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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2011 (09.09.2011)

PCT

(10) International Publication Number
WO 2011/109531 A1

(51) International Patent Classification:
A01N 43/42 (2006.01)

(21) International Application Number:
PCT/US2011/026885

(22) International Filing Date:
2 March 2011 (02.03.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/339,375 3 March 2010 (03.03.2010) US

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(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, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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 2011/109531 A1

(54) **Title**: TREATMENT OF RHEUMATOID ARTHRITIS WITH A COMBINATION OF LAQUINIMOD AND METHOTREXATE

(57) **Abstract**: This invention provides a method of treating a subject afflicted with rheumatoid arthritis comprising periodically administering to the subject an amount of laquimmod or pharmaceutically acceptable salt thereof and an amount of methotrexate wherein the amounts when taken together are effective to treat the subject. This invention also provides laqumimod or pharmaceutically acceptable salt thereof for use in combination with methotrexate in treating a subject afflicted with rheumatoid arthritis. This invention also provides a pharmaceutical composition comprising an amount of laquimmod or pharmaceutically acceptable salt thereof and an amount of methotrexate for use in treating a subject afflicted with rheumatoid arthritis.

Dkt. 2609/81058-A-PCT/JPW/GJG/CSS

TREATMENT OF RHEUMATOID ARTHRITIS WITH A COMBINATION OF LAQUINIMOD AND METHOTREXATE

This application claims priority of U.S. Provisional Application No. 61/339,375, filed March 3, 2010, 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 publications cited in the References section in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as of the date of the invention described herein.

Background

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic syndrome characterized by non-specific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures, with or without generalized manifestations. Although its precise etiology has not yet been determined, genetic predisposition has been determined. In addition, environmental factors are thought to play a role. (The Merck Manual, 7th Ed.)

According to the American College of Rheumatology (1987), at least four of the following criteria have to be met before a condition is classified as rheumatoid arthritis (Arnett, 1988): 1) morning stiffness of >1 hour most mornings for at least 6 weeks; 2) arthritis and soft-tissue swelling of >3 of 14 joints/joint groups, present for at least 6 weeks; 3) arthritis of hand joints, present for at least 6 weeks; 4) symmetric arthritis, present for at least 6 weeks; 5) subcutaneous nodules in specific places; 6) rheumatoid factor at a level above the 95th percentile; and 7) radiological changes suggestive of joint erosion.

There is no known cure for rheumatoid arthritis, but many different types of treatment are available to alleviate symptoms and/or modify the disease process. Pharmacological treatment of RA includes nonsteroidal anti-inflammatory drugs and salicylates (NSAIDs), slow-acting drugs, gold compounds, hydroxychloroquine, sulfasalazine, combinations of slow-acting drugs, corticosteroids, and cytotoxic or immunosuppressive drugs. Other forms of treatment include rest, nutrition, exercise, physiotherapy and surgery. (The Merck Manual, 7th Ed.)

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). Laquinimod and its sodium salt form are described, for example, in U.S. Patent No. 6,077,851. The effects of laquinimod in combination with methotrexate on rheumatoid arthritis have not been reported.

Methotrexate

Methotrexate (MTX) is an antimetabolite drug used in treatment of cancer and autoimmune diseases. It acts by inhibiting the metabolism of folic acid via the inhibition of dihydrogolate redutase and blocks DNA synthesis in rapidly proliferate cells. These actions induce immunosuppression.

MTX is sold under the brand names Rheumatrex® and Trexall™. Rheumatrex® and Trexall™ are indicated to treat certain kinds of cancer, psoriasis and rheumatoid arthritis.

Cytotoxic/immunosuppressive drugs including MTX are increasingly used for severe, active RA. These drugs can suppress inflammation and may allow reduction of corticosteroid doses. (The Merck Manual, 7th Ed.)

The recommended dosage for severe rheumatoid arthritis in humans (consensus-based) is: initial 10 to 15 mg orally once weekly, increased by 5 mg/week every 2 to 3 weeks, up to a maximum of 20 to 30 mg/week. The manufacturer's recommended dosage for severe

rheumatoid arthritis in humans is: initial 7.5 mg orally once weekly or 2.5 mg orally every 12 hours for 3 doses once weekly, up to a maximum of 20 mg/week. (Physicians' Desk Reference)

Combination Therapy

The administration of two drugs to treat a given condition, such as rheumatoid arthritis, 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). 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.

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).

Summary of the Invention

This invention provides a method of treating a subject afflicted with rheumatoid arthritis comprising periodically administering to the subject an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate, wherein the amounts when taken together are effective to treat the subject.

This invention also provides laquinimod or pharmaceutically acceptable salt thereof for use in combination with methotrexate in treating a subject afflicted with rheumatoid arthritis.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate for use in treating a subject afflicted with rheumatoid arthritis.

Brief Description of the Drawings

Figure 1: Figure 1 is a graph of Individual Histopathologic Parameters (Six Joint): a bar graph showing the mean scores (of the six joints) for each histopathologic parameter in the Control and Treatment Groups. ("LAQ" indicates Laquinimod, "MTX" indicates methotrexate) (*p≤0.05 student's t-test to vehicle, #p≤0.05 student's t-test to vehicle, n=10/treatment group, n=4/normal control.) The y-axis shows mean±SE individual histopathology parameters (six joints) (scored: 0 – normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe)

The left most bar in each Treatment Group (black) represent inflammation. The bar second from the left in each Treatment Group (light grey) represents pannus. The bar third from the left in each Treatment Group (white) represents cartilage damage, and the bar fourth from the left in each Treatment Group (dark grey) represents bone damage.

Figure 2: Figure 2 is a graph of Six Joint Animal Score: a bar graph showing the total score (sum of scores in individual histopathologic parameters) of the six joints) in the Control and Treatment Groups. ("LAQ" indicates Laquinimod, "MTX" indicates methotrexate) (*p≤0.05 student's t-test to vehicle, #p≤0.05 student's t-test to vehicle, n=10/treatment group, n=4/normal control.) The y-axis shows mean±SE Six Joint Animal Score (sum of individual parameters).

Figure 3: Figure 3 shows the clinical arthritis score progression in each treatment arm (Scores 0-5). (*p≤0.05 student's t-test to vehicle, #p≤0.05 student's t-test to MTX, n=10/treatment group, n=4/normal control.) The y-axis shows mean±SE Clinical Arthritis Score (scored 0-5).

Detailed Description of the Invention

This invention provides a method of treating a subject afflicted with rheumatoid arthritis comprising periodically administering to the subject an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate, wherein the amounts when taken together are effective to treat the subject.

In one embodiment, the amount of laquinimod or pharmaceutically acceptable salt thereof and the amount of methotrexate when taken together is more effective to treat the subject than when each agent is administered alone.

In one embodiment, the amount of laquinimod or pharmaceutically acceptable salt thereof and the amount of methotrexate when taken together is effective to reduce a clinical symptom of rheumatoid arthritis in the subject. In another embodiment, the pharmaceutically acceptable salt of laquinimod is laquinimod sodium.

In one embodiment, the periodic administration of laquinimod or pharmaceutically acceptable salt thereof is effected orally. In another embodiment, the amount of laquinimod administered is 0.0005 - 10 mg/kg/day. In yet another embodiment, the amount of laquinimod administered is 0.1-2.0 mg/day.

In one embodiment, the periodic administration of methotrexate is effected orally. In another embodiment, the amount of methotrexate administered is 0.02 - 1.0 mg/kg/day. In yet another embodiment, the amount of methotrexate administered is 1-3 mg/day.

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 or pharmaceutically acceptable salt thereof and methotrexate substantially eliminates a symptom associated with rheumatoid arthritis. In another embodiment, the periodic administration of

laquinimod or pharmaceutically acceptable salt thereof and methotrexate reduces the severity of a symptom associated with rheumatoid arthritis. In yet another embodiment, the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate reduces the number of joints affected by a symptom associated with rheumatoid arthritis.

In one embodiment, the symptom is inflammation. In another embodiment, the symptom is formation of pannus tissue. In another embodiment, the symptom is cartilage damage. In another embodiment, the symptom is bone resorption.

In one embodiment, the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate reduces proteinuria in the subject. In another embodiment, the proteinuria reduction is measured by 24 hour urine protein, 24 hour protein to creatinine ratio, spot protein to creatinine ratio, 24 hour urine albumin, 24 hour albumin to creatinine ratio, spot albumin to creatinine ratio, or by a urinary dipstick. In yet another embodiment, the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate eliminates urinary sediments.

In one embodiment, each of the amount of laquinimod or pharmaceutically acceptable salt thereof when taken alone, and the amount of methotrexate when taken alone is effective to treat the subject. In another embodiment, either the amount of laquinimod or pharmaceutically acceptable salt thereof when taken alone, the amount of methotrexate when taken alone, or each such amount when taken alone is not effective to treat the subject.

In one embodiment, the subject is receiving methotrexate therapy prior to initiating laquinimod therapy. In another embodiment, the subject initiates periodic methotrexate administration prior to initiating periodic laquinimod administration.

In one embodiment, the administration of the laquinimod or pharmaceutically acceptable salt thereof substantially precedes the administration of methotrexate. In another embodiment, the

administration of methotrexate substantially precedes the administration of laquinimod or pharmaceutically acceptable salt thereof.

In one embodiment, the subject is a mammal. In another embodiment, the mammal is human.

This invention provides a method of treating rheumatoid arthritis in a subject afflicted therewith comprising periodically administering to the subject an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate, wherein the amounts when taken together are effective to treat the rheumatoid arthritis in the subject.

This invention also provides laquinimod or pharmaceutically acceptable salt thereof for use in combination with methotrexate in treating a subject afflicted with rheumatoid arthritis.

This invention also provides a pharmaceutical composition comprising an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate for use in treating a subject afflicted with rheumatoid arthritis.

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

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, "0.2-5 mg/kg/day" includes 0.2 mg/kg/day, 0.3 mg/kg/day, 0.4 mg/kg/day, 0.5 mg/kg/day, 0.6 mg/kg/day etc. up to 5.0 mg/kg/day.

Disclosed is a method of treating a subject afflicted with rheumatoid arthritis using laquinimod with methotrexate which provides a more efficacious treatment than each agent alone. In accordance with the subject invention, administration of laquinimod with methotrexate is particularly effective in combination to treat a subject afflicted with rheumatoid arthritis.

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, "a subject afflicted with rheumatoid arthritis" means a subject who was been affirmatively diagnosed to have rheumatoid arthritis.

As used herein, an "amount" or "dose" of laquinimod as measured in milligrams refers to the milligrams of laquinimod acid present in a preparation, regardless of the form of the preparation.

As used herein, "effective" when referring to an amount of laquinimod and/or methotrexate refers to the quantity of laquinimod and/or methotrexate 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.

As used herein, "substantially eliminates" a symptom associated with rheumatoid arthritis means decreasing the occurrence of that symptom by at least 96%.

As used herein, "treating" encompasses, e.g., inducing inhibition, regression, or stasis of a disorder, or lessening, suppressing, inhibiting, reducing the severity of, eliminating, or ameliorating a symptom of the disorder.

As used herein, "inhibition" of disease progression or disease complication in a subject means preventing or reducing the disease progression and/or disease complication in the subject.

As used herein, a "symptom" associated with rheumatoid arthritis includes any clinical or laboratory manifestation associated with

rheumatoid arthritis and is not limited to what the subject can feel or observe. Inflammation is a symptom of rheumatoid arthritis.

As used herein, an "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.

As used herein, "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.

When referring to dosing, the designation "BID" indicates that the dose is administered twice daily. The designation "QD" indicates that the dose is administered once daily.

The use of laquinimod for rheumatoid arthritis 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 methotrexate (MTX) is significantly more effective for the treatment of rheumatoid arthritis as compared to each agent alone.

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 Application Publication No. 2005/0192315 and PCT International Application Publication No. WO 2005/074899, which are hereby incorporated by reference into this application.

A dosage unit may comprise a single compound or mixtures of compounds thereof. A dosage unit can be prepared for oral dosage forms, such as tablets, capsules, pills, powders, and granules.

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 is preferably 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

Application Publication No. 2005/0192315, PCT International Application Publication Nos. WO 2005/074899, WO 2007/047863, and WO 2007/146248.

General techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 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.

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 The Effects Of Anti-Inflammatory Agents Administered Orally (PO) and Daily (QD) in 35 Day DBA/10lahsd Mouse Semi-Established Type II Collagen Arthritis (MTTC/TV-9)

Introduction

Mice (DBA/1lacJ, 1J or B10R111) reliably develop polyarthritis when immunized against bovine type II collagen (Trentham, 1977) using a variety of methodologies including day 0, day 15, 16 or 21 immunizations with and without concurrent boosting with endotoxin or recombinant IL-1 (Bendele, 2001). The disease that occurs is usually not symmetrical and any combination of paws/joints may be affected. Since caliper measurement of small mouse ankles is challenging, subjective clinical scoring systems are often used in conjunction with histological scoring methods. Treatments can be prophylactic (generally starting on days 16-21) or therapeutic (after observation of lesions) and depending on the immunization protocol used and extent of destruction desired, can extend from 10 days to several weeks. Lesions in affected joints resemble those occurring in rat collagen arthritis biologic agents such as Interleukin-1 receptor antagonist (IL-1ra) and the soluble TNF receptors (Wooley, 1993; Bakker, 1997; Joosten, 1994; Joosten, 1996; Geiger, 1993). Enhancement of disease incidence and severity has been demonstrated in mice immunized with type II collagen and concurrently given cytokines such as IL-1 (Hom, 1991; Hom, 1988).

This study is designed to determine the efficacy of potential anti-inflammatory agents (Laquinimod 0.2, 1, or 5 mg/kg) administered (po, qd) either alone or in combination with methotrexate (MTX) as potential anti-inflammatory agent in inhibiting the inflammation, cartilage destruction and bone resorption associated with semi-established type II collagen arthritis in mice. Mouse type II collagen arthritis is an art-recognized animal model for rheumatoid arthritis in humans (Bendele, 2001).

Here, male DBA/10laHsd mice with semi-established type II collagen arthritis were dosed orally (PO) daily (QD) on study days 18-33 with

vehicle, Laquinimod (0.2, 1, or 5 mg/kg), methotrexate (0.5 mg/kg, MTX), or Laquinimod (0.2 or 1 mg/kg) in combination with MTX (0.5 mg/kg). Mice were terminated on day 34. Efficacy evaluable was based on animal body weights, daily clinical arthritis scores, arthritis scores expressed as area under the curve (AUC), and histopathology (groups 1-3, 5 and 8 only) on fore paws, hind paws, and knees from mice. Histopathology results were expressed as 4 paws, knees only, or 6 joint (knees included). Evaluation of serum anti-type II collagen antibody levels were also performed (groups 1-3, 6 and 8 only). All animals survived to study termination.

Animals

74 Male DBA/1OlaHsd (Harlan Inc.) that were 5-7 weeks old on arrival and weighed approximately 17-22 grams on study day 18 were obtained. Mice were at least 6 weeks at time of first immunization.

Materials: Agents or drugs in vehicle, Type II collagen (Elastin Products), Freund's complete adjuvant (with supplemental M. tuberculosis, 4 mg/ml) (Difco).

General Study Design

1. Animals (10/group for arthritis, 4/group for normal, housed 5/cage), were acclimated for 8 days after arrival that all animals are at least 7 weeks old.

2. Mice were anesthetized with Isoflurane and given 150µl of Bovine Type II collagen in Freund's complete adjuvant injections (Sigma) containing bovine type II collagen (Elastin Products, Owensville, MO) (2 mg/ml) at the base of the tail (D0 and day 21).

3. Mice were randomized by body weight into treatment groups on study day 18.

4. MTX was provided by Bolder BioPATH, Inc. as a 1 mg/ml stock solution purchased from MWI and was prepared as a 0.05 mg/ml solution in 1% CMC for dosing at 10 ml/kg.

5. All dose solutions were prepared to deliver at 10 ml/kg (0.3ml/30g) mouse.

6. Treatment is initiated on study day 18 and continued once daily, every day (po, qd) according to Table 1.

Table 1: Treatment Dosing Schedule

Group	N	Compound	Route	Regimen	Dose level (Mg/kg)	Dose Concentration (mg/ml)
1	4	Naïve	NA	NA	0	0
2	10	Vehicle Disease Control	NA	NA	0	0
3	10	MTX (0.5 mg/kg)	po	QD	0.5	0.05
4	10	Laquinimod	po	QD	0.2	0.02
5	10	Laquinimod	po	QD	1	0.1
6	10	Laquinimod	po	QD	5	0.5
7	10	Laquinimod and MTX (0.5 mg/kg)	po	QD	0.2	0.02
8	10	Laquinimod and MTX (0.5 mg/kg)	po	QD	1	0.1

*For all test groups: n=10, BW=30g, dose vol=10 ml/kg, dose for 17 days

7. During the period of treatment, clinical scores were given for each of the paws (right front, left front, right rear, left rear) according to Table 2.

Table 2: Clinical Scoring Criteria for Fore and Hind Paws

Score	Description
0	normal
1	1 hind or fore paw joint affected or minimal diffuse erythema and swelling
2	2 hind or fore paw joints affected or mild diffuse erythema and swelling
3	3 hind or fore paw joints affected or moderate diffuse erythema and swelling
4	Marked diffuse erythema and swelling, or =4 digit joints affected
5	Severe diffuse erythema and severe swelling entire paw, unable to flex digits

8. On days 21-35, onset of arthritis occurred. Mice were weighed on arthritis days 18, 20, 22, 24, 26, 28, 30, 32, and prior to tissue collection on day 34 (final day).

9. At necropsy, animals from all groups were bled via cardiac puncture for serum and terminated via cervical dislocation. Fore paws, hind paws and knees were removed and placed in 10% NBF. Whole blood was allowed to clot at room temperature for approximately 2 hours before being spun at 13,000 rpm for 8 minutes.

10. Processing of Joints: Following 1-2 days in fixative and then 4-5 days in decalcifier, the joints were processed, embedded, sectioned and stained with toluidine blue and H&E (2 slides per animal). Only fore and hind paws and knees were processed initially (6 joints/mouse).

11. Morphologic Pathology Methods: Histopathology was performed on groups 1-3, 5 and 8 only. After 1-2 days in fixative and 4-5 days in 5% formic acid for decalcification, tissues were trimmed, processed for paraffin embedding, sectioned at 8 µm and stained with toluidine blue (T blue). Hind paws, fore paws, and knees were embedded and sectioned in the frontal plane. Six joints from each animal were processed for histopathology elevation.

12. Tissue Processing and Evaluation:

    a. place joints in decalcifier,

    b. trim joints, wash, process tissues,

    c. embed joints,

    d. section tissues, stain tissues,

    e. histopathologic evaluation, and

    f. data processing, QC, prepare graphs and report.

Histopathologic Scoring Methods for Mouse Joints with Type II Collagen Arthritis

When scoring paws or ankles from mice with lesions of type II collagen arthritis, severity of changes as well as number of individual joints affected must be considered. When only 1-3 joints of the paws or ankles out of a possibility of numerous metacarpal/metatarsal/digit or tarsal/tibiotarsal joints were affected, an arbitrary assignment of a maximum score of 1, 2 or 3 for parameters below (Tables 3-6) was given depending on severity of changes. If more than 3 joints were involved, the criteria below (Tables 3-6) were applied to the most severely affected/majority of joints.

Table 3: Inflammation

Score	Description
0	normal
1	Minimal infiltration of inflammatory cells in synovium and periarticular tissue of affected joints
2	Mild infiltration of inflammatory cells. If referring to paws, generally restricted to affected joints (1-3 affected)
3	Moderate infiltration with moderate edema. If referring to paws, restricted to affected joints, generally 3-4 joints+wrist or ankle
4	Marked infiltration affecting most areas with marked edema, 1 or 2 unaffected joints may be present
5	Severe diffuse infiltration with severe edema affecting all joints and periarticular tissues

Table 4: Pannus

Score	Description
0	normal
1	Minimal infiltration of pannus in cartilage and subchondral bone, marginal zones
2	Mild infiltration with marginal zone destruction of hard tissue in affected joints
3	Moderate infiltration with moderate hard tissue destruction in affected joints
4	Marked infiltration with marked destruction of joint architecture, affecting most joints
5	Severe infiltration associated with total or near total destruction of joint architecture, affects all joints

Table 5: Cartilage Damage

Score	Description
0	normal
1	Minimal: generally minimal to mild loss of toluidine blue staining with no obvious chondrocyte loss or collagen disruption in affected joints
2	Mild: generally mild loss of toluidine blue staining with focal areas of chondrocyte loss and/or collagen disruption in some affected joints
3	Moderate: generally moderate loss of toluidine blue staining with multifocal chondrocyte loss and/or collagen disruption in affected joints, some matrix remains on any affected surface with areas of severe matrix loss
4	Marked: marked loss of toluidine blue staining with multifocal marked (depth to deep zone) chondrocyte loss and/or collagen disruption in most joints, if knee-one surface with total to near total cartilage loss
5	Severe: severe diffuse loss of toluidine blue staining with multifocal severe (depth to tide mark) chondrocyte loss and/or collagen disruption in all joints, if knee-2 or more surfaces with total to near total cartilage loss

Table 6: Bone Resorption

Score	Description
0	normal
1	Minimal: small areas of resorption, not readily apparent on low magnification, rare osteoclasts in affected joints, restricted to marginal zones
2	Mild: more numerous areas of resorption, not readily apparent on low magnification, osteoclasts more numerous in affected joints, restricted to marginal zones
3	Moderate: obvious resorption of medullary trabecular and cortical bone without full thickness defects in cortex, loss of some medullary trabeculae, lesion apparent on low magnification, osteoclasts more numerous in affected joints
4	Marked: Full thickness defects in cortical bone, often with distortion of profile of remaining cortical surface, marked loss of medullary bone, numerous osteoclasts, affects most joints
5	Severe: Full thickness defects in cortical bone and destruction of joint architecture of all joints

For each animal, the inflammation, pannus, cartilage damage and bone damage scores was determined for each of the 6 joints submitted. A sum total (all 6 joints) animal score and a six joint mean animal score was determined as well as sums and means for each of the individual parameters. Data were also expressed as means for paws (4 joints) or knees (2 joints). Parameters for the various groups are then compared to disease control animals.

Statistical Analysis

Clinical data for paw scores (means for animal) were analyzed by determining the area under the dosing curve (AUC) for study days 18-34. For calculation of AUC, the daily mean scores for each mouse were entered into Microsoft Excel and the area between the treatment days after the onset of disease to the final day was computed. Means for each group were determined and the percent inhibition from arthritis controls was calculated by comparing values for treated and normal animals. Statistical analysis of clinical and histopathology data was performed using a Student's t-test with significance set at $p \leq 0.05$.

Percent inhibition of clinical parameters and AUC is calculated using the following formula:

% Inhibition = B/A X 100,

where A = Mean Disease Control - Mean Normal

B = Mean Treated - Mean Normal

Results

This study assesses the effects of anti-inflammatory agents administered po, qd in an animal model for human rheumatoid arthritis. The results indicate that the effect of the combination of laquinimod and methotrexate on rheumatoid arthritis symptoms is significantly more than the additive effect of each agent alone.

Body weight loss due to arthritis was significantly inhibited by treatment with 1 mg/kg Laquinimod + MTX (62% inhibition) as compared to vehicle treated disease controls. Body weight loss for this group was also significantly (69%) inhibited as compared MTX treated mice. Body weight loss for all other treatment groups did not differ significantly from vehicle controls.

Vehicle treated disease control mice had 100% disease incidence by study day 27. Mice treated with 0.2 mg/kg Laquinimod had 100% disease incidence by study day 28. Animals treated with MTX, 1 mg/kg

Laquinimod, or 0.2 mg/kg Laquinimod + MTX had reduced disease incidence of 90% at study termination. Reduced disease incidence was also seen in mice treated with 5 mg/kg Laquinimod (70% incidence) or 1 mg/kg Laquinimod + MTX (60%).

Daily clinical arthritis scores were significantly reduced for mice treated with MTX (*significant days 27-34), 0.2 mg/kg Laquinimod (*d28-34), 1 mg/kg Laquinimod (*d25-34), 5 mg/kg Laquinimod (*d24-34), 0.2 mg/kg Laquinimod + MTX (*d24-34) or 1 mg/kg Laquinimod + MTX (*d24-34) as compared to vehicle controls. Daily clinical scores were also significantly reduced by treatment with 0.2 mg/kg Laquinimod + MTX (*d29-34) or 1 mg/kg Laquinimod + MTX (*d26-34) as compared to mice treated with MTX only. Prior to disease occurrence in the vehicle control group, daily clinical arthritis scores were significantly elevated in mice treated with 0.2 mg/kg Laquinimod (*d23), 1 mg/kg Laquinimod (*d22-24), or 5 mg/kg Laquinimod (*d22-23). (Figure 3)

Clinical arthritis scores expressed as area under the curve (AUC) were significantly reduced for mice treated with MTX (50% reduction), 0.2 mg/kg Laquinimod (32%), 1 mg/kg Laquinimod (52%), 5 mg/kg Laquinimod (69%), 0.2 mg/kg Laquinimod + MTX (82%), or 1 mg/kg Laquinimod + MTX (95%) as compared to vehicle controls. Clinical arthritis scores AUC were also significantly reduced by treatment with 0.2 mg/kg Laquinimod + MTX (65%) or 1 mg/kg Laquinimod + MTX (90%) as compared to MTX treated mice.

Serum analysis for anti-TTC levels was performed on mice from groups 1-3, 6, and 8 only. Serum analysis revealed that vehicle control mice had anti-TTC levels of 27,062.50 units/ml. Serum Anti-TTC level were not significantly affected by treatment with 5 mg/kg Laquinimod, 1 mg/kg Laquinimod + MTX, or MTX as compared to vehicle controls.

Disease control animals had histopathology changes, consistent with those seen in type II collagen induced arthritis, in most joints, with scores ranging from minimal to severe. Microscopic alteration included infiltration of synovium and periarticular tissue with neutrophils and mononuclear inflammatory cells (inflammation), marginal zone pannus and bone resorption and cartilage damage

(proteoglycan loss, chondrocyte death and collagen matrix destruction).

All paw histopathology parameters were significantly reduced toward normal for mice treated with 1 mg/kg Laquinimod (61% reduction of summed scores), 1 mg/kg Laquinimod + MTX (96%), or MTX (46%) as compared to vehicle controls. Treatment with 1 mg/kg Laquinimod + MTX also significantly (93%) reduced all paw histopathology parameters as compared to MTX treated mice.

All knee histopathology parameters were significantly reduced toward normal for mice treated with 1 mg/kg Laquinimod + MTX (97% reduction of summed scores) as compared to vehicle controls. Treatment of this group also significantly (95%) reduced all knee histopathology parameters as compared to MTX treated mice. Treatment with 1 mg/kg Laquinimod significantly reduced knee inflammation (51% reduction), pannus (59%), cartilage damage (62%), and summed knee scores (57%) as compared to vehicle controls.

All six-joint mean histopathology parameters were significantly reduced toward normal for mice treated with 1 mg/kg Laquinimod (60% reduction of summed scores), 1 mg/kg Laquinimod + MTX (96%), or MTX (43%) as compared to vehicle controls. Treatment with 1 mg/kg Laquinimod + MTX also significantly (93%) reduced all six-joint histopathology parameters as compared to MTX treated mice. (Figures 1 and 2)

As shown in Figures 1 and 2, the administration of laquinimod in combination with methotrexate significantly reduced the severity of various symptoms associated with rheumatoid arthritis, including inflammation, pannus, cartilage damage and bone resorption on the six joints of the DBA/1O1aHsd mouse (four paws and two knees) as compared to the control group, the methotrexate only treatment group, and the laquinimod only treatment group.

Figure 1 shows that the administration of laquinimod in combination with methotrexate substantially eliminated pannus and bone damage in the six joints of the test subjects, reducing their mean scores to nearly zero. Figure 2 shows that the administration of laquinimod in

combination with methotrexate substantially eliminated the overall symptoms associates with rheumatoid arthritis in the test subjects, reducing their cumulative score by 96%.

Thus, these results show that administration of laquinimod in combination with methotrexate is substantially more efficacious in treating a subject afflicted with active rheumatoid arthritis than each agent when administered alone. The inventors have surprisingly found that laquinimod and methotrexate work in synergy in the treatment of active rheumatoid arthritis.

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What is claimed is:

1. A method of treating a subject afflicted with rheumatoid arthritis comprising periodically administering to the subject an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate, wherein the amounts when taken together are effective to treat the subject.

2. The method of claim 1, wherein the amount of laquinimod or pharmaceutically acceptable salt thereof and the amount of methotrexate when taken together is more effective to treat the subject than when each agent is administered alone.

3. The method of claims 1 or 2, wherein the amount of laquinimod or pharmaceutically acceptable salt thereof and the amount of methotrexate when taken together is effective to reduce a clinical symptom of rheumatoid arthritis in the subject.

4. The method of any one of claims 1-3, wherein the pharmaceutically acceptable salt of laquinimod is laquinimod sodium.

5. The method of any one of claims 1-4, wherein the periodic administration of laquinimod or pharmaceutically acceptable salt thereof is effected orally.

6. The method of any one of claims 1-5, wherein the amount of laquinimod administered is 0.0005 - 10 mg/kg/day.

7. The method of any one of claims 1-5, wherein the amount of laquinimod administered is 0.1-2.0 mg/day.

8. The method of any one of claims 1-7, wherein the periodic administration of methotrexate is effected orally.

9. The method of any one of claims 1-8, wherein the amount of methotrexate administered is 0.02 - 1.0 mg/kg/day.

10. The method of any one of claims 1-8, wherein the amount of methotrexate administered is 1-3 mg/day.

11. The method of any one of claims 1-10, 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.

12. The method of any one of claims 1-11, wherein the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate substantially eliminates a symptom associated with rheumatoid arthritis.

13. The method of any one of claims 1-11, wherein the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate reduces the severity of a symptom associated with rheumatoid arthritis.

14. The method of any one of claims 1-11, wherein the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate reduces the number of joints affected by a symptom associated with rheumatoid arthritis.

15. The method of any one of claims 12-14, wherein the symptom is inflammation.

16. The method of any one of claims 12-14, wherein the symptom is formation of pannus tissue.

17. The method of any one of claims 12-14, wherein the symptom is cartilage damage.

18. The method of any one of claims 12-14, wherein the symptom is bone resorption.

19. The method of any one of claims 1-18, wherein the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate reduces proteinuria in the subject.

20. The method of claim 19, wherein proteinuria reduction is measured by 24 hour urine protein, 24 hour protein to creatinine ratio, spot protein to creatinine ratio, 24 hour urine albumin, 24 hour albumin to creatinine ratio, spot albumin to creatinine ratio, or by a urinary dipstick.

21. The method of any one of claims 1-20, wherein the periodic administration of laquinimod or pharmaceutically acceptable salt thereof and methotrexate eliminates urinary sediments.

22. The method of any one of claims 1-21, wherein each of the amount of laquinimod or pharmaceutically acceptable salt thereof when taken alone, and the amount of methotrexate when taken alone is effective to treat the subject.

23. The method of any one of claims 1-21, wherein either the amount of laquinimod or pharmaceutically acceptable salt thereof when taken alone, the amount of methotrexate when taken alone, or each such amount when taken alone is not effective to treat the subject.

24. The method of any one of claims 1-23, wherein subject is receiving methotrexate therapy prior to initiating laquinimod therapy..

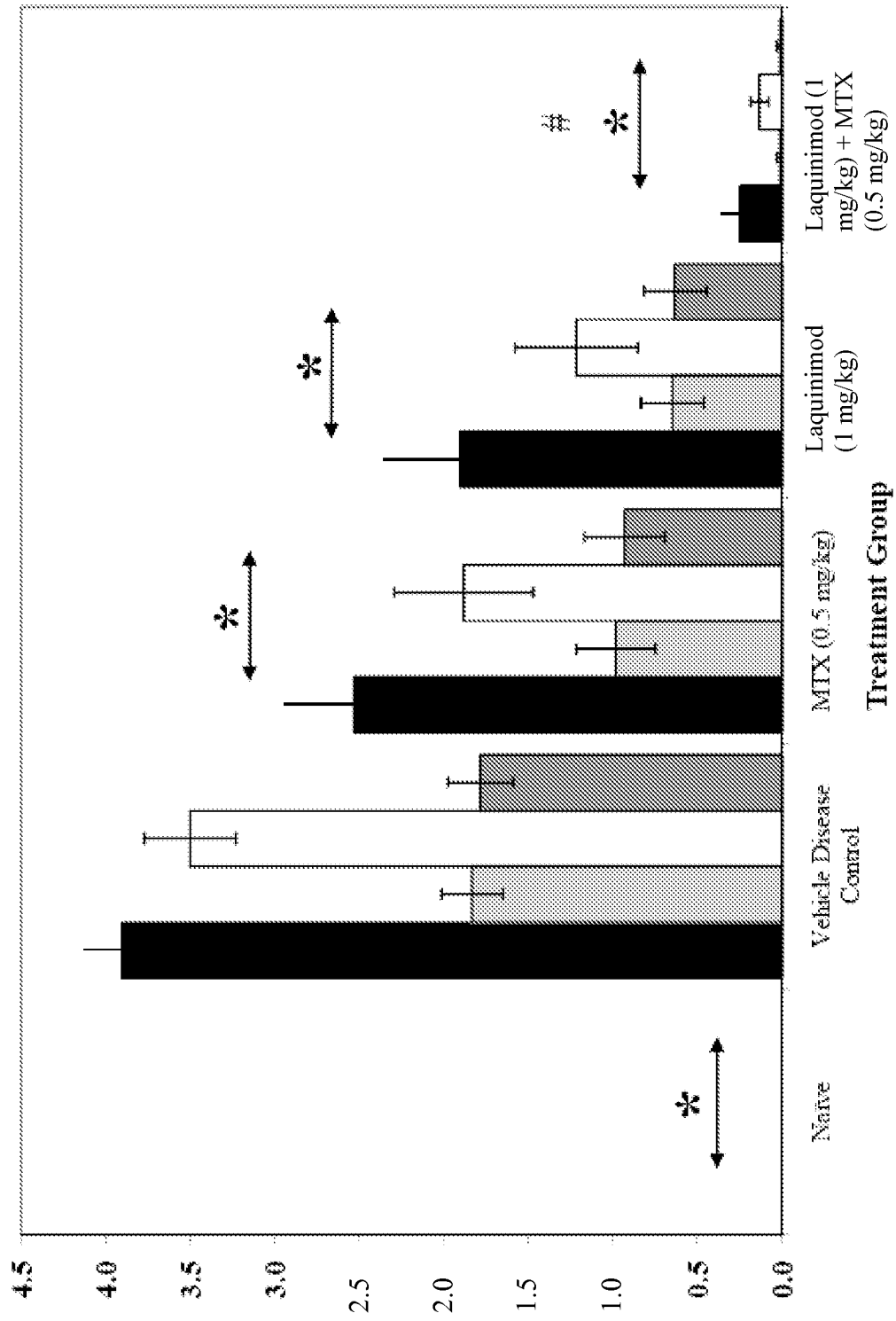
25. The method of any one of claims 1-24, wherein the subject is a mammal.

26. The method of claim 25, wherein the mammal is human.

27. Laquinimod or pharmaceutically acceptable salt thereof for use in combination with methotrexate in treating a subject afflicted with rheumatoid arthritis.

28. A pharmaceutical composition comprising an amount of laquinimod or pharmaceutically acceptable salt thereof and an amount of methotrexate for use in treating a subject afflicted with rheumatoid arthritis.

FIGURE 1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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Naive
Vehicle Disease Control
MTX (0.5 mg/kg)
Laquinimod (1 mg/kg)
Laquinimod (1 mg/kg) + MTX (0.5 mg/kg)
Treatment Group
*
*
*
##

FIGURE 2

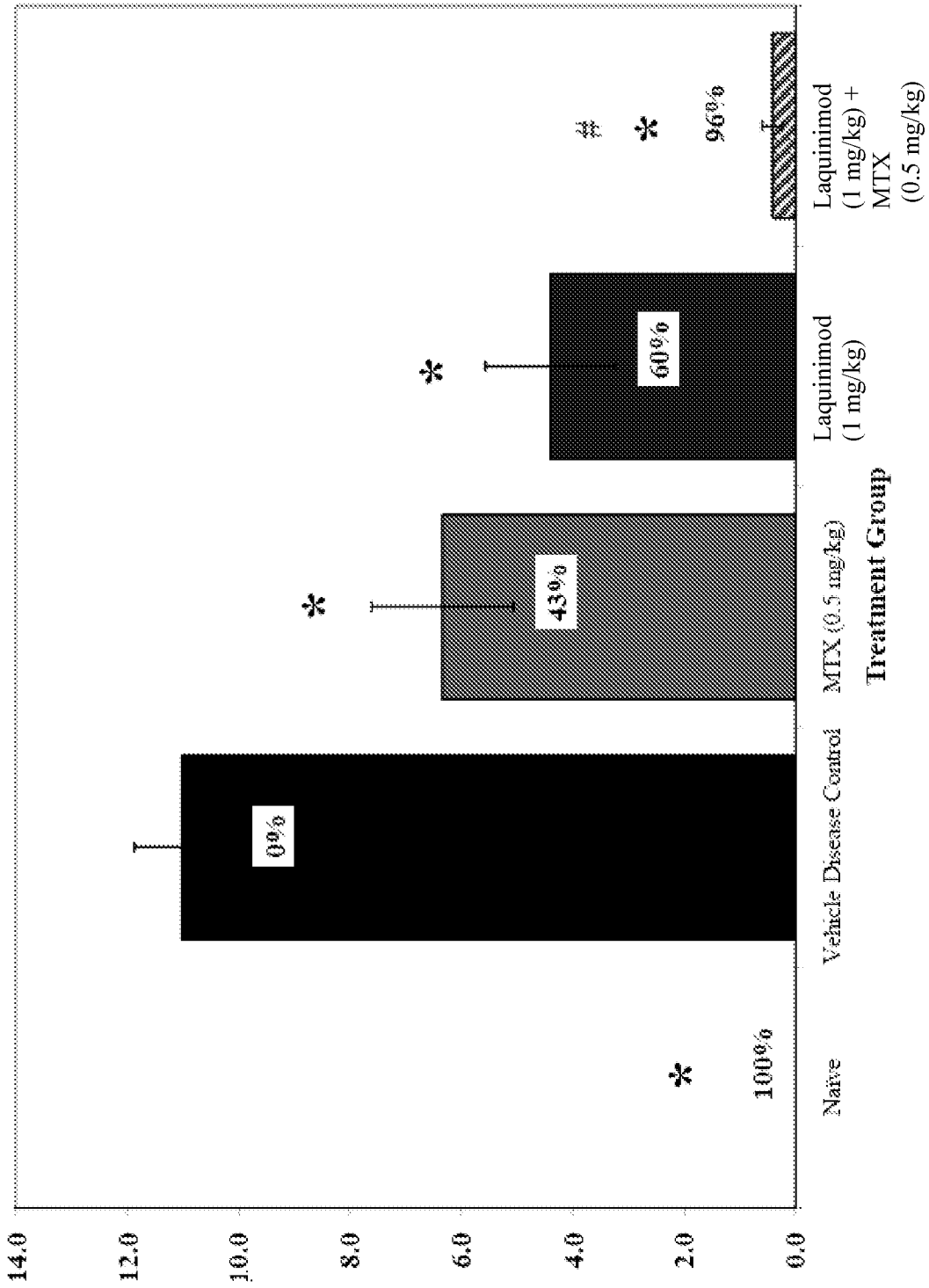
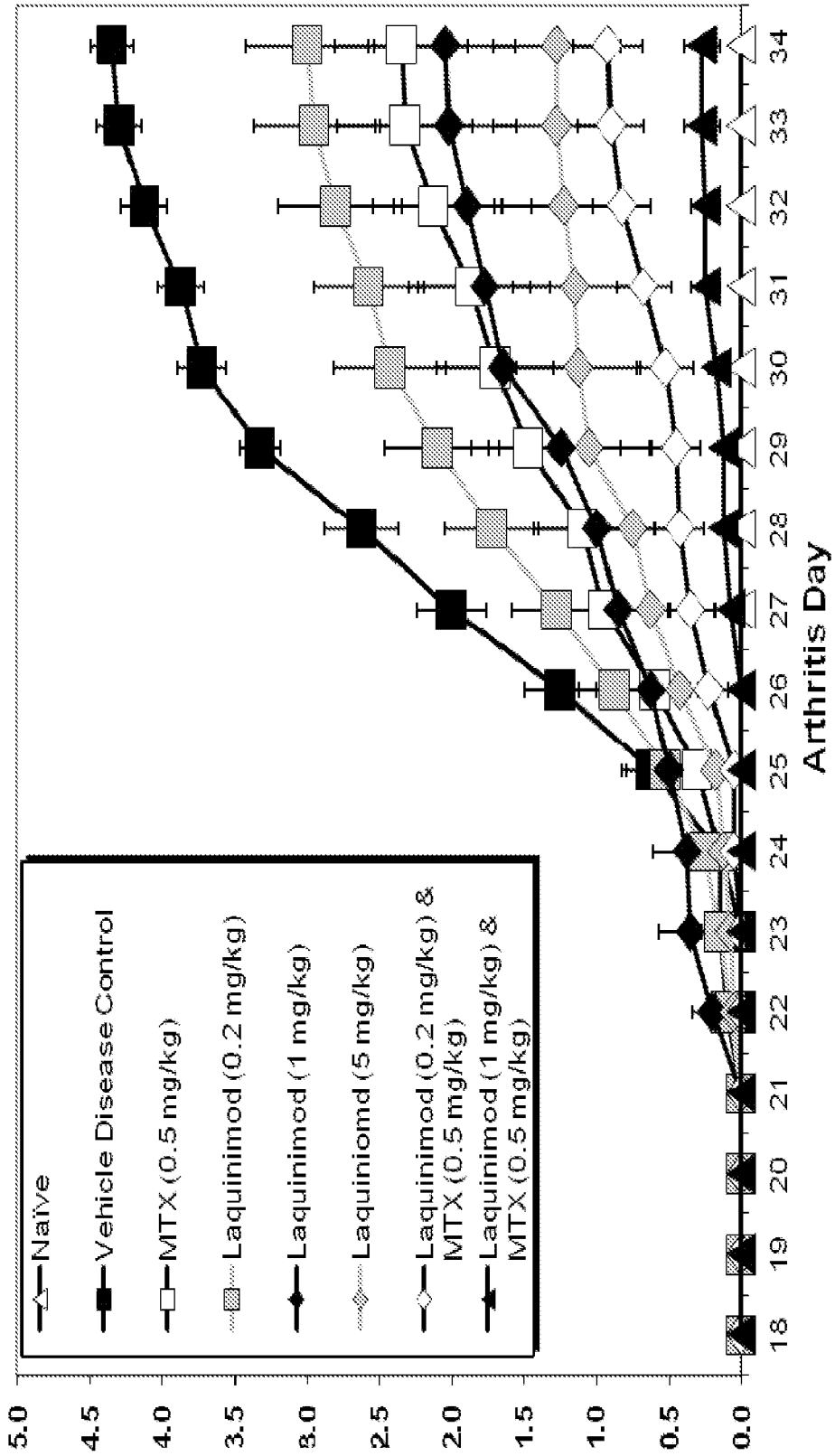

14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
100%
0%
43%
60%
96%
*
*
*
#
Naive
Vehicle Disease Control
MTX (0.5 mg/kg)
Laquinimod (1 mg/kg)
Laquinimod (1 mg/kg) + MTX (0.5 mg/kg)
Treatment Group

FIGURE 3


Naïve
Vehicle Disease Control
MTX (0.5 mg/kg)
Laquinimod (0.2 mg/kg)
Laquinimod (1 mg/kg)
Laquiniomd (5 mg/kg)
Laquinimod (0.2 mg/kg) & MTX (0.5 mg/kg)
Laquinimod (1 mg/kg) & MTX (0.5 mg/kg)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
Arthritis Day

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/26885

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/42 (2011.01)
USPC - 514/312, 514/249
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)
USPC - 514/312, 514/249

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/161, 514/249, 514/251, 514/260, 514/312, 514/235.2, 514/789 (words only)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
*** Databases: WEST (PGPB, USPT, USOC, EPAB, JPAB); Google *** Search Terms Used: Teva, Kaye, Blaugrund, Tarcic, rheumatoid, arthritis, laquinimod, SAIK-MS, ABR-215062, methotrexate, amethopterin, MTX, Rheumatrex, Trexall, pharmaceutical, combination, administering, administered, administeration, non-steroidal, anti-

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/0166348 A1 (Kupper et al.) 10 July 2008 (10.07.2008),especially para [0003], [0226], [0246], [0255], [0278], [0282], [0285],	1, 3 and 27-28
X -- Y	US 2008/0063607 A1 (Tamarkin et al.) 13 March 2008 (13.03.2008), especially para [0013] [0016], [0047], [0173]-[0176], [0342], [0365], [0494]	1, 3 and 27-28 ---------- 2
Y	US 2005/0074451 A1 (Yednock et al.) 07 April 2005 (07.04.2005), especially para [0029], [0369], [0371], [2666]	2
Y	Preiningerova, "Oral laquinimod therapy in relapsing multiple sclerosis," 01 July 2009 (01.07.2009). Expert Opinion on Investigational Drugs, Vol 18, No 7, Pg 985-989, especially pg 986, col 2, para 3	2

☐ 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
07 April 2011 (07.04.2011)	29 APR 2011
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)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/26885

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.: 4-26
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.