) and for fingolimod (0.5 mg/day) in humans (FDA News Release, 2010; U.S. Patent Application Publication 2010-0322900). The National Institutes of Health (NIH) provides a table of Equivalent Surface Area Dosage Conversion Factors below (Table 1) which provides conversion factors that account for surface area to weight ratios between species.

Table 1: Equivalent Surface Area Dosage Conversion Factors

	To					
FROM		Mouse 20 g	Rat 150g	Monkey 3kg	Dog 8kg	Man 60kg
	Mouse	1	½	¼	1/6	1/12
	Rat	2	1	½	¼	1/7
	Monkey	4	2	1	3/5	1/3
	Dog	6	4	1 2/3	1	½
	Man	12	7	3	2	1

Accordingly, the data from this mice study is representative of what can be expected in human patients with the treatment of laquinimod and fingolimod at the corresponding human dosages.

Procedure

Disease was induced in all mice by the injection of the encephalitogenic emulsion (MOG/CFA) and intraperitoneal injection of pertussis toxin on the first day and 48 hours later.

- Fingolimod at dose levels of 0.3 (sub optimal) and 1 mg/kg (optimal) were administered by the oral dose, once daily (QD).
- Laquinimod at dose levels of 10 (sub optimal) and 25 mg/kg (optimal) were administered by the oral route, once daily (QD).
- Both fingolimod and laquinimod were administered prophylactic from disease induction – Day 1 until termination of the study.

Induction of EAE:

EAE was induced by subcutaneous injection of encephalitogenic emulsion at a volume of 0.2 ml/mouse in the right flank. On the day of induction, pertussis toxin was injected i.p. at a volume dose of 0.2 ml/mouse. The injection of the pertussis toxin was repeated after 48 hours.

Test Procedure:

Day 0: Subcutaneous injection of MOG into right flank, i.p. injection of Pertussis toxin, beginning of daily laquinimod treatment.

Day 2: i.p. injection of Pertussis toxin.

Day 10: Initiation of scoring of mice for EAE clinical signs.

Day 30: Termination of study.

Materials:

1. Fingolimod
2. Laquinimod
3. Mycobacterium tuberculosis (MT), Difco
4. Pertussis toxin, Sigma
5. MOG 35-55, Mnf Novatide
6. Complete Freund's Adjuvant (CFA), Sigma
7. Saline, Mnf- DEMO S.A
8. Sterile double distilled water (DDW)

Experimental animals:

Healthy, nulliparous, non-pregnant female mice of the C57BL/6 strain were used in the study.

The animals weighed 18-22 grams, and were approximately 8 weeks old on receipt.

The body weights of the animals were recorded on the day of delivery.

Overtly healthy animals were assigned to study groups arbitrarily before treatment commenced.

The mice were individually identified by using ear tags. A color-coded card on each cage gave information including cage number, group number and identification.

EAE induction:

EAE was induced by injecting the encephalitogenic mixture (emulsion) consisting of MOG (150.0 μg/mouse) and CFA containing *M. tuberculosis* (2 mg MT /mL CFA).

A volume of 0.2 ml of emulsion was injected subcutaneously into the flanks of the mice.

Pertussis toxin in 0.2 ml dosage volume was injected intraperitoneally on the day of induction and 48 hours later (total amount will be 0.1 + 0.1 =0.2 μg/mouse).

Study Design: The mice were allocated randomly into 6 groups according to Table 2 below.

Group	Treatment Groups (treatment initiation)	dose/day	Administration Route	Regimen
1	Vehicle	10 ml/kg	Oral, QD	Both fingolimod and laquinimod from Day 1 to 30 daily
2	laquinimod	10 mg/kg	Oral, QD	
2	laquinimod	25mg/kg	Oral, QD	
4	fingolimod	0.3 mg/kg	Oral, QD	
5	fingolimod	1 mg/kg	Oral, QD	
6	laquinimod + fingolimod	10 mg/kg + 0.3 mg/kg	Oral (QD) + Oral (QD)	

Preparation and administration of encephalitogenic emulsion:

Oil portion: 20 mg MT was added to 20 ml CFA to yield 1 + 1 = 2 mg/ml MT).

Liquid portion: 15mg MOG or equivalent was diluted in 10 ml Normal Saline to yield 1.5 mg/ml MOG stock solution.

The emulsion was made from equal parts of oil and liquid portions (1:1) in two syringes connected to each other with Leur lock to yield 0.75 mg/ml and 1 mg/ml MT. The emulsion was transferred to insulin syringe and 0.2 ml was injected to the right flank of each mouse. Dose = 0.15 mg MOG and 0.2 mg MT/mouse.

Preparation and administration of Pertussis toxin:

50 µL Pertussis toxin (200 µg/ml) was added to 19.95 ml saline to yield 500 ng/ml. The pertussis toxin was administered intraperitoneally on the day of encephalitogen injection and 48 hours later (100.0 ng/0.2ml/mouse) - Total 200 ng/mouse.

Preparation and administration of test articles

Fingolimod formulations:

Fingolimod was weighed and sterile DDW was added to yield 0.03 and 0.1 mg/ml for dose levels of 0.3 and 1.0 mg/kg respectively. The mice were administered with the two concentrations of fingolimod (0.03 and 0.1 mg/ml) a volume dose level of 200µl/mouse by the oral route for dose levels of 0.3 and 1.0 mg/kg respectively.

Laquinimod formulations:

A concentration of 1.0 and 2.5 mg/ml laquinimod was prepared in DDW. The test formulations were stored at 2 - 8°C until use in amber colored bottles.

The mice were administered with the two concentrations of laquinimod (1.0 and 2.5 mg/ml) a volume dose level of 200 µl/mouse by the oral route for dose levels of 10 and 25 mg/kg respectively.

Both the fingolimod and the laquinimod formulations were administered from Day 1, once daily (QD).

Six hours interval was maintained daily between administration of laquinimod and fingolimod.

EAE CLINICAL SIGNS: The mice were observed daily from the 10th day post-EAE induction (first injection of MOG) and the EAE clinical signs were scored according to the grades described in the table presented below.

Table 3: Evaluation of the EAE clinical signs

Score	Signs	Description
0	Normal behavior	No neurological signs.
1	Limp tail	Part or the whole tail is limp and droopy.
2	righting reflex	Animal has difficulties rolling onto his feet when laid on its back
3	Hind leg weakness	wobbly walk - when the mouse walks the hind legs are unsteady
4	Hind leg paralysis	The mouse drags its hind legs but is able to move around using its fore legs
5	Full paralysis	The mouse can't move around, it looks thinner and emaciated.
6	Moribund/Death	

All mice with score 1 and above were considered sick. When the first clinical sign appears all mice were given food soaked in water, which was spread on different places on the bedding of the cages.

Interpretation of Results

Calculation of the incidence of disease (Disease ratio)

- The number of sick animals in each group were summed.

- The incidence of disease was calculated as

$$INCIDENCE\ of\ DISEASE = \left(\frac{No.of\ sick\ mice\ in\ treated\ group}{No.of\ sick\ mice\ in\ control\ group} \right)$$

- The percent inhibition according to incidence was calculated as

$$INHIBITION\ (\%) of\ INCIDENCE\ = \left(1 - \frac{Number\ of\ sick\ mice\ in\ treated\ group}{Number\ of\ sick\ mice\ in\ control\ group} \right) \times 100$$

Calculation of the mortality/moribundity rate (mortality ratio)

- The number of dead or moribund animals in each group were summed.
- The mortality of disease was calculated as

$$MORTALITY\ of\ DISEASE = \left(\frac{No.of\ dead\ or\ moribound\ mice\ in\ treated\ group}{No.of\ dead\ or\ moribound\ mice\ in\ control\ group} \right)$$

- -The percent inhibition according to mortality was calculated as

$$INHIBITION\ (\%)\ of\ MORTALITY\ = \left(1 - \frac{Number\ of\ dead\ or\ moribound\ mice\ in\ treated\ group}{Number\ of\ dead\ or\ moribound\ mice\ in\ control\ group} \right) \times 100$$

Calculation of duration of disease

- *The mean duration of disease expressed in days was calculated as*

$$Mean\ Duration = \left(\frac{\Sigma\ Duration\ of\ disease\ \ of\ each\ mouse}{No.of\ mice\ in\ the\ group} \right)$$

Calculation of mean delay in onset of disease

- The mean onset of disease expressed in days was calculated as

$$Mean\ Onset = \left(\frac{\Sigma\ Onset\ of\ disease\ \ of\ each\ mouse}{No.of\ mice\ in\ the\ group} \right)$$

- The mean delay in onset of disease expressed in days was calculated by subtracting the mean onset of disease in control group from test group.

Calculation of the mean maximal score and percent inhibition

- The mean maximal score (MMS) of each group was calculated as

$$MMS = \left(\frac{\Sigma\, Maximal\ Score\ \ of\ ea\,\text{ch}\ mouse}{No.of\ \ mice\ in\,\text{th}\ e\ group} \right)$$

- The percent inhibition according to MMS was calculated as

$$INHIBITION\ (\%)\ of\ MMS = \left(1 - \frac{MMS\ of\ \ treated\ \ group}{MMS\ of\ control\ \ group} \right) \times 100$$

Calculation of the group mean score and percent inhibition

- The daily scores of each mouse in the test group were summed and the individual mean daily score (IMS) was calculated as

$$IMS = \left(\frac{\Sigma\, Daily\ score\ of\ \ mouse}{Observation\ period\ (days)} \right)$$

- The mean group score (GMS) was calculated as

$$GMS = \left(\frac{\Sigma\, IMS\ of\ ea\,\text{ch}\ mouse}{No.of\ \ mice\ in\,\text{th}\ e\ group} \right)$$

- The percent inhibition was calculated as

$$INHIBITION\ (\%)\ of\ GMS = \left(1 - \frac{GMS\ of\ treated\ \ group}{GMS\ of\ control\ \ group} \right) \times 100$$

Results

A summary of the incidence, mortality, Group Mean Score (GMS), duration of the disease, onset of the disease and the activity of each group compared to the vehicle treated control group is shown in the Summarized Table 4. The Clinical profile of the treatment groups are presented graphically in Figure 1.

In groups treated with fingolimod at dose levels of 0.3 mg/kg (sub optimal dose), and 1 mg/kg (optimal dose), 56.3 and 81.3% activity, respectively, was observed according to GMS when compared to the vehicle administered control group.

In groups treated with laquinimod at dose levels of 10 mg/kg (sub optimal dose), and 25 mg/kg (optimal dose), 53.1 and 81.1% activity, respectively, was observed according to GMS when compared to the vehicle administered control group.

The total blocking of EAE in the group treated with fingolimod at sub optimal dose level of 0.3 mg/kg in combination with sub optimal dose of laquinimod (10 mg/kg) exhibited activity superior to optimal dose of fingolimod (1 mg/kg) alone where 81.3% activity was observed and optimal dose of laquinimod (25 mg/kg) alone where 81.1% activity was observed according to GMS when compared to the vehicle administered control group.

Table 4: Test Article: laquinimod and fingolimod alone and in combination

Mortality, incidence, GMS, Duration and Onset.

Treatment	Mortality	Incidence	GMS value	Mean Onset (days)	Duration (days)
Negative Control Vehicle 10 ml/kg	1/15	15/15	3.2 ± 0.6 p < 0.001	9.1 ± 0.9	21.9 ± 0.9
Laquinimod 10 mg/kg	0/15	13/15	1.5 ± 0.8 p < 0.001	17.1± 6.3 p < 0.001	14.1 ± 6.4 p < 0.001
Laquinimod 25 mg/kg	0/15	7/15	0.6 ± 0.8 p < 0.001	22.9 ± 9.0 p < 0.001	8.1 ± 9.0 p < 0.001
Fingolimod 0.3 mg/kg	0/15	13/15	1.4 ± 0.8 p < 0.001	16.0 ± 6.7 p < 0.001	15.0 ± 6.7 p < 0.001
Fingolimod 1 mg/kg	0/15	8/15	0.6 ± 0.8 p < 0.001	21.7 ± 9.3 p < 0.001	7.59 ± 9.1 p < 0.001
Laquinimod + Fingolimod 10 mg/kg + 0.3 mg/kg	0/15	0/15	0.0 ± 0.0 p < 0.001	31.0± 0.0 p < 0.001	0.0 ± 0.0 p < 0.001

Conclusions

In this study, each compound alone showed a dose dependent inhibition of disease severity.

However, while the lower dosages tested (10 mg/kg laquinimod and 0.3 mg/kg fingolimod) were moderately effective individually, the combination of fingolimod and laquinimod when each was

administered at its respective lower dosage was so potent that it completely abrogated disease. This unexpected result suggest that lower and suboptimal dosages of laquinimod and fingolimod can be used in combination to achieve a greater than additive therapeutic result, and provides evidence that such a combination can be used for therapeutic treatment of human MS and CIS patients.

EXAMPLE 2: Assessment of Efficacy of Laquinimod As Add-On Therapy To Fingolimod In Multiple Sclerosis (MS) Patients

Periodic oral administration of laquinimod (p.o. 0.6 mg/day or 1.2 mg/day) as an add-on therapy for a human patient afflicted with a form of MS who is already receiving fingolimod (p.o. 0.5 mg/day) provides a clinically meaningful advantage and is more effective (provides at least an additive effect or more than an additive effect) in treating the patient than when fingolimod is administered alone (at the same dose).

Periodic oral administration fingolimod (p.o. 0.5 mg/day) as an add-on therapy for a human patient afflicted with a form of MS who is already receiving of laquinimod (p.o. 0.6 mg/day or 1.2 mg/day) provides a clinically meaningful advantage and is more effective (provides at least an additive effect or more than an additive effect) in treating the patient than when laquinimod is administered alone (at the same dose).

The add-on therapies also provides efficacy (provides at least an additive effect or more than an additive effect) in treating the patient without undue adverse side effects or affecting the safety of the treatment. As compared to when each agent is administered alone:

1. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in reducing the decrease in brain volume (determined by the percent brain volume change (PBVC)), in multiple sclerosis patients.

2. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in increasing the time to confirmed disease progression (CDP), in multiple sclerosis patients, where CDP is defined as a sustained increase in EDSS of ≥1 point from Baseline for at least 3 months. Progression cannot be confirmed during a relapse.

3. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in reducing abnormalities observed in whole Brain MTR histogram, in multiple sclerosis patients.

4. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in reducing the number of confirmed relapses and therefore the relapse rate, in multiple sclerosis patients.

5. The add-on therapy is also more effective (provides an additive effect or more than an additive effect) in reducing the accumulation of physical disability in multiple sclerosis patients, as measured by the time to confirmed progression of EDSS.

6. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in reducing MRI-monitored disease activity in multiple sclerosis patients, as measured by the cumulative number of T1 Gd-enhancing lesions on T1-weighted images, the cumulative number new T1 hypointense lesions, the cumulative number of new T2 lesions, the cumulative number of new T1 hypointense lesions on T1-weight images (black holes), the number of active (new T2 or GdE-T1) lesions, presence or absence of GdE lesions, change in total volume of T1 Gd-enhancing lesions, change in total volume of T2 lesions, and/or cortical thickness.

7. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in reducing brain atrophy in multiple sclerosis patients.

8. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in reducing the frequency of relapses, the frequency of clinical exacerbation, and the risk for confirmed progression in multiple sclerosis patients.

9. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in increasing the time to confirmed relapse in multiple sclerosis patients.

10. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in improving the general health status (as assessed by the EuroQoL (EQ5D) questionnaire), symptom severity on work (as assessed by the work productivity and activities impairment General Health (WPAI-GH) questionnaire) and quality of life, in multiple sclerosispatients.

11. The add-on therapy is more effective (provides an additive effect or more than an additive effect) in decreasing cerebral dysfunction/cognitive impairment (as assessed by Symbol Digit Modalities Test (SDMT)), in multiple sclerosis patients during the double blind study period.

Administration of laquinimod (p.o., 0.6 mg/day and 1.2 mg/day) as an add-on therapy to fingolimod (p.o., 0.5 mg/day) provides a clinically meaningful advantage and is more effective

(provides an additive effect or more than an additive effect) in delaying the conversion to clinically definite MS in patients presenting a CIS suggestive of MS than when fingolimod is administered alone (at the same dose).

Administration of laquinimod (p.o., 0.6 mg/day and 1.2 mg/day) as an add-on therapy to fingolimod (p.o., 0.5 mg/day) provides a clinically meaningful advantage and is more effective (provides an additive effect or more than an additive effect) in reducing the rate of development of clinically definite MS, the occurrence of new MRI-detected lesions in the brain, the accumulation of lesion area in the brain and brain atrophy in persons at high risk for developing MS, and is more effective in reducing the occurrence of clinically definite MS and preventing irreversible brain damage in these persons than when fingolimod is administered alone (at the same dose).

Administration of fingolimod (p.o., 0.5 mg/day) as an add-on therapy to laquinimod (p.o., 0.6 mg/day and 1.2 mg/day) provides a clinically meaningful advantage and is more effective (provides an additive effect or more than an additive effect) in delaying the conversion to clinically definite MS in patients presenting a CIS suggestive of MS than when laquinimod is administered alone (at the same dose).

Administration of fingolimod (p.o., 0.5 mg/day) as an add-on therapy to laquinimod (p.o., 0.6 mg/day and 1.2 mg/day) provides a clinically meaningful advantage and is more effective (provides an additive effect or more than an additive effect) in reducing the rate of development of clinically definite MS, the occurrence of new MRI-detected lesions in the brain, the accumulation of lesion area in the brain and brain atrophy in persons at high risk for developing MS, and is more effective in reducing the occurrence of clinically definite MS and preventing irreversible brain damage in these persons than when laquinimod is administered alone (at the same dose).

EXAMPLE 3: Assessment of Efficacy of Laquinimod In Combination With Fingolimod In Multiple Sclerosis (MS) Patients

Periodic oral administration of laquinimod (0.6 mg/day or 1.2 mg/day) in combination with fingolimod (p.o., 0.5 mg/day) to a human patient afflicted with relapsing form of multiple sclerosis provides increased efficacy (provides at least an additive effect or more than an additive effect) in treating the patient than when laquinimod is administered alone or when fingolimod is administered alone (at the same dose). The combination therapy also provides efficacy (provides at least an additive effect or more than an additive effect) in treating the patient without undue adverse side effects or affecting the safety of the treatment.

The combination therapy provides a clinically meaningful advantage and is more effective (provides at least an additive effect or more than an additive effect) in treating the patient than when laquinimod or fingolimod is administered alone (at the same dose) in the following manner:

1. The combination therapy is more effective (provides an additive effect or more than an additive effect) in reducing the decrease in brain volume (determined by the percent brain volume change (PBVC)), in multiple sclerosis patients.

2. The combination therapy is more effective (provides an additive effect or more than an additive effect) in increasing the time to confirmed disease progression (CDP), in multiple sclerosis patients, where CDP is defined as a sustained increase in EDSS of ≥1 point from Baseline for at least 3 months. Progression cannot be confirmed during a relapse.

3. The combination therapy is more effective (provides an additive effect or more than an additive effect) in reducing abnormalities observed in whole Brain MTR histogram, in multiple sclerosis patients during.

4. The combination therapy is more effective (provides an additive effect or more than an additive effect) in reducing the number of confirmed relapses and therefore the relapse rate, in multiple sclerosis patients.

5. The combination therapy is also more effective (provides an additive effect or more than an additive effect) in reducing the accumulation of physical disability in multiple sclerosis patients, as measured by the time to confirmed progression of EDSS.

6. The combination therapy is more effective (provides an additive effect or more than an additive effect) in reducing MRI-monitored disease activity in multiple sclerosis patients, as measured by the cumulative number of T1 Gd-enhancing lesions on T1-weighted images, the cumulative number new T1 hypointense lesions, the cumulative number of new T2 lesions, the cumulative number of new T1 hypointense lesions on T1-weight images (black holes), the number of active (new T2 or GdE-T1) lesions, presence or absence of GdE lesions, change in total volume of T1 Gd-enhancing lesions, change in total volume of T2 lesions, and/or cortical thickness.

7. The combination therapy is more effective (provides an additive effect or more than an additive effect) in reducing brain atrophy in multiple sclerosis patients.

8. The combination therapy is more effective (provides an additive effect or more than an additive effect) in reducing the frequency of relapses, the frequency of clinical exacerbation, and the risk for confirmed progression in multiple sclerosis patients.

9. The combination therapy is more effective (provides an additive effect or more than an additive effect) in increasing the time to confirmed relapse in multiple sclerosis patients.

10. The combination therapy is more effective (provides an additive effect or more than an additive effect) in improving the general health status (as assessed by the EuroQoL (EQ5D) questionnaire), symptom severity on work (as assessed by the work productivity and activities impairment General Health (WPAI-GH) questionnaire) and quality of life, in multiple sclerosis patients.

11. The combination therapy is more effective (provides an additive effect or more than an additive effect) in decreasing cerebral dysfunction/cognitive impairment (as assessed by Symbol Digit Modalities Test (SDMT)), in multiple sclerosis patients during the double blind study period.

Administration of laquinimod (p.o., 0.6 mg/day and 1.2 mg/day) in combination with fingolimod (p.o., 0.5 mg/day) provides a clinically meaningful advantage and is more effective (provides an additive effect or more than an additive effect) in delaying the conversion to clinically definite MS in patients presenting a CIS suggestive of MS than when fingolimod is administered alone (at the same dose).

Administration of laquinimod (p.o., 0.6 mg/day and 1.2 mg/day) in combination with fingolimod (p.o., 0.5 mg/day) provides a clinically meaningful advantage and is more effective (provides an additive effect or more than an additive effect) in reducing the rate of development of clinically definite MS, the occurrence of new MRI-detected lesions in the brain, the accumulation of lesion area in the brain and brain atrophy in persons at high risk for developing MS, and is more effective in reducing the occurrence of clinically definite MS and preventing irreversible brain damage in these persons than when fingolimod is administered alone (at the same dose).

References

1. "COPAXONE®" in Physician's Desk Reference, Thompson Reuters – Physician's Desk Reference Inc., Montvale, NJ, 2008, 3110-3113.

2. "FDA approves first oral drug to reduce MS relapses" FDA NEWS RELEASE, Sept. 22, 2010.

3. Alejandro Horga; Xavier Montalban 06/04/2008; Expert Rev Neurother. 2008;8(5):699-714.

4. Barkhof, F. (1999) "MRI in Multiple Sclerosis: Correlation with Expanded Disability Status Scale (EDSS)", Multiple Sclerosis. 5(4):283-286 (Abstract).

5. Berdyshev et al. (2009). "FTY720 inhibits ceramide synthases and up-regulates dihydrosphingosine 1-phosphate formation in human lung endothelial cells.". *Journal of Biological Chemistry* 284 (9): 5467–77.

6. Billich A et al. (2003). "Phosphorylation of the immunomodulatory drug FTY720 by sphingosine kinases". *J Biol Chem* 278 (48): 47408–15.

7. Bjartmar C and Fox RI. (2002) "Pathological mechanisms and disease progression of multiple sclerosis: therapeutic implication", Drugs of Today. 38:7-29.

8. Brex et al., (2002) "A longitudinal study of abnormalities on MRI and disability from multiple sclerosis", N Engl J Med. Jan 17, 2002 346(3):158-64.

9. Brod et al. (2000) Annals of Neurology, 47:127-131.

10. Brück (2011) "Insight into the mechanism of laquinimod action." J Neurol Sci. 2011 Jul 15;306(1-2):173-9.

11. Brunmark C et al., (2002) "The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis", J Neuroimmunology. 130:163-172.

12. Chabot and Yong, Interferon-1b increases IL-10 in a model of T cell - microglia interaction: Relevance to MS, *Neurol.* 2000, 55: 1497-1505.

13. Chabot et al., Cytokine production in T lymphocyte-microglia interaction is attenuated by glatiramer acetate: A mechanism for therapeutic efficacy in multiple sclerosis, *Mult. Scler.*, in press.

14. Clinical Trials Website, article entitled "Study of Fampridine-ER Tablets in Patients With Multiple Sclerosis", retrieved July 10, 2012, <http://clinicaltrials.gov/ct2/show?term=fampridine&cond=multiple+sclerosis&phase=2&rank=7>.

15. Comi et al. (2007) LAQ/5062 Study Group. "The Effect of Two Doses of Laquinimod on MRI-Monitored Disease Activity in Patients with Relapsing-Remitting Multiple Sclerosis: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study", Presented at: 59th Annual Meeting of the American Academy of Neurology; April 28–May 5, 2007; Boston, MA.

16. Compston, Genetic susceptibility to multiple sclerosis, in McAlpine's Mutiple Sclerosis, Matthews, B. ed., London: Churchill Livingstone, 1991, 301-319.

17. Conway and Cohen (2010) "Combination therapy in multiple sclerosis", LancetNeurol, 9:299-308.

18. Costello et al. (2007) "Combination therapies for multiple sclerosis: scientific rationale, clinical trials, and clinical practice", Current Opinion in Neurology, 20:281-285.

19. Dal Canto et al. (1977) Multiple sclerosis. Animal model: Theiler's virus infection in mice. *Am. J. Path.* 88:497-500.

20. De Stefano et al. (1999) "Evidence of early axonal damage in patients with multiple sclerosis", Neurology. 52(Suppl 2):A378.

21. Dunitz, M. Multiple sclerosis therapeutics, Ed. Rudick and Goodkin. London: Taylor & Francis, 1999.

22. Durelli et al. and the Independent Comparison of Interferon (INCOMIN) Trial Study Group. (2002) "Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN)", Lancet. 359:1453-60.

23. EMEA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis (CPMP/EWP/561/98 Rev. 1, Nove.2006).

24. EPAR, Rebif®, Scientific Discussion.

25. Fernández (2007) "Combination therapy in multiple sclerosis", Journal of the neurological sciences, 259:95-103.

26. Filippi et al., Glatiramer acetate reduces the proportion of MS lesions evolving into black holes, *Neurol.*, 2001, 57:731-733.

27. Fischer et al., (1999) "The Multiple Sclerosis Functional Composite measure (MSFC): an integrated approach to MS clinical outcome assessment" Multiple Sclerosis, 5(4):244-250.

28. Fisk et al., (1994) "Measuring the Functional Impact of Fatigue: Initial Validation of Fatigue Impact Scale", Clin Inf Dis. 18 Suppl 1:S79-83.

29. Fisk et al., (1994) "The Impact of Fatigue on Patients with Multiple Sclerosis", Can J Neurol Sci. 21:9-14.

30. Frenández (2007) "Combination therapy in multiple sclerosis", Journal of the neurological sciences, 259:95-103.

31. Frohman et al., (2003) "The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology", Neurology. Sep 9, 2003, 61(5):602-11.

32. Gold (2008) "Combination therapies in multiple sclerosis", J Neurol, 255[Suppl 1]:51-60.

33. Golder W, (2007) "Magnetic resonance spectroscopy in clinical oncology", Onkologie. 27(3): 304–9.

34. Grossman et al., (1994) Magnetization transfer: theory and clinical applications in neuroradiology", RadioGraphics. 14:279-290.

35. Guidance for Industry. *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling, U.S. Dept. Health and Human Svcs., FDA, Ctr. for Drug Eval. and Res., Ctr. For Biologics Eval. and Res., Clin. / Pharm., Nov. 1999 <http://www.fda.gov/cber/gdlns/metabol.pdf>.

36. Gurevich et al. (2010) "Laquinimod suppress antigen presentation in relapsing-remitting multiple sclerosis: in vitro high-throughput gene expression study" (J Neuroimmunol. 2010 Apr 15;221(1-2):87-94. Epub 2010 Mar 27.

37. Guyatt et al. (1985) "The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure", Can Med Assoc J., 132:919-823.

38. Hafler and Weiner, MS: A CNS and systemic autoimmune disease, *Immunol. Today*, 1989, 10:104-107.

39. Hartung et al. (2005) "Significance of neutralizing antibodies to interferon beta during treatment of multiple sclerosis: expert opinions based on the Proceedings of an International Consensus Conference", Eur J Neurol. 12:588-601.

40. Hauser et al. (1983) "Intensive immunosuppression in progressive multiple sclerosis", New Engl J Med. 308:173-180.

41. Hla T, Lee MJ, Ancellin N, Paik JH, Kluk MJ (2001). "Lysophospholipids--receptor revelations". *Science* 294 (5548): 1875–8.

42. Hohlfeld et al. (2000) "The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis", J Neuroimmunol. 107:161-166.

43. Johnson et al., Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group, *Neurol.*, 1995, 45:1268.

44. Kleinschmidt-DeMasters et al. (2005) New England Journal of Medicine, 353:369-379.

45. Kurtzke JF, (1983) "Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS)", Neurology 33(11):1444-1452.

46. Lampert, Autoimmune and virus-induced demyelinating diseases. A review, *Am. J. Path.*, 1978, 91:176-208.

47. Langer-Gould et al. (2005) New England Journal of Medicine, 353:369-379.

48. Lublin FD, Reingold SC (1996) "Defining the clinical course of multiple sclerosis", Neurol. 46:907-911.

49. Martyn, The epidemiology of multiple sclerosis, in McAlpine's Multiple Sclerosis, Matthews, B., ed., London: Churchil Livingstone, 1991, 3-40.

50. McDonald et al., Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann. Neurol.*, 2001, 50:121-127.

51. McDonald, (2001) "Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis" Ann. Neurol. 50:121-127.

52. Mehta et al. (1996) "Magnetization transfer magnetic resonance imaging: a clinical review", Topics in Magnetic Resonance Imaging 8(4):214-30.

53. Miki et al. (1999) "Relapsing-Remitting Multiple Sclerosis: Longitudinal Analysis of MR Images – Lack of Correlation between Changes in T2 Lesion Volume and Clinical Findings", Radiology. 213:395-399.

54. Milo and Panitch (2011) "Combination therapy in multiple sclerosis", Journal of Neuroimmunology, 231(2011):23-31.

55. Moraal et al. (2008) "Subtraction MR Images in a Multiple Sclerosis Multicenter Clinical Trial Setting", Radiology, 250(2):506-514.

56. Multiple sclerosis: its diagnosis, symptoms, types and stages, 2003 <http://www.albany.net/~tjc/multiple-sclerosis.html>.

57. National MS Society Website, retrieved July 10, 2012 <http://www.nationalmssociety.org/for-professionals/researchers/clinical-study-measures/t25-

58. Neuhaus et al. (2003) "Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection", Trends Pharmacol Sci. 24:131-138.

59. Noseworthy et al. (2000) "Multiple sclerosis", N Engl J Med. 343:938-952.

60. Olsson, Immunology of multiple sclerosis, *Curr. Opin. Neurol. Neurosurg.*, 1992, 5:195-202.

61. Panitch et al. for the EVIDENCE (Evidence of Interferon Dose-response: European North American Comparative Efficacy) Study Group and the University of British Columbia MS/MRI Research Group. (2002) "Randomized comparative study of interferon β-1a treatment regiments in MS", The EVIDENCE Trial. Neurology. 59:1496-1506.

62. Parkman, Graft-versus-host Disease, *Ann. Rev. Med.*, 1991, 42: 189-197.

63. Paugh SW, et al. (2006). "Sphingosine and its analog, the immunosuppressant 2-amino-2-(2-[4-octylphenyl]ethyl)-1,3-propanediol, interact with the CB1 cannabinoid receptor.". *Mol Pharmacol.* 70 (1): 41–50.

64. Paugh SW et al. (2003). "The immunosuppressant FTY720 is phosphorylated by sphingosine kinase type 2". *FEBS Lett* 554 (1–2): 189–93.

65. Payne SG, Oskeritzian CA, Griffiths R, Subramanian P, Barbour SE, Chalfant CE, Milstien S, Spiegel S. (2007). "The immunosuppressant drug FTY720 inhibits cytosolic phospholipase A2 independently of sphingosine-1-phosphate receptors.". *Blood* 109 (3): 1077–85. doi:10.1182/blood-2006-03-011437.

66. PCT International Application Publication No. WO 1998/30227, published July 16, 1998.

67. PCT International Application Publication No. WO 2000/05250, published February 3, 2000.

68. PCT International Application Publication No. WO 2000/18794, published April 6, 2000.

69. PCT International Application Publication No. WO 2003/048735, published June 12, 2003.

70. PCT International Application Publication No. WO 2004/103297, published December 2, 2004.

71. PCT International Application Publication No. WO 2006/016036, published November 2, 2006.

72. PCT International Application Publication No. WO 2006/029393, published March 16, 2006.

73. PCT International Application Publication No. WO 2006/029411, published March 16, 2006.

74. PCT International Application Publication No. WO 2006/083608, published August 10, 2006.

75. PCT International Application Publication No. WO 2006/089164, published August 24, 2006.

76. PCT International Application Publication No. WO 2006/116602, published November 2, 2006.

77. PCT International Application Publication No. WO 2007/047863, published April 26, 2007.

78. PCT International Application Publication No. WO 2007/146248, published December 21, 2007, international filing date June 12, 2007.

79. PCT International Application Publication No. WO 2009/070298, published June 4, 2009.

80. PCT International Application Publication No. WO 2011/008274, published January 20, 2011.

81. PCT International Application Publication No. WO 2011/022063, published February 24, 2011.

82. PCT International Application Publication No. WO 2012/051106, published April 19, 2012.

83. Polman et al. (2011) "Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria", Ann N eural, 69:292-302.

84. Polman et al., (2005) "Diagnostic criteria for multiple sclerosis: 2005 revisions to the McDonald Criteria", Annals of Neurology, Volume 58 Issue 6, Pages 840 – 846.

85. Polman et al., (2005) "Treatment with laquinimod reduces development of active MRI lesions in relapsing MS", Neurology. 64:987-991.

86. Poser et al. (1983) "New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols", Annals of Neurology, March 1983, 13(3):227-230.

87. Rodriguez et al. (1987) Theiler's murine encephalomyelitis: a model of demyelination and persistence of virus. *Crit. Rev. Immunol.*, 7:325.

88. Rosen Y, (2007) "The Recent advances in magnetic resonance neurospectroscopy", Neurotherapeutics. 27(3):330-45.

89. RTT News Article dated April 12, 11, entitled "Teva Pharma, Active Biotech Post Positive Laquinimod Phase 3 ALLEGRO Results".

90. Rudick et al. (2006) New England Journal of Medicine, 354:911-923.

91. Rudick, R. (1999) "Disease-Modifying Drugs for Relapsing-Remitting Multiple Sclerosis

and Future Directions for Multiple Sclerosis Therapeutics", Neurotherpatueics. 56:1079-1084.

92. Runström et al. (2002) "Laquinimod (ABR-215062) a candidate drug for treatment of Multiple Sclerosis inhibits the development of experimental autoimmune encephalomyelitis in IFN-β knock-out mice", (Abstract), Medicon Valley Academy, Malmoe, Sweden.

93. Runström et al. (2006) "Inhibition of the development of chronic experimental autoimmune encephalomyelitis by laquinimod (ABR-215062) in IFN-β k.o. and wild type mice" Journal of Neuroimmunology, 173(2006):69-78.

94. Salama et al. (2003) Multiple Sclerosis, 9:28-31.

95. Sanchez, T; Estrada-Hernandez, T; Paik, JH; Wu, MT; Venkataraman, K; Brinkmann, V; Claffey, K; Hla, T (2003). "Phosphorylation and action of the immunomodulator FTY720 inhibits vascular endothelial cell growth factor-induced vascular permeability." *The Journal of biological chemistry* 278 (47): 47281–90.

96. Sandberg-Wollheim et al. (2005) "48-week open safety study with high-dose oral laquinimod in patients", Mult Scler. 11:S154 (Abstract).

97. Sorenson PS. (2006) "Neutralising antibodies to interferon-β – measurement, clinical relevance, and management", J Neurol. 253[Suppl 6]:VI/16-VI/22.

98. Teitelbaum et al., Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide, *Eur. J. Immunol.*, 1971, 1: 242-248.

99. Teitelbaum et al., Suppression of Experimental Allergic Encephalomyelitis with Basic Polymers, *Eur. J. Immunol.*, 1973, 3: 273-279.

100. Teva Press Release dated August 1, 2011, entitled "Results of Phase III BRAVO Trial Reinforce Unique Profile of Laquinimod for Multiple Sclerosis Treatment".

101. The National MS Society (USA), The Disease Modifying Drug Brochure, October 19, 2006.

102. U.S. Patent Application Publication No. 2008-0207526, published August 28, 2008 (Strominger et al.).

103. U.S. Patent Application Publication No. 2010-0322900, published December 23, 2010 (Tarcic et al.).

104. U.S. Patent Application Publication No. 2011-0027219, published February 3, 2011 (Tarcic et al.).

105. U.S. Patent Application Publication No. 2011-0034508, published February 10, 2011 (Liat Hayardeny).

106. U.S. Patent Application Publication No. 2011-0217295, published September 8, 2011 (Haviv and Tarcic).

107. U.S. Patent Application Publication No. 2011-0218179, published September 8, 2011 (Haviv and Tarcic).

108. U.S. Patent Application Publication No. 2011-0218203, published September 8, 2011 (Joel Kaye et al.).

109. U.S. Patent Application Publication No. 2011-0230413, published September 22, 2011 (Suhayl Dhib-Jalbut).

110. U.S. Patent Application Publication No. 2012-0010238, published January 12, 2012 (Fristedt).

111. U.S. Patent Application Publication No. 2012-0010239, published January 12, 2012 (Piryatinsky et al.).

112. U.S. Patent Application Publication No. 2012-0142730, published June 7, 2012 (Tarcic et al.).

113. U.S. Patent No. 3,849,550, issued November 19, 1974 (Teitelbaum et al).

114. U.S. Patent No. 5,800,808, issued September 1, 1998 (Konfino et al).

115. U.S. Patent No. 5,858,964, issued January 12, 1999 (Aharoni et al).

116. U.S. Patent No. 5,981,589, issued November 9, 1999 (Konfino et al).

117. U.S. Patent No. 6,048,898, issued April 11, 2000 (Konfino et al).

118. U.S. Patent No. 6,054,430, issued April 25, 2000 (Konfino et al).

119. U.S. Patent No. 6,077,851, issued Jun 20, 2000 (Bjork et al).

120. U.S. Patent No. 6,214,791, issued April 10, 2001 (Arnon et al).

121. U.S. Patent No. 6,342,476, issued January 29, 2002 (Konfino et al).

122. U.S. Patent No. 6,362,161, issued March 26, 2002 (Konfino et al).

123. U.S. Patent No. 7,566,767, issued July 28, 2009 (Strominger et al.).

124. U.S. Patent No. 7,589,208, issued September 15, 2009 (Jansson et al).

125. U.S. Patent no. 7,884,208, issued February 8, 2011 (Frenkel et al.).

126. U.S. Patent No. 7,989,473, issued August 2, 2011 (Patashnik et al.).

127. U.S. Patent No. 8,008,258, issued August 30, 2011 (Aharoni et al).

128. U.S. Patent No. 8,178,127, issued May 15, 2012 (Safadi et al.).

129. Vollmer et al. (2008) "Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis" Multiple Sclerosis, 00:1-8.

130. Yang et al., (2004) "Laquinimod (ABR-215062) suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF-β in Lewis rats", J. Neuroimmunol. 156:3-9.

131. Yong (2002) "Differential mechanisms of action of interferon-β and glatiramer acetate in MS" Neurology, 59:1-7.

132. Zou et al. (2002) "Suppression of experimental autoimmune neuritis by ABR-215062 is associated with altered Th1/Th2 balance and inhibited migration of inflammatory cells into the peripheral nerve tissue", Neuropharmacology. 42:731.

What is claimed is:

1. A method of treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome comprising periodically administering to the subject an amount of laquinimod and an amount of fingolimod, wherein the amounts when taken together are effective to treat the subject.

2. The method of claim 1, wherein the amount of laquinimod or and the amount of fingolimod when administered together is more effective to treat the subject than when each agent at the same amount is administered alone.

3. The method of claims 1 or 2, wherein the multiple sclerosis is relapsing multiple sclerosis.

4. The method of claim 3, wherein the relapsing multiple sclerosis is relapsing-remitting multiple sclerosis.

5. The method of any one of claims 1-4, wherein the amount of laquinimod and the amount of fingolimod when taken together is effective to reduce a symptom of multiple sclerosis in the subject.

6. The method of claim 5, wherein the symptom is a MRI-monitored multiple sclerosis disease activity, relapse rate, accumulation of physical disability, frequency of relapses, decreased time to confirmed disease progression, decreased time to confirmed relapse, frequency of clinical exacerbation, brain atrophy, neuronal dysfunction, neuronal injury, neuronal degeneration, neuronal apoptosis, risk for confirmed progression, deterioration of visual function, fatigue, impaired mobility, cognitive impairment, reduction of brain volume, abnormalities observed in whole Brain MTR histogram, deterioration in general health status, functional status, quality of life, and/or symptom severity on work.

7. The method of claim 6, wherein the amount of laquinimod and the amount of fingolimod when taken together is effective to decrease or inhibit reduction of brain volume.

8. The method of claim 7, wherein brain volume is measured by percent brain volume change (PBVC).

9. The method of claim 6, wherein the amount of laquinimod and the amount of fingolimod when taken together is effective to increase time to confirmed disease progression.

10. The method of claim 9, wherein time to confirmed disease progression is increased by 20-60%.

11. The method of claim 9, wherein time to confirmed disease progression is increased by at least 50%.

12. The method of claim 6, wherein the amount of laquinimod and the amount of fingolimod when taken together is effective to decrease abnormalities observed in whole Brain MTR histogram.

13. The method of claim 6, wherein the accumulation of physical disability is measured by Kurtzke Expanded Disability Status Scale (EDSS) score.

14. The method of claim 6, wherein the accumulation of physical disability is assessed by the time to confirmed disease progression as measured by Kurtzke Expanded Disability Status Scale (EDSS) score.

15. The method of claims 13 or 14, wherein the subject had an EDSS score of 0-5.5 at baseline.

16. The method of claims 13 or 14, wherein the subject had an EDSS score of 1.5-4.5 at baseline.

17. The method of claims 13 or 14, wherein the subject had an EDSS score of 5.5 or greater at baseline.

18. The method of any one of claims 13-17, wherein confirmed disease progression is a 1 point increase of the EDSS score.

19. The method of any one of claims 13-17, wherein confirmed disease progression is a 0.5 point increase of the EDSS score.

20. The method of claim 6, wherein impaired mobility is assessed by the Timed-25 Foot Walk test.

21. The method of claim 6, wherein impaired mobility is assessed by the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) self-report questionnaire.

22. The method of claim 6, wherein impaired mobility is assessed by the Ambulation Index (AI).

23. The method of claim 6, wherein impaired mobility is assessed by the Six-Minute Walk (6MW) Test.

24. The method of claim 6, wherein impaired mobility is assessed by the Lower Extremity Manual Muscle Test (LEMMT) Test.

25. The method of claim 6, wherein the amount of laquinimod and the amount of fingolimod when taken together is effective to reduce cognitive impairment.

26. The method of claim 25, wherein cognitive impairment is assessed by the Symbol Digit Modalities Test (SDMT) score.

27. The method of claim 6, wherein general health status is assessed by the EuroQoL (EQ5D) questionnaire, Subject Global Impression (SGI) or Clinician Global Impression of Change (CGIC).

28. The method of claim 6, wherein functional status is measured by the subject's Short-Form General Health survey (SF-36) Subject Reported Questionnaire score.

29. The method of claim 6, wherein quality of life is assessed by SF-36, EQ5D, Subject Global Impression (SGI) or Clinician Global Impression of Change (CGIC).

30. The method of claims 28 or 29, wherein the subject's SF-36 mental component summary score (MSC) is improved.

31. The method of any one of claims 28-30, wherein the subject's SF-36 physical component summary sore (PSC) is improved.

32. The method of claim 6, wherein fatigue is assessed by the EQ5D, the subject's Modified Fatigue Impact Scale (MFIS) score or the French valid versions of the Fatigue Impact Scale (EMIF-SEP) score.

33. The method of claim 6, wherein symptom severity on work is measured by the work productivity and activities impairment General Health (WPAI-GH) questionnaire.

34. The method of any one of claims 1-33, wherein laquinimod is laquinimod sodium.

35. The method of any one of claims 1-34, wherein fingolimod is fingolimod hydrochloride.

36. The method of any one of claims 1-35, wherein the laquinimod and/or the fingolimod is administered via oral administration.

37. The method of any one of claims 1-36, wherein the laquinimod and/or the fingolimod is administered daily.

38. The method of any one of claims 1-36, wherein the laquinimod and/or the fingolimod is administered more often than once daily.

39. The method of any one of claims 1-36, wherein the laquinimod and/or the fingolimod is administered less often than once daily.

40. The method of any one of claims 1-39, wherein the amount laquinimod administered is less than 0.6 mg/day.

41. The method of any one of claims 1-40, wherein the amount laquinimod administered is 0.1-40.0 mg/day.

42. The method of claim 41, wherein the amount laquinimod administered is 0.1-2.5 mg/day.

43. The method of claim 42, wherein the amount laquinimod administered is 0.25-2.0 mg/day.

44. The method of claim 43, wherein the amount laquinimod administered is 0.5-1.2 mg/day.

45. The method of claim 41, wherein the amount laquinimod administered is 0.25 mg/day.

46. The method of claim 41, wherein the amount laquinimod administered is 0.3 mg/day.

47. The method of claim 41, wherein the amount laquinimod administered is 0.5 mg/day.

48. The method of claim 41, wherein the amount laquinimod administered is 0.6 mg/day.

49. The method of claim 41, wherein the amount laquinimod administered is 1.0 mg/day.

50. The method of claim 41, wherein the amount laquinimod administered is 1.2 mg/day.

51. The method of claim 41, wherein the amount laquinimod administered is 1.5 mg/day.

52. The method of claim 41, wherein the amount laquinimod administered is 2.0 mg/day.

53. The method of any one of claims 1-52, wherein the amount fingolimod administered is less than 0.5 mg/day.

54. The method of any one of claims 1-53, wherein the amount fingolimod administered is 0.01-2.5 mg/day.

55. The method of claim 54, wherein the amount fingolimod administered is 2.5 mg/day.

56. The method of claim 54, wherein the amount fingolimod administered is 0.01-1 mg/day.

57. The method of claim 56, wherein the amount fingolimod administered is 0.1 mg/day.

58. The method of claim 56, wherein the amount fingolimod administered is 0.25 mg/day.

59. The method of claim 56, wherein the amount fingolimod administered is 0.5 mg/day.

60. The method of any one of claims 1-59, wherein a loading dose of an amount different form the intended dose is administered for a period of time at the start of the periodic administration.

61. The method of claim 60, wherein the loading dose is double the amount of the intended dose.

62. The method of any one of claims 1-61, wherein the subject is receiving laquinimod therapy prior to initiating fingolimod therapy.

63. The method claim 62, wherein the administration of laquinimod substantially precedes the administration of fingolimod.

64. The method of any one of claims 1-61, wherein the subject is receiving fingolimod therapy prior to initiating laquinimod therapy.

65. The method of claims 64, wherein the administration of fingolimod substantially precedes the administration of laquinimod.

66. The method of claim 64, where in the subject is receiving fingolimod therapy for at least 24 weeks prior to initiating laquinimod therapy.

67. The method of claim 66, where in the subject is receiving fingolimod therapy for at least 28 weeks prior to initiating laquinimod therapy.

68. The method of claim 67, where in the subject is receiving fingolimod therapy for at least 48 weeks prior to initiating laquinimod therapy.

69. The method of claim 68, where in the subject is receiving fingolimod therapy for at least 52 weeks prior to initiating laquinimod therapy.

70. The method of any one of claims 1-69, further comprising administration of nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, slow-acting drugs, gold compounds, hydroxychloroquine, sulfasalazine, combinations of slow-acting drugs, corticosteroids, cytotoxic drugs, immunosuppressive drugs and/or antibodies.

71. The method of any one of claims 1-70, wherein the periodic administration of laquinimod and fingolimod continues for at least 3 days.

72. The method claim 71, wherein the periodic administration of laquinimod and fingolimod continues for more than 30 days.

73. The method of claim 72, wherein the periodic administration of laquinimod and fingolimod continues for more than 42 days.

74. The method of claim 73, wherein the periodic administration of laquinimod and fingolimod continues for 8 weeks or more.

75. The method of claim 74, wherein the periodic administration of laquinimod and fingolimod continues for at least 12 weeks.

76. The method of claim 75, wherein the periodic administration of laquinimod and fingolimod continues for at least 24 weeks.

77. The method of claim 76, wherein the periodic administration of laquinimod and fingolimod continues for more than 24 weeks.

78. The method of claim 77, wherein the periodic administration of laquinimod and fingolimod continues for 6 months or more.

79. The method of any one of claims 1-78, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 20%.

80. The method claim 79, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 30%.

81. The method of claim 80, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 50%.

82. The method of claim 81, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by at least 70%.

83. The method of claim 82, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by more than 100%.

84. The method of claim 83, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by more than 300%.

85. The method of claim 84, wherein the administration of laquinimod and fingolimod inhibits a symptom of relapsing multiple sclerosis by more than 1000%.

86. The method of any one of claims 1-85, wherein each of the amount of laquinimod or pharmaceutically acceptable salt thereof when taken alone, and the amount of fingolimod when taken alone is effective to treat the subject.

87. The method of any one of claims 1-85, wherein either the amount of laquinimod or pharmaceutically acceptable salt thereof when taken alone, the amount of fingolimod when taken alone, or each such amount when taken alone is not effective to treat the subject.

88. The method of any one of claims 1-87, wherein the subject is a human patient.

89. A package comprising:

a) a first pharmaceutical composition comprising an amount of laquinimod and a pharmaceutically acceptable carrier;

b) a second pharmaceutical composition comprising an amount of fingolimod and a pharmaceutically acceptable carrier; and

c) instructions for use of the first and second pharmaceutical compositions together to treat a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

90. The package of claim 89, wherein the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in an aerosol, an inhalable powder, an injectable, a liquid, a solid, a capsule or a tablet form.

91. The package of claim 89, wherein the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in a liquid or a solid form.

92. The package of claim 91, wherein the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in capsule form.

93. The package of claim 91, the first pharmaceutical composition, the second pharmaceutical composition, or both the first and the second pharmaceutical composition are in tablet form.

94. The package of claim 93, wherein the tablets are coated with a coating which inhibits oxygen from contacting the core.

95. The package of claim 94, wherein the coating comprises a cellulosic polymer, a detackifier, a gloss enhancer, or pigment.

96. The package of anyone of claims 89-95, wherein the first pharmaceutical composition further comprises mannitol.

97. The package of anyone of claims 89-96, wherein the first pharmaceutical composition further comprises an alkalinizing agent.

98. The package of claim 97, wherein the alkalinizing agent is meglumine.

99. The package of anyone of claims 89-98, wherein the first pharmaceutical composition further comprises an oxidation reducing agent.

100. The package of anyone of claims 89-96, wherein the first pharmaceutical composition is stable and free of an alkalinizing agent or an oxidation reducing agent.

101. The package of claim 100, wherein the first pharmaceutical composition is free of an alkalinizing agent and free of an oxidation reducing agent.

102. The package of anyone of claims 89-101, wherein the first pharmaceutical composition is stable and free of disintegrant.

103. The package of anyone of claims 89-102, wherein the first pharmaceutical composition further comprises a lubricant.

104. The package of claim 103, wherein the lubricant is present in the composition as solid particles.

105. The package of claims 103 or 104, wherein the lubricant is sodium stearyl fumarate or magnesium stearate.

106. The package of anyone of claims 89-105, wherein the first pharmaceutical composition further comprises a filler.

107. The package of claim 106, wherein the filler is present in the composition as solid particles.

108. The package of claims 106 or 107, wherein the filler is lactose, lactose monohydrate, starch, isomalt, mannitol, sodium starch glycolate, sorbitol, lactose spray dried, lactose anhydrouse, or a combination thereof.

109. The package of claim 108, wherein the filler is mannitol or lactose monohydrate.

110. The package of anyone of claims 89-109, further comprising a desiccant.

111. The package of claim 110, wherein the desiccant is silica gel.

112. The package of anyone of claims 89-111, wherein the first pharmaceutical composition is stable and has a moisture content of no more than 4%.

113. The package of anyone of claims 89-112, wherein laquinimod is present in the composition as solid particles.

114. The package of anyone of claims 89-113, wherein the package is a sealed packaging having a moisture permeability of not more than 15 mg/day per liter.

115. The package of claim 114, wherein the sealed package is a blister pack in which the maximum moisture permeability is no more than 0.005 mg/day.

116. The package of claim 114, wherein the sealed package is a bottle.

117. The package of claim 116, wherein the bottle is closed with a heat induction liner.

118. The package of anyone of claims 114-117, wherein the sealed package comprises an HDPE bottle.

119. The package of anyone of claims 114-118, wherein the sealed package comprises an oxygen absorbing agent.

120. The package of claim 119, wherein the oxygen absorbing agent is iron.

121. The package of any one of claims 89-120, wherein the amount of laquinimod in the first composition is less than 0.6 mg.

122. The package of any one of claims 89-121, wherein the amount of laquinimod in the first composition is 0.1-40.0 mg.

123. The package of claim 122, wherein the amount of laquinimod in the first composition is 0.1-2.5 mg.

124. The package of claim 123, wherein the amount of laquinimod in the first composition is 0.25-2.0 mg.

125. The package of claim 124, wherein the amount of laquinimod in the first composition is 0.5-1.2 mg.

126. The package of claim 122, wherein the amount of laquinimod in the first composition is 0.25 mg.

127. The package of claim 122, wherein the amount of laquinimod in the first composition is 0.3 mg.

128. The package of claim 122, wherein the amount of laquinimod in the first composition is 0.5 mg.

129. The package of claim 122, wherein the amount of laquinimod in the first composition is 0.6 mg.

130. The package of claim 122, wherein the amount of laquinimod in the first composition is 1.0 mg.

131. The package of claim 122, wherein the amount of laquinimod in the first composition is 1.2 mg.

132. The package of claim 122, wherein the amount of laquinimod in the first composition is 1.5 mg.

133. The package of claim 122, wherein the amount of laquinimod in the first composition is 2.0 mg.

134. The package of any one of claim 89-133, wherein the amount of fingolimod in the second composition is less than 0.5 mg.

135. The package of any one of claim 89-133, wherein the amount of fingolimod in the second composition is 0.01-2.5 mg.

136. The package of claim 135, wherein the amount of fingolimod in the second composition is 2.5 mg.

137. The package of claim 135, wherein the amount of fingolimod in the second composition is 0.01-1 mg.

138. The package of claim 137, wherein the amount of fingolimod in the second composition is 0.1 mg.

139. The package of claim 137, wherein the amount of fingolimod in the second composition is 0.25 mg.

140. The package of claim 137, wherein the amount of fingolimod in the second composition is 0.5 mg.

141. Laquinimod for use as an add-on therapy or in combination with fingolimod in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome.

142. A pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, wherein the laquinimod and the fingolimod are administered simultaneously, contemporaneously or concomitantly.

143. A pharmaceutical composition comprising an amount of laquinimod and an amount of fingolimod.

144. The pharmaceutical composition of claims 142 or 143, wherein laquinimod is laquinimod sodium.

145. The pharmaceutical composition of any one of claims 142-144, wherein fingolimod is fingolimod hydrochloride.

146. The pharmaceutical composition of any one of claims 142-145, in an aerosol, an inhalable powder, an injectable, a liquid, a solid, a capsule or a tablet form.

147. The pharmaceutical composition of any one of claims 142-145, in a liquid or a solid form.

148. The pharmaceutical composition of claim 147, in capsule form.

149. The pharmaceutical composition of claim 147, in tablet form.

150. The pharmaceutical composition of claim 149, wherein the tablets are coated with a coating which inhibits oxygen from contacting the core.

151. The pharmaceutical composition of claim 150, wherein the coating comprises a cellulosic polymer, a detackifier, a gloss enhancer, or pigment.

152. The pharmaceutical composition of anyone of claims 142-151, further comprising mannitol.

153. The pharmaceutical composition of anyone of claims 142-152, further comprising an alkalinizing agent.

154. The pharmaceutical composition of claim 153, wherein the alkalinizing agent is meglumine.

155. The pharmaceutical composition of anyone of claims 142-154, further comprising an oxidation reducing agent.

156. The pharmaceutical composition of anyone of claims 142-152, which is free of an alkalinizing agent or an oxidation reducing agent.

157. The pharmaceutical composition of claim 156, which is free of an alkalinizing agent and free of an oxidation reducing agent.

158. The pharmaceutical composition of anyone of claims 142-157, which is stable and free of disintegrant.

159. The pharmaceutical composition of anyone of claims 142-159, further comprising a lubricant.

160. The pharmaceutical composition of claim 159, wherein the lubricant is present in the composition as solid particles.

161. The pharmaceutical composition of claims 159 or 160, wherein the lubricant is sodium stearyl fumarate or magnesium stearate.

162. The pharmaceutical composition of anyone of claims 142-161, further comprising a filler.

163. The pharmaceutical composition of claim 162, wherein the filler is present in the composition as solid particles.

164. The pharmaceutical composition of claims 162 or 163, wherein the filler is lactose, lactose monohydrate, starch, isomalt, mannitol, sodium starch glycolate, sorbitol, lactose spray dried, lactose anhydrouse, or a combination thereof.

165. The pharmaceutical composition of claim 164, wherein the filler is mannitol or lactose monohydrate.

166. The pharmaceutical composition of any one of claims 142-165, wherein the amount of laquinimod in the composition is less than 0.6 mg.

167. The pharmaceutical composition of any one of claims 142-166, wherein the amount of laquinimod in the composition is 0.1-40.0 mg.

168. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 0.1-2.5 mg.

169. The pharmaceutical composition of claim 168, wherein the amount of laquinimod in the composition is 0.25-2.0 mg.

170. The pharmaceutical composition of claim 169, wherein the amount of laquinimod in the composition is 0.5-1.2 mg.

171. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 0.25 mg.

172. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 0.3 mg.

173. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 0.5 mg.

174. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 0.6 mg.

175. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 1.0 mg.

176. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 1.2 mg.

177. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 1.5 mg.

178. The pharmaceutical composition of claim 167, wherein the amount of laquinimod in the composition is 2.0 mg.

179. The pharmaceutical composition of any one of claims 142-178, wherein the amount of fingolimod in the composition is less than 0.5 mg.

180. The pharmaceutical composition of any one of claims 142-179, wherein the amount of fingolimod in the composition is 0.01-2.5 mg.

181. The pharmaceutical composition of claim 180, wherein the amount of fingolimod in the composition is 2.5 mg.

182. The pharmaceutical composition of claim 180, wherein the amount of fingolimod in the composition is 0.01-1 mg.

183. The pharmaceutical composition of claim 182, wherein the amount of fingolimod in the composition is 0.1 mg.

184. The pharmaceutical composition of claim 182, wherein the amount of fingolimod in the composition is 0.25 mg.

185. The pharmaceutical composition of claim 182, wherein the amount of fingolimod in the composition is 0.5 mg.

186. Use of an amount of laquinimod and an amount of fingolimod in the preparation of a combination for treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome wherein the laquinimod and the fingolimod are administered simultaneously, contemporaneously or concomitantly.

187. A pharmaceutical composition comprising an amount of laquinimod for use in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome as an add-on therapy or in combination with fingolimod by periodically administering the pharmaceutical composition and the fingolimod to the subject.

188. A pharmaceutical composition comprising an amount of fingolimod for use treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome as an add-on therapy or in combination with laquinimod by periodically administering the pharmaceutical composition and the laquinimod to the subject.

189. A therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises:

a) one or more unit doses, each such unit dose comprising:

i) an amount of laquinimod and

ii) an amount of fingolimod

wherein the respective amounts of said laquinimod and said fingolimod in said unit dose are effective, upon concomitant administration to said subject, to treat the subject, and

b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

190. The therapeutic package of claim 189, wherein the respective amounts of said laquinimod and said fingolimod in said unit dose when taken together is more effective to treat the subject than when compared to the administration of said laquinimod in the absence of said fingolimod or the administration of said fingolimod in the absence of said laquinimod.

191. A pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with multiple sclerosis or presenting a clinically isolated syndrome, which comprises:

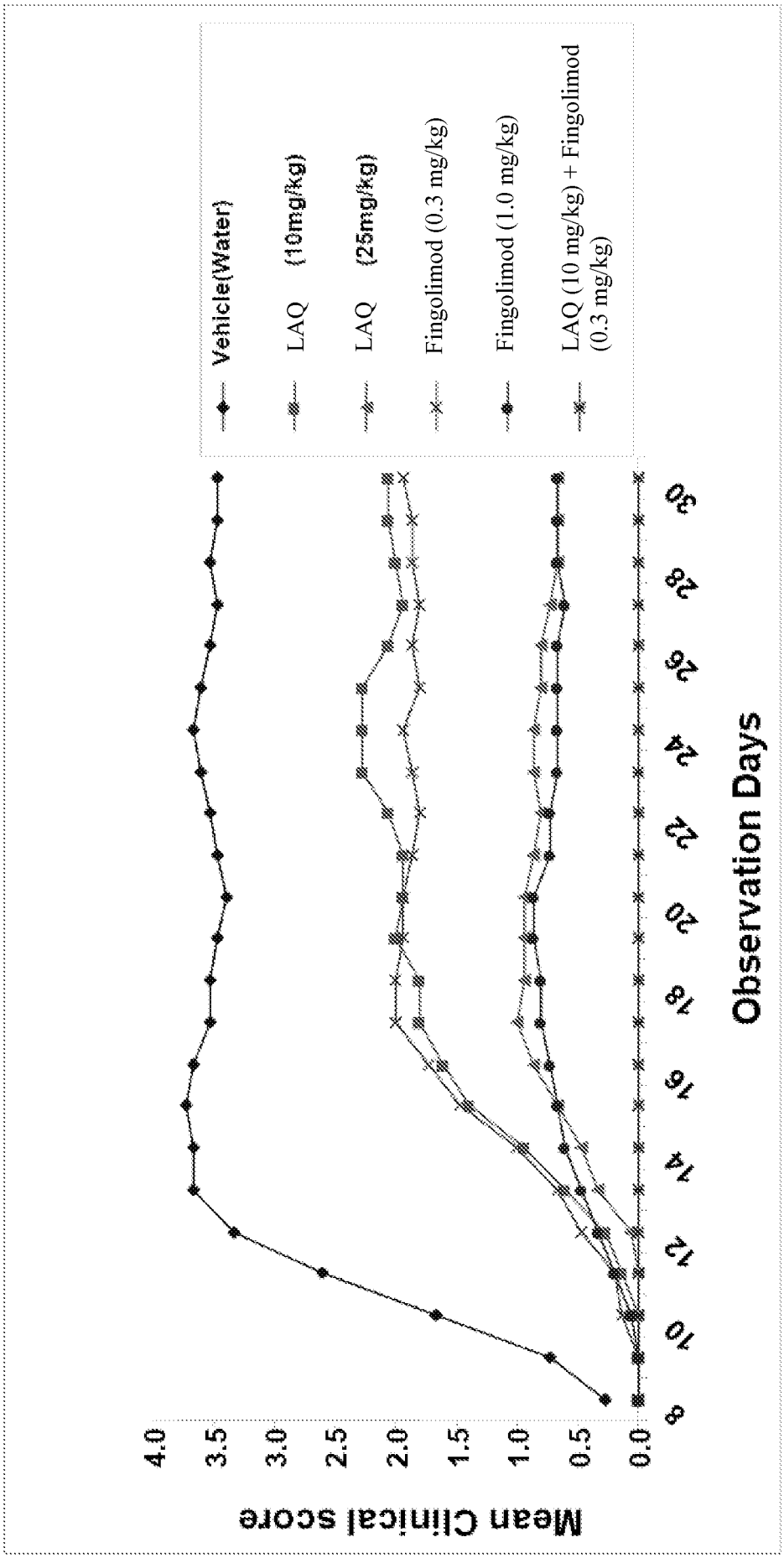
a) an amount of laquinimod;

b) an amount of fingolimod,

wherein the respective amounts of said laquinimod and said fingolimod in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject.

192. The pharmaceutical composition of claim 191, wherein the respective amounts of said laquinimod and said fingolimod in said unit dose when taken together is more effective to treat the subject than when compared to the administration of said laquinimod in the absence of said fingolimod or the administration of said fingolimod in the absence of said laquinimod.

FIGURE 1


Mean Clinical score
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
8
10
12
14
16
18
20
22
24
26
28
30
Observation Days
Vehicle(Water)
LAQ (10mg/kg)
LAQ (25mg/kg)
Fingolimod (0.3 mg/kg)
Fingolimod (1.0 mg/kg)
LAQ (10 mg/kg) + Fingolimod (0.3 mg/kg)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/59733

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-88, 97-140 and 145-185
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/59733

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/47; A61K 31/135 (2012.01)
USPC - 514/312; 514/653
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/47; A61K 31/135 (2012.01)
USPC: 514/312; 514/653 (text search)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 564/355 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar, PatBase
multiple sclerosis, treat$, laquinimod, fingolimod, FTY720, gilenya, combination, therapy, simultaneous, contemporaneous, sequential, administ$, kit, package, single formulation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2010/0260716 A1 (STOHR et al.) 14 October 2010 (14.10.2010) para [0044], [0169]-[0181], [0192], claim 33	1-4, 141-143, 186-188 ---------- 89-96, 144, 189-192
Y	US 2009/0162432 A1 (SAFADI et al.) 25 June 2009 (25.06.2009) para [0062], [0089]	89-96, 144
Y	US 2010/0322900 A1 (TARCIC et al.) 23 December 2010 (23.12.2010) para [0016]	189-192
Y	US 2010/0310547 A1 (SOLIVEN) 09 December 2010 (09.12.2010) para [0013]	89-96

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2012 (27.11.2012)	07 DEC 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)