



Autoimmunity Research Foundation

3423 Hill Canyon Ave, Thousand Oaks, CA 91360
www.AutoimmunityResearch.org

Directors: Trevor G Marshall PhD, Meg Mangin RN,
Liz Marshall RPh, Belinda Fenter BS
email: Foundation@AutoimmunityResearch.org
phone: +1-805-492-3693
cell: +1-805-300-1679
FAX: +1-877-805-9941

Application for Designation under the Orphan Drug Act (1983), as amended Minocycline Hydrochloride in Treatment of Post-Treatment Lyme Disease Syndrome Sponsor: Autoimmunity Research Inc, Thousand Oaks, California.

In compliance with

Orphan Drug Regulations § 316.20 - Content and format of a request for orphan drug designation.

This sponsor hereby requests designation of an orphan indication for the drug Minocycline Hydrochloride in the indication 'Post-Treatment Lyme Disease Syndrome (PTLDS)', specifically as a bacteriostatic antibiotic to be used symbiotically with the antibiotic Clindomycin Hydrochloride and the ARB Olmesartan Medoxomil, which drugs are specified in two additional designation requests submitted concurrently with this application for designation.

The designated agent for Autoimmunity Research Inc (a California non-profit Corporation) is Dr. Trevor G Marshall,
3423 Hill Canyon Ave
Thousand Oaks, CA, 91360 USA
Phone: (805)492-3693 email: Foundation@AutoimmunityResearch.org

Minocycline Hydrochloride is an 'old antibiotic,' marketed as a generic medication in the USA, with an excellent safety profile.

One manufacturer is:

Ranbaxy Pharmaceuticals Inc. (marketed under ANDA 65-062, Nov 30, 2000)
(US Agent for Ranbaxy Laboratories Limited)

600 College Road East
Princeton, NJ 08540

Further details can be found in NDA 50-649 (8/8/95) Minocycline Hydrochloride Capsules

A description of the rare condition PTLDS follows on pages 2-5, with authoritative references in Appendix 6. The Scientific Rationale is outlined on pages 6-10, with Appendices (including peer-reviewed published papers and a Physician's case summary) in Appendices 1-5. As detailed on pages 2-5, PTLDS is an essentially idiopathic condition for which no therapy has been proven effective. Consequently, patients suffering from PTLDS are desperately in need of an effective intervention.

Based on the success of our Phase 2 study, no sub-setting of this indication is considered necessary.

This sponsor is the real party of interest in the development and marketing of this intervention.

1. Post-Treatment Lyme Disease Syndrome (PTLDS)

The US Centers for Disease Control (CDC) recognizes a disease caused by the organism *Borrelia burgdorferi* with the name “Lyme Disease.” It is a reportable disease, on the basis of the surveillance case definition. At this point we will focus on defining the condition called “Post-Treatment Lyme Disease Syndrome” (PTLDS) and in section 2 we will discuss the prevalence statistics, and demonstrate that it is an Orphan condition.

The CDC Publication “Emerging Infectious Diseases” recently assessed the economic impact of Lyme Disease in the USA. and concluded:

“Lyme disease (LD) is a multisystem, multistage, inflammatory tickborne disorder caused by the spirochete *Borrelia burgdorferi*. LD usually begins with an initial expanding skin lesion, erythema migrans (EM), which may be followed by musculoskeletal, neurologic, and cardiac manifestations in later stages of the disease.”

“ .. almost 5% of all patients had clinically defined late-stage LD.”

Zhang X, Meltzer MI, Pena CA, Hopkins AB, Wroth L, Fix AD: **Economic impact of Lyme disease.** *Emerg Infect Dis.* 2006 Apr;12(4):653-60. PMID 16704815

This less common, “late-stage LD” is more correctly called PTLDS, although a number of pseudonyms have been used from time to time, instead of this rather clumsy acronym. Common pseudonyms include “Chronic Lyme Disease,” “Tertiary Lyme Disease,” and “Post-Lyme Syndrome (PLS).”

In their Brochure “Lyme Disease – A Public Information Guide” the CDC advises:

“Patients treated with antibiotics in the early stages of the infection usually recover rapidly and completely. Most patients who are treated in later stages of the disease also respond well to antibiotics. A few patients may have persistent or recurrent symptoms and may require a second 4-week course of antibiotic treatment. Longer courses of antibiotics have not been shown to be beneficial in patients who have been previously treated and have chronic symptoms. Varying degrees of permanent damage to joints or the nervous system can develop in patients with late Lyme disease. Typically these are patients in whom Lyme disease was unrecognized in the early stages or for whom the initial treatment was inadequate.”

(Available from URL http://www.cdc.gov/ncidod/dvbid/lyme/lyme_brochure.pdf)

PTLDS is a debilitating condition. Although showing clinical signs of infection, patients with PTLDS no longer respond to antibiotics, and their treatment options are essentially non-existent. Klempner, et al, performed a blinded study of both IV and oral antibiotic therapies and found that the PTLDS group did not respond to any of the antibiotics used:

“In summary, patients with chronic musculoskeletal pain, neurocognitive symptoms, or both that persist after antibiotic treatment for well-documented Lyme disease have considerable impairment in their health-related quality of life. The patients enrolled in these studies did not have evidence of persistent infection by *B. burgdorferi*, as judged on the basis of the available microbiologic and molecular methods of detection. There were no significant differences between clinical responses of patients who received intravenous and oral antibiotics for 90 days and those of patients who received placebo.”

Klempner MS, et al: Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med.* 2001 Jul 12;345(2):85-92. PMID:11450676

Steere, et al, concluded:

Post-Lyme Disease syndrome: A small percentage of patients with well-documented Lyme disease may develop disabling musculoskeletal pain, neurocognitive symptoms, or fatigue

along with or soon after symptoms of the infection (S59–S62). This post–Lyme disease syndrome, or chronic Lyme disease (the terms are used interchangeably), which is similar to chronic fatigue syndrome or fibromyalgia, persists for months or years after standard antibiotic treatment of the infection .. In those with post–Lyme disease syndrome, we follow the guidelines for treating chronic fatigue syndrome or Fibromyalgia”

Steere AC, Coburn J, Glickstein L: The emergence of Lyme disease. *J Clin Invest.* 2004 Apr;113(8):1093-101. PMID:15085185

However, A study by Gaudino, et al, showed significant differences between PTLDS and Chronic Fatigue Syndrome (CFS):

“Despite symptom overlap, patients with PLS show greater cognitive deficits than patients with CFS compared with healthy controls. This is particularly apparent among patients with PLS who lack premorbid psychiatric illness”

Gaudino EA, Coyle PK, Krupp LB: Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences. *Arch Neurol.* 1997 Nov;54(11):1372-6. PMID:9362985

A meta-analysis of reported symptoms was published in 2005, which concluded:

“This meta-analysis provides strong evidence that some patients with .. < Post-Lyme Lyme Borreliosis Syndrome> .. have fatigue, musculoskeletal pain, and neurocognitive difficulties that may last for years despite antibiotic treatment”

Cairns V, Godwin J: Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol.* 2005 Dec;34(6):1340-5. PMID:16040645

Although PTLDS is clearly idiopathic, there can no doubt that PTLDS exists, it persists, that it is diagnosable, and it is a totally separate entity from what is commonly known as “Lyme Disease.”

Nothing can confirm this more clearly than the currently recruiting NIH NIAID study on “Evaluation, Treatment, and Follow-Up of Patients with Lyme Disease” which states

“Inclusion Criteria: Clinical diagnosis of active Lyme disease at the time of the initial NIH evaluation based on the CDC case definition”

“Exclusion Criteria: Post treatment Lyme disease syndrome”

(Available from URL <http://clinicaltrials.gov/ct/show/NCT00028080>)

2. PTLDS is an Orphan Disease, and deserves benefits under the Orphan Drug Act.

Lyme Disease (LD) is a reportable disease (on the basis of the surveillance case definition.) Thus the CDC is our best source of prevalence data for this disease. Since both early and late-stage cases of Lyme Disease are reported, the gross total will have to be adjusted by the percentage progressing to PTLDS (late-stage), which the CDC EID publication by Zhang, et al, (cited in Section 1) set at 5% of the total.

Here is the table of CDC reported incidence of LD for the USA, compiled from the CDC reports listed in the box below:

1990	7943	1996	16455	2002	23763
1991	9470	1997	12801	2003	21273
1992	9908	1998	16801	2004	20310
1993	8257	1999	16273		
1994	13043	2000	17730		
1995	11700	2001	17029		

SOURCES OF 1990-2004 INCIDENCE DATA (see Appendix F)

The last cumulative incidence data reported by the CDC was in the year 1999:

“During 1990--1996, the number of reported LD cases was 7943, 9470, 9908, 8257, 13,043, 11,700, and 16,455, respectively. In 1999, 16,273 LD cases were reported .. a 3% decrease from 16,801 cases reported in 1998 and a 21% increase from 12,801 cases reported in 1997”

Available from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5010a1.htm>

“Lyme Disease --- United States, 2000” reported:

“During 2000, a total of 17,730 LD cases”

Available from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5102a3.htm>

In 2002 a compendium was issued “Lyme Disease --- United States, 2001—2002” which stated:

“In 2001, a total of 17,029 cases of LD were reported to CDC .. In 2002, the number of reported cases increased 40% to 23,763 cases”

Available from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5317a4.htm>

While the 2003 CDC report states:

“A total of 21,273 cases of Lyme disease were reported in 2003, approximately 10% fewer cases than were reported in 2002.”

Available from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5254a1.htm>

The CDC’s “Summary of Notifiable Diseases --- United States, 2004” states:

“The number of reported Lyme disease cases decreased for the second consecutive year, with 17% fewer cases reported in 2004 than in 2002. However, much of this decrease can be attributed to modifications of the surveillance systems or reporting mechanisms in two high-incidence states”

(17% less than 2002 = 20,310)

Available from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5353a1.htm>

This makes a cumulative total prevalence for the 15 years 1990-2004 of 222,756 for both LD and PTLDS. The proportion of incidence (5%) would give a best-estimate for PTLDS prevalence at 11,138 over this 15 year interval.

The sources of error in this estimate for prevalence come from

- a. Errors in the incidence numbers reported to the CDC
- b. Errors in the proportion of LD patients progressing to PTLDS (5%)
- c. Uncertainty in the life expectancy for patients who develop PTLDS

We will pursue a worst-case analysis. Using the average US life expectancy of 78 years (Source: National Center for Health Statistics, URL <http://www.cdc.gov/nchs/fastats/lifexpec.htm>) we should scale the past 15 years of prevalence data by the life expectancy and get a (crude) linear estimate of $222756 * ((78/2)/15) * 0.05 = 28,958$

Based on this 28,958 estimate, no reasonable degree of error in the three factors above, or of approximation inherent in linear extrapolation of the CDC prevalence data, could yield a prevalence higher than 200,000

This sponsor therefore submits that PTLDS is an Orphan Disease, and is entitled to the benefits of the Orphan Drug Act (1983) as amended.

3. The Scientific Rationale underpinning this proposed intervention

Bacteria were observed to exist in a Cell Wall Deficient L-form by Emmy Klieneberger-Nobel at the Lister Institute in 1934, but are poorly understood, even to this day. An excellent backgrounder paper which Klieneberger-Nobel wrote in 1951, describing L-forms, has been attached as Appendix 5. It does not form part of this submission, but is included to assist OOPD staff in understanding the following pathogenic description.

This sponsor has described how chronic Th1 immune disease, such as is present in the PTLDS study cohort, is caused by persistent parasitization of the cytoplasm of phagocytes by these L-form bacterial organisms. The bacteria have developed resistance to common antibiotics, even when they are administered by the IV route.

A review was recently published in “Emerging Infectious Diseases,” a journal published by the US CDC, which explores in more depth the plausibility, indeed, the likelihood, that pathogens are responsible for much chronic disease. It concludes:

“Evidence now confirms that noncommunicable chronic diseases can stem from infectious agents. Furthermore, at least 13 of 39 recently described infectious agents induce chronic syndromes .. infectious agents likely determine more cancers, immune-mediated syndromes, neurodevelopmental disorders, and other chronic conditions than currently appreciated.”

O'Connor SM, Taylor CE, Hughes JM: Emerging Infectious Determinants of Chronic Diseases. *Emerg Infect Dis.* 2006 Jul;12(7):1051-7.
(available from URL <http://www.cdc.gov/ncidod/EID/vol12no07/06-0037.htm>)

Although, at first glance, it might seem surprising to find a variety of chronic disease diagnoses which spring from essentially the same pathogenesis, such as the bacterial L-forms which have evolved a mechanism for intra-phagocytic survival, the likelihood of a common pathogenesis becomes much easier to understand when one traces the current epidemic of immune disease back to its roots in the mid-20th Century.

Dr. Marshall's presentations for DMM 2006 at the Karolinska Institute[Appendix 1], and at this sponsor's 2005 and 2006 scientific conferences, identified two of the most-probable causative factors – the commencement of supplementation of the food chain with ‘Vitamin D,’ starting in the 1950's, and the inappropriate use of Beta-lactam antibiotics from the late 1940's. This family of antibiotics has been proven to encourage the development of the bacterial L-forms which are at the root of chronic Th1 immune disease. See, for example:

- Dienes L, et al: The Transformation of Typhoid Bacilli into L Forms under Various Conditions. *J Bacteriol.* 1950 June; 59(6): 755–764. PMID:15436450
- Dienes L: The Isolation of L Type Cultures from Bacteroides with the Aid of Penicillin and Their Reversion into the Usual Bacilli. *J Bacteriol.* 1948 Oct; 56(4): 445–456. PMID:16561593

The secosteroid known as “Vitamin D” was discovered early in the 20th Century, when biochemistry was in its infancy. The first commercial process for the manufacture of “Vitamin D3” was invented at the University of Wisconsin in the 1920's. When the patents expired in the 1940's this substance started being added to the food chain, and it is now prolific. In the latter half of the 20th Century it became very difficult to avoid ingestion of significant concentrations of this substance as it is being added to a wide range of staple foods, ranging from milk products to some brands of orange juice.

In the past, science has accepted, without adequate questioning, the assertion that “Vitamin D” is indeed a vitamin, and that the body needs exogenous supplies of it. In fact, “Vitamin D” is a secosteroid which is manufactured endogenously from 7-dehydrocholesterol. It is at the heart of the immune system, being responsible for activating the VDR nuclear receptor and thence the expression

of, inter alia, Toll-Like-Receptors TLR2 and TLR4, which are at the heart of a phagocyte's recognition of bacterial lipoproteins and lipopolysaccharides. Too much 'Vitamin D' causes the immune system to malfunction, as the functions of the VDR, as well as the Glucocorticoid and alpha-Thyroid receptors, are inhibited by higher concentrations of the D metabolites.

Recently, Molecular Genomics has been illuminating the precise actions of the nuclear receptors, and it has become clear that Vitamin D is not a vitamin, but a steroid hormone. Dr. Marshall's Karolinska presentation[Appendix 1] says, inter alia:

"It is clear that 'Vitamin D' supplementation which raises the 25-D assay above approx 20 ng/ml is immunosuppressive. But nutritionists have chosen this same level as indicating 'deficiency', a terrible mistake"

The mistake arises because the metabolite most frequently used to measure 'Vitamin D deficiency', 25-hydroxyvitamin-D; is down-regulated by the processes in Chronic Th1 immune disease, giving the appearance of "deficiency" when the whole concept of supply-and-demand of this secosteroid is much more complex than science has heretofore envisioned:

Waterhouse JC, Marshall TG, Fenter B, Mangin M, Blaney G: "High levels of active 1,25-dihydroxyvitamin D despite low levels of the 25-hydroxyvitamin D precursor - Implications of dysregulated vitamin D for diagnosis and treatment of Chronic Disease." In *Vitamin D: New Research*. Volume 1. Edited by: Stoltz VD. New York: Nova Science Publishers; 2006. ISBN: 1-60021-000-7 [Appendix 2]

Recently, a Fellow of the Salk Institute, Professor Ronald M. Evans, delivered a CME seminar to FDA CDER. In response to a question of what the impact on Public Health policy should be, given that 'Vitamin D' is actually a secosteroid, rather than a vitamin, he indicated that he would not supplement with 'Vitamin D' in the food chain.

Ronald M. Evans, Ph.D. "Nuclear Receptors in Drug-Drug Interactions and Metabolic Disease" Wednesday, June 7, 2006, 1:30 - 2:30 pm: in White Oak 2205

Dr. Trevor Marshall, a Director of this Foundation, and his colleagues, have published the precise, testable, molecular biology upon which the subject intervention is based[Appendices 1,2,3], and, although radical, it has withstood the test of extensive peer review. There are three keys to the intervention

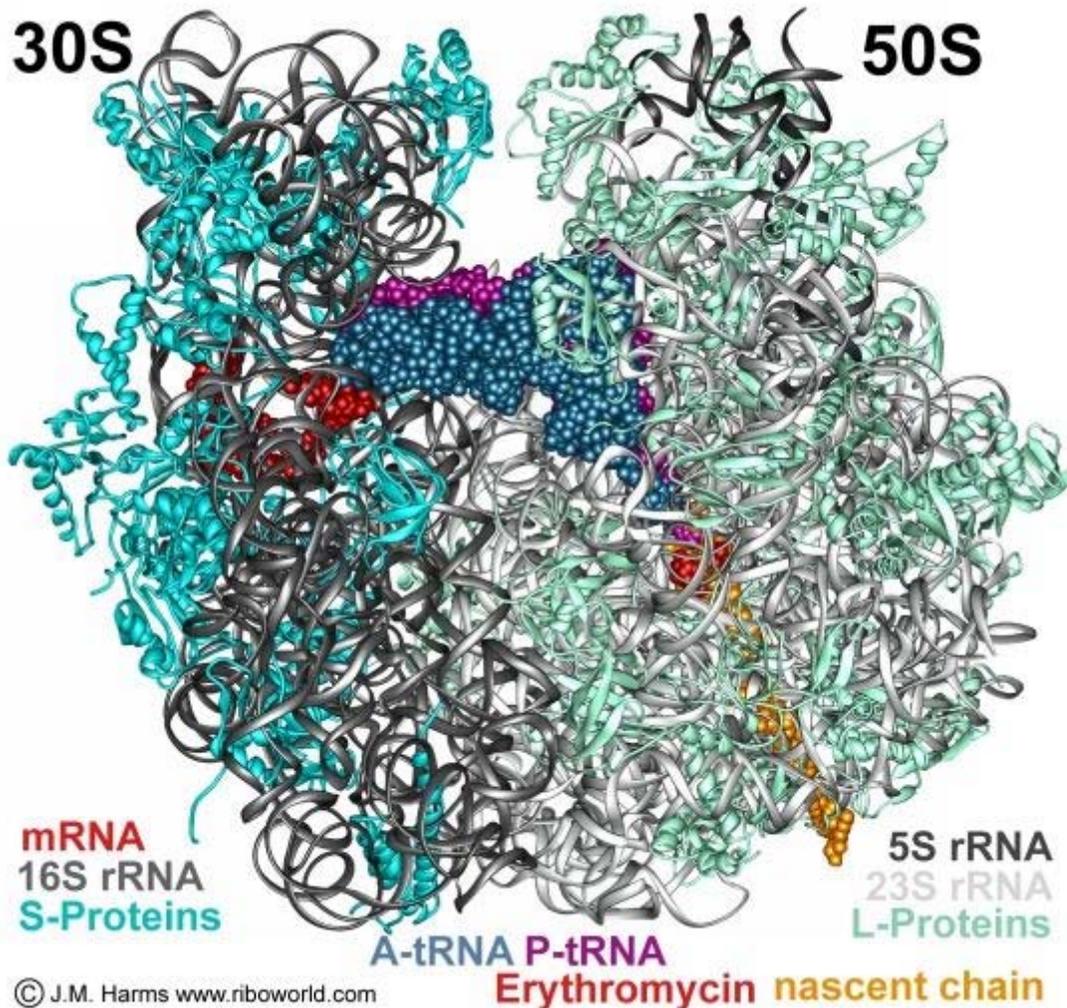
1. Use of the VDR agonist, Olmesartan Medoxomil, to reactivate innate immunity, and
2. Avoiding ingestion of the secosteroid "Vitamin D," and
3. Use of antibiotics which symbiotically block protein synthesis by the bacterial 70S ribosome

Olmesartan Medoxomil is key to this intervention, as it is a VDR Agonist (VDR is one of the nuclear receptors which mediates innate immunity, for more information please see the detailed molecular biology in Appendices 1&3, and Dr. Marshall's FDA CDER "Visiting Professor" presentation):

Marshall TG: Molecular genomics offers new insight into the exact mechanism of action of common drugs - ARBs, Statins, and Corticosteroids. *FDA CDER Visiting Professor presentation*, FDA Biosciences Library, Accession QH447.M27 2006
Available from URL <http://autoimmunityresearch.org/fda-visiting-professor-7mar06.ram>

The immune system is assisted by judicious use of bacteriostatic antibiotics designed to prevent transcription of proteins by the bacterial 70S Ribosome.

The sponsor's research has identified multiple symbiotic antibiotics which are capable of retarding the actions of both the 30S and 50S subunits of the 70S bacterial Ribosome, more effectively overcoming the resistance mechanisms of the intraphagocytic bacteria which cause morbidity in PTLDS.



This diagram shows the RNA and protein strands which make up the 70S bacterial Ribosome of *Thermus thermophilus*, and shows both the 30S and 50S subunits. Demeclocycline and Minocycline bind to inhibit the dark grayish helical structure at the top of the 30S unit, and thus obstruct mRNA advance. A molecule of Erythromycin is shown docked into the protein exit-channel on the 50S side. Azithromycin also binds at this point (so as to obstruct the assembly of proteins) and Clindamycin bonds symbiotically just above, near the t-RNA Peptidyl Transferase Center (PTC)

It is intended to go through to Phase 3 trials using Olmesartan Medoxomil, together with the antibiotics Minocycline Hydrochloride and Clindamycin Hydrochloride . This Application for Designation as an Orphan Product is for Minocycline Hydrochloride, and separate applications have been filed for the bacteriostatic antibiotics Olmesartan Medoxomil and Clindamycin Hydrochloride.

Experts in Europe, Japan, Canada, Australia and the United States have agreed that not only is this intervention plausible, but that the “scientific rationale” is sound.

4. The Sponsor's Phase 2 study demonstrated response.

The rigorous adaptive methodology used in this Observational, Open Label, study has delivered spectacular results. The antibacterial intervention initially devised by Dr. Marshall has been shown to produce a response, indeed, even to induce recovery, in a wide variety of previously idiopathic chronic disease diagnoses (see below).

There are currently 51 patients with PTLDS diagnoses who have been tracked in the study cohort for more than 6 months, some for more than 18 months, and 29 are reporting tangible recovery. Less than 10% have been lost to follow-up.

The levels of 25-hydroxyvitamin-D and 1,25-dihydroxyvitamin-D present in this PTLDS cohort are consistent with the presence of Th1 immune inflammation. Dr. Joyce Waterhouse recently wrote, in the book "Vitamin D: New Research" (using the terminology "Tertiary Lyme Disease" in lieu of PTLDS):

"To date, we have identified a pattern of Vitamin D dysregulation which may include elevated 1,25D, depleted 25D, or an elevated D-ratio in a variety of Th1 diseases, including Rheumatoid Arthritis, Hashimoto's Thyroiditis, Lupus Pernio, Meniere's disease, CFS/ME, Tertiary Lyme Disease, Attention Deficit Hyperactivity Disorder, Sarcoidosis and Fibromyalgia."

Waterhouse JC, Marshall TG, Fenter B, Mangin M, Blaney G: **High levels of active 1,25-dihydroxyvitamin D despite low levels of the 25-hydroxyvitamin D precursor - Implications of dysregulated vitamin D for diagnosis and treatment of Chronic Disease.** In *Vitamin D: New Research*. Volume 1. Edited by: Stoltz VD. New York: Nova Science Publishers; 2006. ISBN: 1-60021-000-7)[Appendix 2]

At this sponsor's recent scientific conferences in Chicago, 2005 and Los Angeles, 2006, many of the participating physicians gathered to validate the response data, discuss the past successes, and future directions, of this innovative, adaptive study. DVD transcripts of the presentations and panels at the Chicago 2005 Conference were supplied to OOPD as part of designation application 05-2131, and additional copies, as well as copies of the 2006 DVD transcript, are available upon request.

This sponsor's extensive Phase 2 clinical study of the proposed intervention in PTLDS uses modalities espoused by Dr. Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs, HHS/FDA, in a speech before the 2006 Conference on Adaptive Trial Design, Washington, DC. July 10, 2006

"The good news is we are already seeing a lot of interest in adaptive approaches, especially in early-stage clinical trials .. Ultimately, technology enables advances in trial design, but it is the creativity of people that really moves things forward .. By working together, I am confident that we can develop better science about how to test new drugs, and in turn, better science on how to prescribe them."

(transcript available from the FDA, URL <http://www.fda.gov/oc/speeches/2006/trialdesign0710.html>)

This Foundation consequently looks forward to working together with FDA OOPD when this designation has been granted, as we move forward with the planning of the Phase 3 studies.

5. Summary

There is clearly a pressing need for an effective intervention for patients with PTLDS, as all previous attempts to treat this orphan disease have failed, and the effects of the disease are debilitating.

This sponsor is therefore requesting designation of Minocycline Hydrochloride as an antibacterial agent in PTLDS, specifically as an agent which activates the innate immune system, to be used symbiotically with the antibiotic Clindamycin Hydrochloride and Olmesartan Medoxomil, which drugs are specified in two designation requests submitted concurrently with this application for designation.

To simplify OOPD's assessment task, given that this is merely an application for designation, and not approval, we have submitted a PTLDS case summary from an expert Physician, Dr. Greg Blaney, of British Columbia, Canada [Appendix 4].

This case study shows that the intervention for which designation is being sought arrested the advance of disease processes. Indeed, the subject patient's renewed performance at Dental School, and in the workplace, attest to the apparent effectiveness of the intervention. The subject patient had failed to respond to conventionally available therapies for PTLDS, including the customary antibiotic therapies.

Please do not hesitate to phone the Foundation at (805)492-3693,
or write to us by email using Foundation@AutoimmunityResearch.org
or FAX us at (877)805-9941,
if we can be of any assistance with your understanding of anything in this application.

Sincerely
/s/ The Board of Directors, Autoimmunity Research Inc,
25 July 2006

/per/ designated officer: Trevor G Marshall, PhD, Director

TABLE OF APPENDICES

Appendix 1:

Marshall TG: VDR Nuclear Receptor Competence is the Key to Recovery from Chronic Inflammatory and Autoimmune Disease. Abstract presentation, Days of Molecular Medicine, 2006. Available from URL <http://autoimmunityresearch.org/karolinska-handout.pdf>

Appendix 2:

Waterhouse JC, Marshall TG, Fenter B, Mangin M, Blaney G: "High levels of active 1,25-dihydroxyvitamin D despite low levels of the 25-hydroxyvitamin D precursor - Implications of dysregulated vitamin D for diagnosis and treatment of Chronic Disease." In *Vitamin D: New Research*. Volume 1. Edited by: Stoltz VD. New York: Nova Science Publishers; 2006. ISBN: 1-60021-000-7

Appendix 3:

Marshall TG, Lee RE, Marshall FE: Common angiotensin receptor blockers may directly modulate the immune system via VDR, PPAR and CCR2b. *Theor Biol Med Model*. 2006 Jan 10;3(1):1. Available from URL <http://www.tbiomed.com/content/3/1/1>

Appendix 4:

PTLDS case summary from expert Physician, Dr. Greg Blaney, of British Columbia, Canada.

Appendix 5:

KLIENEBERGER-NOBEL E: Filterable forms of bacteria. *Bacteriol Rev*. 1951 Jun;15(2):77-103. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=440979>

Appendix 6:

"appended authoritative references, to demonstrate that the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States" to be read in conjunction with page 4 of this application for designation.

Case Study, Post-Treatment Lyme Disease Syndrome
Dr. Greg Blaney,
Vancouver, British Columbia, Canada
July 24, 2006

Patient: RW, male, DOB – August 1, 1983
Occupation: University Student, Dentistry

History:

Patient seeing GP for strep & mono & acne (Blackshaw), specialist for shoulder (Gordon)

November 28, 2004 – weight training injury to left shoulder, sore for several weeks, then became asymptomatic

December 18, 2004 – developed sore throat during time of high stress due to exams

December 24, 2004 – diagnosed with strep throat & prescribed amoxicillin

December 27, 2004 – low CD4 count, diagnosed with infectious mononucleosis

January 3, 2005 – developed severe bilateral shoulder pain with increased intensity during sleeping hours and necessitating use of Tylenol #3. After several days, right shoulder pain discontinued

January 8, 2005 – prescribed Naproxen for pain with no benefit

January 13, 2005 – developed gastrointestinal symptoms, discontinued Naproxen, later diagnosed as infective in origin

January-mid, 2005 – left shoulder pain changed from sharp & severe to dull pain with movement, associated with significant loss of strength, notably with biceps curl and overhead shoulder press; placing steering lock mechanism on steering wheel and wrapping towel around body

February, 2005 – dull pain persists, no change in strength despite extensive rehabilitation exercise and T.E.N.S. therapy

March 30, 2005 – X-ray of shoulder showed no abnormalities, started on Accutane 40 for acne

Referred for first examination, April 8, 2005

Positive findings:

Marked atrophy of left supraspinatus & infraspinatus muscles, absent left biceps deep tendon reflex, enlarged left cervical lymph nodes

Lab results:

Hgb: 171 g/L **High** (range 133-165)

RBC: 5.75 tera/L **High** (range 4.2-5.4)

WBC: 4.7 giga/L **Low Normal**

MCV: 85 fl

Platelets: 185 giga/L

WBC Differential

Neutrophils: 2.4 giga/L **Low Normal**

Lymphocytes: 1.6 giga/L

Monocytes: 0.6 giga/L

Eosinophils : 0.0 giga/L

Basophils : 0.0 giga/L

CK: 97 U/L

TSH: 2.0 mU/L

25OH Vitamin D: 100 nmol/L

125OH Vitamin D: 150 pmol/L

Serology, BCCDC & CDC, National

EBV capsid antigen IgM, EIA – reactive

Bartonella henselae, IFA-IgG – unsatisfactory, non-specific fluorescence observed

Rickettsia rickettsii, IFA-IgG – 1:32

Anaplasma phagocytophilia, IFA-IgG: <1:32; WB-IgG: non-reactive

Borrelia burgdorferi, ELISA IgM/IgG: reactive

Borrelia burgdorferi, WB IgM: reactive

Borrelia burgdorferi, WB IgG: non-reactive

Neurological Consultation

Left infraspinatus weakness, 4/5

Left supraspinatus weakness suspected with strong deltoid likely compensating

Left biceps, slight weakness, graded 5-/5

Nerve conduction studies – normal left arm sensory & motor conductions

Needle electromyography – grade 3+ denervation in left supraspinatus & infraspinatus muscles with no motor units recruited in these muscles; left deltoid (also C5 innervated) was normal; left triceps & brachioradialis normal

Neurological Diagnosis:

Acute brachial neuritis affecting primarily left suprascapular nerve

Therapy

Doxycycline 200 mg BID, mid April to mid May

Response to therapy

No significant Jarisch-Herxheimer reaction

conversion to WB seronegative post Abx.

Lab tests, May 5, 2005

Hgb: 164 **High Normal** (range 133-165)

RBC: 5.51 **High** (range 4.2-5.4)

WBC: 6.4

Platelets: 167

Neutrophils: 3.6

Lymphocytes: 2.0

Monocytes: 0.7

Eosinophils: 0.1

Basophils: 0.0

AST: 44 U/L **High (range 15-35)**

ALT: 49

GGT: 15

Lab tests, July 6, 2005

Hgb: 158

RBC: 5.15

WBC: 5.0

Platelets: 195
Neutrophils 2.3
Lymphocytes: 2.0
Monocytes: 0.6
Eosinophils: 0.1
Basophils: 0.0

LDH: 416
CK: 146

Serology

Borrelia burgdorferi, ELISA: reactive
Borrelia burgdorferi, WB-IgG- non-reactive
Borrelia burgdorferi, WB-IgM – non-reactive
Rickettsia rickettsii, IFA-IgG – 1:32

Neurological re-assessment, August 19, 2005
No change in denervation pattern or severity

Clinical re-assessment, September 15, 2005

No change in strength left arm, several episodes of otitis media, fatigue, poor concentration, comprehension, 'brain fog', anxiety concerning returning to studies, 1st year dental college
No significant change in muscle mass of left infraspinatus or supraspinatus muscles

Lab tests, September 22, 2005

25OHD: 95 nmol/L
125OHD: 190 pmol/L

November 24, 2005

Symptoms

Frequent URI's with otitis media, fatigue, muscle soreness, continued cognitive symptoms, difficulty with maintaining class work

Lab tests, November 24, 2005

Hgb: 161
RBC: 5.33 **High Normal** (range 4.2-5.4)
WBC: 4.5
Platelets: 183
Neutrophils: 2.2
Lymphocytes: 1.8
Monocytes: 0.4
Eosinophils: 0.1
Basophils: 0.0

CK: 124
C reactive protein: <0.3

Serology

Bartonella henselae IFA-IgG: <1:100
EBV capsid antigen IgG: reactive
EBV capsid antigen IgM: non-reactive

Initial Borrelia was CDC positive IgM, and was reported. That, plus lack of positive IgG WB in July (which should have been positive), a negative IgM post-antibiotic therapy and persistent symptoms of fatigue, muscle symptoms, impaired immunity and cognitive loss, **diagnosis PTLDS**

MP Therapy initiated December, 2005 for PTLDS

Olmesartan 40 mg q6h

Minocycline 25 mg q48h, gradual ramping up to 100 mg q48h

February 23, 2006

Increased left shoulder pain, transient left thigh 'burning' pain, decreased cervical lymph nodes, no recurrence of URI symptoms, fibromyalgia pain especially intrascapular, light sensitivity, right jaw pain and clicking

Examination revealed increase bulk and strength of left supraspinatus and caudad aspect of infrapinatus

Treatment

Olmesartan 40 mg q6h, minocycline 100 mg q48h, add 1/8 azithromycin 250 tab every 10 days

Lab tests, April 4, 2006

Hgb: 151

RBC: 4.89

WBC: 5.0

Platelets: 170

Neutrophils: 2.2

Lymphocytes: 2.0

Monocytes: 0.7

Eosinophils: <0/1

Basophils: <0.1

25OHD: 49 noml/L

125OHD: 80 pmol/L, test delayed so possible falsely low

June 21, 2006

Improved, continued increasing strength & bulk left shoulder, decreased fatigue, improved cognitive function, completed first year with honours, decreased light sensitivity, able to work during summer where he could not last year

Treatment;

Olmesartan 40 mg q6h, minocycline 100 mg q48h, azithromycin 125 mg q10days, clindamycin 37.5 mg q48h

Response to MP (olmesartan, minocycline, azithromycin/clindamycin)

Bartonella went from non-specific fluorescence to less than 1: 100. Non-specific fluorescence indicates antibody presence, but not at 1:100, but not negative. Also, regeneration of muscle mass and function after MP initiated.
