UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

MERCK SERONO SA,
Patent Owner.

Case IPR2023-00480
Patent 7,713,947

DECLARATION OF FRED D. LUBLIN, M.D.
UNDER 37 C.F.R. § 1.68

Merck 2051
Hopewell v Merck
IPR2023-00480

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I, Fred D. Lublin, M.D., declare as follows:

I. INTRODUCTION

1. I am over eighteen years of age, and I am competent to testify as to the matters set forth herein if I am called upon to do so.

2. I have prepared this Declaration for consideration by the Patent Trial and Appeal Board in the following *Inter Partes* Review proceeding: IPR2023-00480. I understand that IPR2023-00480 corresponds to *Inter Partes* Review of U.S. Patent No. 7,713,947 (the "'947 patent") (Ex. 1001).

3. I have written this Declaration on behalf of Merck Serono SA in connection with the above-captioned *Inter Partes* Review proceeding. I am being compensated for my time at my normal consulting rate of $900 per hour for non-deposition time and a $9,000 flat fee per day for deposition time. My compensation is not dependent on the substance of my testimony or the outcome of the proceedings.

4. In forming my opinions, in addition to my knowledge and experience, I have considered the materials cited herein and listed in Appendix A.

5. All statements in my Declaration, unless indicated otherwise, are based on my knowledge and experience in the field.

II. BACKGROUND AND QUALIFICATIONS

6. I am a Professor of Neurology and the Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at the Icahn School of

Medicine at Mount Sinai in New York City. I am also an Attending Neurologist at Mount Sinai Hospital. My full qualifications are below and in my CV, a copy of which is attached as Appendix B to this Declaration.

7. My professional interests relate primarily to neurology and neuroimmunology, and specifically to (1) the scientific and clinical aspects of multiple sclerosis ("MS") and (2) the research and development of therapies for treating MS. I have authored or co-authored over 250 peer-reviewed academic publications in the field of neurology, with an emphasis on MS. I have also written or co-written over 240 textbook chapters, editorials, abstracts, and letters in my areas of interest, including the textbook Multiple Sclerosis in Clinical Practice, Martin Dunitz, Ltd. (2003).

8. I received my A.B. in Biology from Temple University in 1968 (*magna cum laude*), and my M.D. from Jefferson Medical College in 1972 (*summa cum laude*). From 1972-1973, I interned at the Bronx Municipal Hospital-Albert Einstein Medical Center in New York City, specializing in internal medicine. I also completed an externship at the National Hospital for Nervous Disease in London in 1972. From 1973-1976, I was a resident in Neurology at New York Hospital-Cornell Medical Center in New York City, NY.

9. For the last 47 years, I have maintained an active neurology practice. I started as a resident at New York Hospital (1973-1976) and then as an attending

physician at Thomas Jefferson University Hospital (1976-1996), Medical College of Pennsylvania Hospital and Hahnemann University Hospital (1996-2000), and Mount Sinai Hospital (2000-present). Throughout this time, I have been regularly treating Multiple Sclerosis patients and have treated thousands of Multiple Sclerosis patients since 1976. I currently treat hundreds of Multiple Sclerosis patients a year.

10. In addition to my clinical practice, I have been actively engaged in the training of medical students, residents, fellows, and practicing clinicians in neurology and neuroimmunology throughout my career. I was an Instructor in Neurology at Cornell Medical College (1975-1976) and then an Instructor in Neurology and a Research Associate in Biochemistry (Immunology) at Jefferson Medical College of Thomas Jefferson University (1976-1978). In 1978, I was promoted to Assistant Professor of Neurology and Assistant Professor of Biochemistry and in 1982, to Associate Professor of Neurology. In 1983, I was promoted to Associate Professor of Biochemistry & Molecular Biology, and in 1986, to Professor of Neurology. In 1987, I was appointed Director of the Division of Neuroimmunology, and was named Vice-Chairman of the Department of Neurology. In 1995, I was promoted to Acting Chairman of the Department of Neurology.

11. I then joined MCP Hahnemann University (formerly Allegheny University of the Health Sciences) in 1996 as a Professor of Neurology, Vice-Chairman for Clinical Affairs in Neurology, Director of the University's newly-created Multiple Sclerosis Center, and Director of the Neurological Clinical Trials Center.

12. Since 2000, I have been Professor of Neurology and Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai School of Medicine. Four years after joining Mount Sinai School of Medicine (2004), I was named the Saunders Family Professor of Neurology, an endowed chair that is an honor I hold to this day.

13. In addition to research and teaching, I have also served as a reviewer for numerous scientific journals, including Annals of Neurology, Neurology, Science, Brain, Lancet, Laboratory Investigation, Journal of Neuroimmunology, Annals of Internal Medicine, Pediatrics, Journal of the Neurological Sciences, Clinical Therapeutics, Multiple Sclerosis Journal, Journal of NeuroVirology, Archives of Neurology, BioDrugs, Acta Neurologica Scandinavica, Lancet Neurology, Multiple Sclerosis and Related Disorders, New England Journal of Medicine, and JAMA Neurology. I have also served on the editorial boards of several influential journals in my field. For example, I have served as Co-Chief

Editor for the journal Multiple Sclerosis and Related Disorders since its inception in 2011 until December 2017.

14. I am a member of several professional medical organizations, including the American Academy of Neurology, where I was named a Fellow in 2004, and the American Neurological Association, where I was named a Fellow in 2013. I am also a member of the National Multiple Sclerosis Society, where I have chaired several committees.

15. I have been the recipient of numerous major grants from respected institutions, including one of the largest grants ever given for MS research by the National Institutes of Health.

16. I have served as either Principal or Co-Investigator for numerous clinical trials relating to a wide range of MS treatments, including interferons, of which beta interferon (Betaseron®) was the first FDA-approved drug for MS, as well as biologic medical products (e.g., Avonex®, Rebif®, Tysabri®) and chemical drugs (e.g., cladribine, linomide, tizanidine, Copaxone®, Novantrone®, Ampyra®). I have also served as a member for the Data Safety and Monitoring Boards for many MS treatments, including Antegren (Biogen-Idec), and Gilenya (Novartis). In my work in clinical trials, I have witnessed first-hand how drug doses are determined.

17. I have also consulted with various pharmaceutical companies, including Serono. I have received one research grant from Serono to support a clinical study on "Rebif Injection with and without the use of Rebiject Mini in Relapsing-Remitting Multiple Sclerosis."

III. SUMMARY OF OPINIONS

18. I understand that the Petition for IPR2023-00480 ("Pet.") challenges claims 36, 38, 39, and 41-46 of the '947 patent ("challenged claims") as allegedly obvious over Bodor and Stelmasiak. Pet. 8-9. It is my opinion that the challenged claims would not have been obvious over Bodor and Stelmasiak.

19. ***First***, neither Bodor nor Stelmasiak discloses or suggests all limitations of the challenged claims, including (1) the claimed weight-based induction or maintenance dosing and (2) the claimed maintenance period. A POSA would have understood that both Bodor and Stelmasiak teach flat, fixed dosing, which is fundamentally different from weight-based dosing. Indeed, even Dr. Miller distinguished between weight-based dosing and fixed dosing for MS drugs, characterizing MAVENCLAD®'s weight-based dosing as "unique."

20. Further, as I will discuss in detail below, a POSA would not have understood Bodor to teach re-treatment immediately after its 10-month cladribine-free period at least because (1) a POSA would have been concerned about the safety of cladribine treatment; (2) dosing of approved disease-modifying

treatments for MS was based on pharmacological effects, efficacy, and safety rather than based on the purported "cyclical" nature of MS; and (3) the art did not suggest a maintenance period as claimed. A POSA would have understood that any subsequent re-treatment would have been based on a combination of factors, such as evidence of disease progression, time course of therapeutic effects, and safety considerations, rather than automatically re-treating after a set period of time, as the Petition suggests. Stelmasiak does not remedy the deficiencies of Bodor, at least because Stelmasiak does not teach or suggest the claimed maintenance period, occurring about 8-10 months after the induction period; instead, Stelmasiak teaches treatment after only two months of no treatment.

21. ***Second***, a POSA would not have been motivated to arrive at the claimed dosing methods via routine optimization or have had a reasonable expectation of success in doing so. Petitioner's routine optimization argument is premised on measuring a patient's lymphocyte counts and evaluating the efficacy of a given dose based on the change in the count. However, as I explain in detail below, lymphocyte count is a metric of safety, not a metric of efficacy. Indeed, Dr. Miller admitted during his deposition that "[l]ymphocyte suppression is not a measure of efficacy." As such, a POSA would not have used lymphocyte count to evaluate the efficacy of any "optimization" to a dosing regimen.

22. Further, Petitioner's "routine optimization" suggestion disregards the variable and complex nature of MS, including that MS is a chronic disease in which changes occur relatively slowly in most people. A POSA would have understood that due to the complex nature of MS disease course, including that disability in MS evolves slowly over years, the therapeutic effects of any dosing schedule can likewise only be assessed over time.

23. Petitioner's "routine optimization" suggestion also ignores the numerous possible combinations of dose, dosing period length/number, and drug-free period length/number that a POSA could have "optimized." As of 2004, nothing in the prior art taught a POSA what specific combination (if any) of the different variables—dose, length and number of dosing periods or drug-free periods—would result in a safe and effective MS treatment method.

24. ***Third***, a POSA would not have been motivated to adopt weight-based dosing or have reasonably expected to arrive at the claimed weight-based dosing regimen. Neither Bodor nor Stelmasiak would have motivated a POSA to shift from their respective flat, fixed dosing method to a weight-based dosing method. Further, Stelmasiak teaches the effects of cladribine were not related to its dose per body weight and thus teaches away from weight-based dosing.

25. ***Fourth***, a POSA would not have been motivated to combine Bodor with Stelmasiak to arrive at the claimed induction doses or have had a reasonable

expectation of success in doing so. A POSA would not have started with Bodor's treatment regimen at least because (1) Bodor's maximum cladribine dose of 140 mg is lower than Stelmasiak's 150 mg dose (after three months) and (2) Bodor's oral cladribine formulation has lower bioavailability than Stelmasiak's, and thus Bodor's treatment regimen would have been less likely to reduce lymphocytes to a level below 1000 cells/μL, under Dr. Miller's theory that lymphocyte suppression to such a level is required for an MS "therapeutic effect." Further, a POSA would not have been motivated to modify the teachings of Bodor and Stelmasiak to arrive at the claimed induction dose at least because Stelmasiak's higher dosing regimen did not ultimately result in any change in EDSS score at the end of the study. Even if one were to convert Stelmasiak's 300 mg initial dose into mg/kg based on the reported patient weight range, that would correspond to 4.0-5.77 mg/kg—this is significantly higher than the claimed induction period doses of about 1.7-3.5 or 1.7 mg/kg. A POSA would not have been motivated to lower Stelmasiak's dose to arrive at the claimed induction period dose of about 1.7-3.5 or 1.7 mg/kg, nor have had a reasonable expectation of success in doing so.

26. ***Fifth***, a POSA would not have been motivated to immediately re-treat patients after Bodor's 10-month cladribine-free period or have had a reasonable expectation of success in doing so. Contrary to the Petition's suggestion, a POSA would not have understood there to be a "general

immunosuppression framework common with MS therapies" based on the purported "cyclical" nature of MS. Pet. 36. Instead, by 2004, the art showed that approved disease-modifying treatments for MS were dosed continuously to maintain the drug's pharmacological effects, efficacy, and safety. Further, as I explain in detail below, that some "patients may relapse during or after cladribine therapy" does not suggest that a POSA "would have been motivated to retreat the relapsing patients with cladribine after [Bodor's] 'ten months of no treatment.'" *See* Ex. 1002, ¶100. A POSA could have treated a relapsing patient by switching the patient to an alternative MS therapy. Further, in view of the reported inability of Stelmasiak's dosing regimen to maintain efficacy during a 9-month cladribine-free period, a POSA would not have had a reasonable expectation of success in re-treating patients after Bodor's 10-month cladribine-free period.

27. ***Sixth***, a POSA would not have been motivated to combine Bodor with Stelmasiak to arrive at the claimed 1.7 mg/kg maintenance dose or have had a reasonable expectation of success in doing so. Dr. Miller opines that a POSA would have been motivated to administer a lower total dose of cladribine in the maintenance period compared to the total dose in the induction period. However, regardless of whether any alleged maintenance dose would have been the same as or lower than the initial dose, a POSA would not have had any teaching or guidance from Bodor or Stelmasiak as to what cladribine dose would have been

required to maintain any effects of Bodor's treatment method comprising using 100-140 mg cladribine.

28. ***Lastly***, the non-obviousness of challenged claims of the '947 patent is further demonstrated by at least: (1) the skepticism of others, (2) the unexpected durable efficacy and safety of the claimed dosing regimen, and (3) the satisfaction of a long-felt unmet need for a short-course, oral therapy for MS.

IV. LEVEL OF SKILL IN THE ART

29. I understand that a person having ordinary skill in the art ("POSA") is a hypothetical person from whose perspective the patentability analysis is performed, and who is presumed to have knowledge of the relevant art at the time of the invention. In my opinion, the definition of a POSA for the '947 patent should be a person having an M.D. with at least two years of experience treating neurological conditions, with a focus on autoimmune disorders, including but not limited to multiple sclerosis, and prescribing immunotherapies to treat such neurological conditions, and that a POSA would also be part of a team including individuals with experience in investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, pharmaceutical drug development, and clinical trial design.

30. I understand that Petitioner has also proposed a definition of a POSA for the '947 patent, specifically: "A POSA for the '947 patent would have the

knowledge of multiple disciplines, such as immunology, biochemistry, and human physiology and anatomy, and also typically be a clinician with experience and/or training in neurology" and that "[t]he POSA typically would be a medical doctor with a specialty in neurology, specifically in treating autoimmune disorders of the nervous system, such as multiple sclerosis, and typically at least 2 years of experience with administering treatments to patients and evaluating results of such treatments, as well as experience or knowledge in related research and development." Pet. 28-29.

31. As of the priority date of the '947 patent in 2004, I qualified as a POSA under either of these definitions.

32. I provide my analysis from the perspective of a POSA. My analysis would be the same regardless of which party's definition is applied.

V. LEGAL STANDARDS

33. This section sets forth certain legal standards that have been provided to me by attorneys for Patent Owner, Merck Serono SA. I understand that the issues presented in this *Inter Partes* Review proceeding must be considered in view of these legal standards.

A. OBVIOUSNESS

34. I understand that a claim is obvious in light of the prior art if the difference or differences between the claimed subject matter and the prior art are

such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art.

35. I understand that several factual inquiries underlie a determination of obviousness. These inquiries include (1) scope and content of the prior art, (2) the level of ordinary skill in the field of the invention, (3) the differences between the claimed invention and the prior art, and (4) any objective evidence of non-obviousness. Such objective evidence of non-obviousness may include the invention's commercial success, commercial acquiescence (i.e., licensing), satisfaction of a long felt but unresolved need, the failure of others, skepticism, praise by others, teaching away by others, recognition of a problem, laudatory statements by an infringer, unexpected and superior results, and copying of the invention by others. I understand that for objective indicia to be given weight, there must be a nexus between the evidence and the claimed invention.

36. In connection with obviousness, I have been informed that there must have been some reason or motivation that would have led a person of ordinary skill in the art to combine or modify the relevant teachings in the prior art to obtain the claimed invention, and one of ordinary skill in the art must have had a reasonable expectation of success in doing so. I understand further that it is incorrect to evaluate obviousness from a hindsight perspective using the teachings of the patent at issue as a guide.

B. CLAIM CONSTRUCTION

37. I understand that each term of the claims of a patent should be interpreted according to its plain and ordinary meaning to a POSA at the time of the invention in the context of the patent.

38. I have reviewed the Decision on Institution and understand that in its preliminary findings, the Board found the challenged claims do not require that the total maintenance dose be lower than the total induction dose. Paper 10, 17. Additionally, the Board found the challenged claims cover embodiments in which the same total dose, e.g., about 1.7 mg/kg, is used for both the induction and the maintenance periods. *Id.*, 13-14, 17.

VI. TECHNICAL FIELD OF THE ART

A. Multiple Sclerosis

39. MS is an autoimmune disease of the central nervous system (CNS). Ex. 2010, 18; Ex. 1001, 1:24-26. The body's immune system attacks the CNS, leading to destruction of myelin, the substance that surrounds and insulates nerve fibers. Ex. 2010, 18; Ex. 1001, 1:24-26; Ex. 1007, 131. Without myelin, the nerve fibers, or axons, become damaged, and the loss of axons correlates with permanent functional deficit. Ex. 1001, 1:24-26; Ex. 2010, 56, 58. The dead nerve cells accumulate in the brain and spinal cord during the course of the disease, leading to lesions, or scars; hence, the name "multiple sclerosis," which literally means "many scars." Ex. 2010, 29.

40. While the cause of MS is unknown, by 2004, MS was thought to be a lymphocyte-dependent autoimmune disease, in which lymphocytes, a type of white blood cell that is part of the immune system, become "auto-reactive," i.e., they recognize and react with endogenous antigens. Ex. 1016, 421. By 2004, these "autoantigen-specific T lymphocytes" were thought to be activated peripherally, i.e., outside of the CNS, before migrating to the CNS. *Id*. However, the specific antigens and triggering agents involved were unknown. *Id*. Following migration to the CNS, the T lymphocytes (either CD4+ or CD8+) were thought to be reactivated, where they released pro-inflammatory Th1 (T helper 1) cell cytokines and mediated the destruction of the myelin sheath by various types of immune cells. Ex. 1007, 131. Thus, as of 2004, "T cells and the inflammatory molecules they secrete [we]re not the only players. Many cells and molecules of the immune system … participate in demyelination. The entire cascade of immune system events eventually culminates in myelin destruction." Ex. 2010, 68-70.

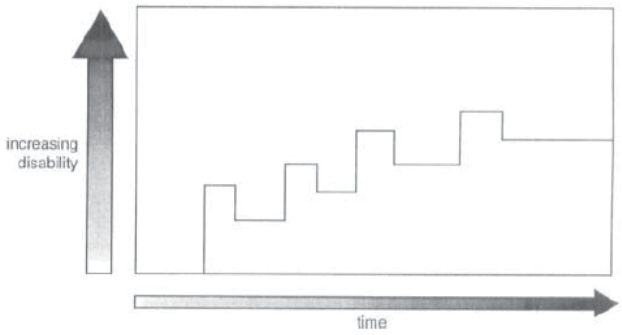
1. MS Clinical Course and Diagnosis

41. MS is a complex neurological disease. *Id.*, 1. The clinical course of MS is variable such that patients experience the disease and its effects in disparate ways, making it difficult to predict for individual patients. Ex. 1037, 907. Nevertheless, MS "usually can be characterized by either episodic acute periods of

worsening (relapses, exacerbations, bouts, attacks), gradual progressive deterioration of neurologic function, or combinations of both." *Id.*

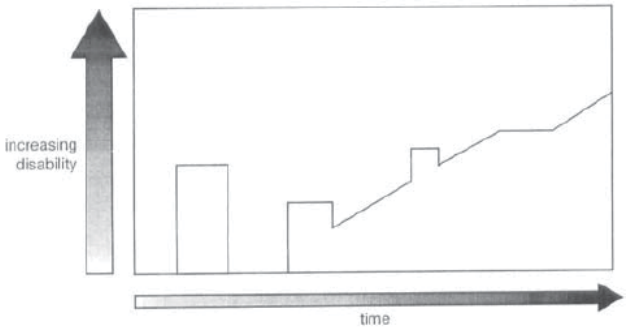
42. The disease course has been used to define the clinical subtypes of MS. As of 2004, the clinical subtypes included (1) "relapsing-remitting" MS ("RRMS"), (2) "secondary progressive" MS ("SPMS"), (3) "primary progressive" MS ("PPMS"), and (4) progressive-relapsing ("PRMS"). Ex. 1001, 1:48-50.

43. RRMS is the most common presenting form of MS. RRMS patients experience relapses or attacks, i.e., "episodes of acute worsening of neurologic function followed by a variable degree of recovery, with a stable course between attacks" characterized by a lack of disease progression. Ex. 1037, 908. The disease course of RRMS, as understood in 2004, is shown in the following graph, in which periods between attacks, i.e., disease relapses, are characterized by lack of disease progression. *Id.*

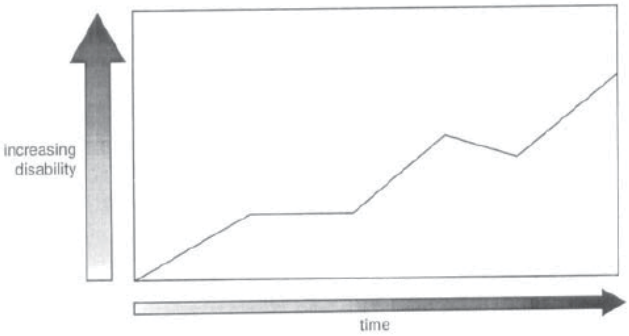


44. The RRMS disease course can be followed by disease progression with or without relapses, leading to SPMS. *Id*. An initial, transitional stage of

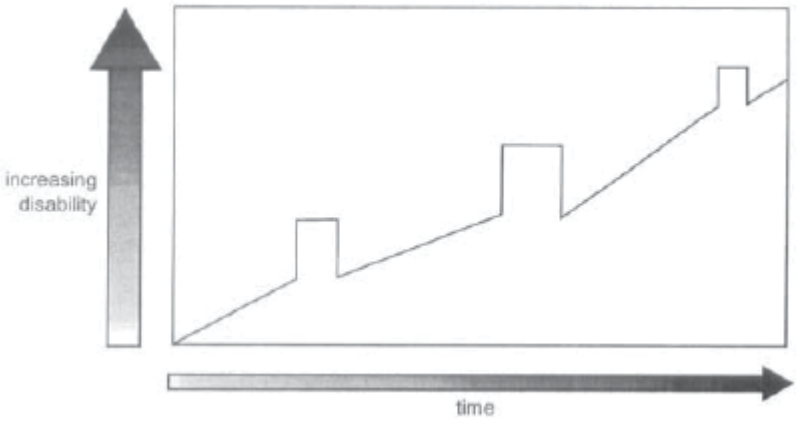
SPMS can be referred to as early SPMS. Ex. 1038, 60-63. As shown in the following graph of a disease course for SPMS, progression worsens and includes occasional relapses and minor remissions. Ex. 1037, 909.



45. In contrast to SPMS patients, PPMS patients experience disease progression from the onset, and is characterized by a "gradual[,] nearly continuously worsening baseline with minor fluctuations but no distinct relapses." *Id.*, 908. The disease course of PPMS, as understood in 2004, is shown in the following graph, and shows "progression of disability from onset," with occasional plateaus and temporary minor improvements." *Id.*, 909.



46. PRMS patients also experience disease progression from the onset, but with clear acute relapses and periods between relapses characterized by continuing progression. *Id.*, 909-10.



2. MS Treatment as of 2004

47. It was not until the 1990s that MS was considered a "treatable" neurologic disease. *Id.*, 907; Ex. 2011, 3.

48. Initially, in the 1960s, corticosteroids were used to reduce the severity of relapses but were "***not effective*** at reducing the number of relapses or the rate of disease progression." Ex. 2011, 4.[1] Notably, corticosteroids have not been proven to alter the natural course of MS, i.e., they are not established disease modifying agents ("DMAs"), and were taken ***as needed*** to treat attacks when they occur. Ex. 2006, 273; Ex. 2011, 4; Ex. 1016, 431; Ex. 1006, 946 ("Corticosteroids are often used to treat clinically significant relapses in an attempt to hasten recovery[.]");

[1] Hereinafter, all emphasis is added unless otherwise noted.

Ex. 1017, 1607 ("Corticosteroid therapy shortens the duration of the relapse and accelerates recovery[.]"); Ex. 2013, 176.

49. By 2004, therapy for MS generally involved disease modifying agents, which segregate into immunosuppressive and immunomodulatory therapies. Ex. 2006, 273. Immunosuppressants cause general suppression of the immune system and can inhibit crucial components of the immune system, leading to generalized immune dysfunction. *Id.*; Ex. 1007, 131. In contrast, immunomodulators do not cause general suppression of the immune system, but have more targeted effects and are usually less toxic. Ex. 2006, 273. For example, immunomodulators can shift immune responses from pro-inflammatory autoimmune conditions towards more beneficial anti-inflammatory circumstances. Ex. 1007, 131.

50. The therapeutic era in MS finally started in 1993, when FDA approved interferon beta-1b (IFNβ-1b; Betaseron®), the first therapy proven effective in altering the natural history of RRMS. Ex. 2011, 3; Ex. 1037, 907. By 2004, FDA had approved six MS drugs, all disease-modifying agents (or therapies): three beta interferons (IFNβ) (Betaseron®; Avonex®; Rebif®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®). Ex. 1001, 2:14-21; Ex. 2014, 1; Ex. 2015, 1; Ex. 2016, 1-2; Ex. 2017, 1; Ex. 2018, 3, 34; Ex. 2019, 1, 5; Ex. 2006, 275, 278. Of the six FDA-approved

drugs, four were immunomodulators. Ex. 2014, 1; Ex. 2015, 1; Ex. 2016, 1-2; Ex. 2017, 1. Mitoxantrone was an immunosuppressant while natalizumab was thought to strongly suppresses existing inflammatory activity at the disease site. Ex. 2018, 3; Ex. 2019, 5; Ex. 2006, 278; Ex. 2020, 572.

51. By 2004, the two most commonly used FDA-approved drugs were interferon beta and glatiramer acetate, neither of which used suppression of lymphocytes as its mechanism of action. However, I understand that according to Dr. Miller, "'the most common therapeutic approach' to MS before December 2004 was with immunosuppressive drugs." Ex. 1002, ¶30 (quoting Ex. 1013, 4). This, however, mischaracterizes Ex. 1013, which states instead that "[t]he most common therapeutic approach to ***autoimmune diseases*** is based on the use of drugs producing general immunosuppression." Ex. 1013, 4. Indeed, Dr. Miller's own 2002 publication, which I co-authored with him, states, "[t]herapy for MS generally involves either disease-modifying agents (DMA) (i.e., those that alter the long-term course of MS), treatments of acute exacerbations, or symptomatic therapies … The DMA segregate into immunosuppressive therapies … and immunomodulatory therapy, … the best-studied agents have been ***immunomodulatory***." Ex. 2006, 273. Thus, a POSA would have understood that by 2004, "the best-studied [disease-modifying] agents have been ***immunomodulatory***." *Id.*

52. Notably, immunosuppressant approaches for MS did not necessarily suppress lymphocytes. For example, "[n]atalizumab produced ***increased levels*** of circulating white blood cells (i.e., ***lymphocytes***, monocytes and eosinophils)," which "is consistent with the mechanism of action of natalizumab-inhibition of the migration of leukocytes to areas of inflammation by binding to α_4-integrin receptors." Ex. 2020, 573; *see also* Ex. 2021, 918 ("[n]atalizumab-treated patients had ***increases in lymphocytes***, monocytes, eosinophils, and basophils—changes consistent with the drug's known pharmacodynamic effects[.]"; Ex. 2019, 2. Thus, while I understand that Dr. Miller opines that "suppressing … lymphocytes was a target of MS therapies before December 2004" (Ex. 1002, ¶30), a POSA would have understood that by 2004, immunosuppressant agents for MS targeted various pharmacological effects, not just lymphocyte suppression, and some immunosuppressant agents even ***increased*** lymphocyte levels. As such, to the extent immunosuppressants were a "common approach" to MS, a POSA also would have understood that "a sustained decrease in [lymphocyte] count" was not necessarily characteristic of treatment response for MS, as Dr. Miller also opines. *See* Ex. 1002, ¶31.

53. All of the FDA-approved MS drugs in 2004 were also injectables—none was approved for oral administration, and none was dosed by bodyweight. Ex. 2014, 1; Ex. 2015, 1; Ex. 2016, 1; Ex. 2017, 1; Ex. 2018, 1; Ex. 2019, 2.

According to Dr. Miller, when MAVENCLAD® was approved in 2019, it was "the only MS medicine … that [was] not given in a fixed dose but rather the dose is determined by how much the individual weighs." Ex. 2007, 3:53-4:18; Ex. 2008, 4:20-5:1; Ex. 2009, 127:5-20. I agree with Dr. Miller that MAVENCLAD® was the only MS medicine given based on how much the individual patient weighs, i.e., by bodyweight.

54. Further, by 2004, FDA-approved MS drugs were dosed continuously to maintain the pharmacologic effects of the drug, while maximizing its efficacy and minimizing associated risks. *See* Ex. 2024, 9; Ex. 2020, 571, 573; Ex. 2025, 1879, 1883.

55. For example, the interferons Betaseron®, Avonex®, and Rebif® are administered 0.25 mg every other day, 30 mcg/week, and 44 mcg three times/week, respectively, and by 2004, there was a "pharmacological rationale indicating that frequent dosing … is ***necessary to sustain the activity*** of intracellular molecular signalling pathways responsible for regulating IFNβ-induced gene expression." Ex. 2024, 9; Ex. 2014, 1, 12; Ex. 2015, 1, 3; Ex. 2016, 2, 17.

56. Likewise, natalizumab is dosed 300 mg once every four weeks to maintain "maximal saturation … of α_4-integrin receptors on the surface of lymphocytes." Ex. 2020, 571, 573; Ex. 2019, 10. And the dosing of glatiramer

acetate, which was 20 mg/day (Ex. 2017, 19) in 2004,[2] was later reported as providing "***daily***" and "***constant activation*** [that] seems to have an important impact on the induction and ***maintenance*** of the regulatory/suppressive immune cells." Ex. 2026, 1126.

57. Finally, mitoxantrone, a cytotoxic agent that is dosed quarterly at 12 mg/m^2 via IV,[3] "appears to distribute into a deep tissue compartment from which it is slowly released[, which] provide[s] a pharmacological rationale for … an intermittent dosing schedule." Ex. 2025, 1879, 1883; Ex. 2018, 29. However, due to its cytotoxicity, "[c]omplete blood counts, including platelets, should be ***monitored prior to each course*** of NOVANTRONE" and patients are limited to a total lifetime cumulative dose of 140 mg/m^2. Ex. 2018, 18, 29-30. A POSA would have understood that mitoxantrone was dosed continuously for as long as it is safe to do so, and even then, there is a maximum lifetime dose.

58. Indeed, a 2020 review paper confirms the understanding that FDA-approved MS drugs were dosed "continuously[,] without an intended interruption in dosing, because clinical efficacy is tightly linked to the period of dosing." Ex.

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[2] In 2014, FDA approved an alternative 40-mg glatiramer acetate dose injected three-times weekly. Ex. 2059, 1.

[3] By 2004, mitoxantrone was dosed by surface area.

2032, 1923. Further, "[t]he effects of these drugs are closely related to their short half-lives and pharmacokinetic and pharmacodynamic profiles; therefore, while some need to be administered more frequently than others, all require regular dosing." *Id.*

59. Accordingly, a POSA would have understood that as of 2004, FDA-approved MS drugs were dosed continuously to maintain their respective pharmacologic effects while ensuring patient safety, rather than based on the purported "cyclical" nature of MS. *See* Ex. 1002, ¶54; Pet. 17, 54.

3. Outcome Measures In MS Clinical Trials

60. Clinical outcome variables are the mainstay for assessing MS treatment efficacy, with relapse rate and physical disability status being the primary outcome measures in most MS clinical trials. Ex. 2011, 4. Relapse rate is a "routine measure of disease activity that is easy to quantify and included in almost all trials," while "[a]ssessment of disability as a measure of disease progression is equally, if not more, important." *Id*. The most widely used measure of physical disability is the Kurtzke Expanded Disability Status Scale (EDSS), which is based on a neurologic exam of functional systems throughout the body. Ex. 1010, 1445-49; Ex. 1016, 425-26.

61. Non-clinical outcome measures, such as MRI may provide useful information about acute disease activity. Ex. 2011, 4. However, despite the utility

of MRI, the correlation between the MRI findings and physical disability is often insufficient, leading to a clinical-MRI paradox. *See, e.g.*, Ex. 1018, 1153; Ex. 2004, 341; Ex. 2014, 5.

62. I understand that Dr. Miller has acknowledged that "studies of cladribine continue to show an enigmatic ***dissociation*** between positive effects on MRI and ***unconvincing clinical benefit***." Ex. 2004, 341. I agree with Dr. Miller that MRI findings from certain cladribine studies for MS have been found to have insufficient correlation with clinical benefit. *See* Ex. 2011, 7 ("Studies with cladribine in primary progressive MS and SPMS, for example, showed evidence for a good response in terms of gadolinium-enhancing lesions in the absence of any benefit on clinical parameters, suggesting a dissociation between inflammatory changes and relapses in progressive MS."). As such, "[a]n important principle when interpreting clinical trial data is that of coherence." *Id.*, 4. In my opinion, "[a] study in which all outcomes point to the same effect, even if they are not all statistically significant, provides confidence that the outcomes observed are real." *Id.* Thus, a POSA would have understood that when assessing MS treatment efficacy, outcome measures should be considered collectively; and when all outcome measures point to the same effect, a POSA would have been confident that the observed outcomes are real.

63. In particular, given the complex nature of MS disease course and the slow progression of MS, a POSA would have understood that it would require years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact clinical outcomes and to draw any meaningful conclusions regarding efficacy and safety. "[T]he most important therapeutic aim of any disease-modifying treatment of MS is to prevent or postpone long-term disability," but disability in MS evolves slowly over years. Ex. 2013, 169. As Dr. Miller explains, assessing the efficacy of an MS drug in an "open trial in a few patients with known disease … still take[s] ***many months to a year or longer*** because of the variable nature of MS." Ex. 2005, 49. As such, it is "important that the treatment duration in a clinical trial is long enough to provide meaningful information about expected benefits." Ex. 2011, 4. Thus, a POSA would have understood that the benefits of an MS drug can only be assessed over time and that it would require years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact clinical outcomes. *Id.*

4. Cladribine Investigations For MS

64. Cladribine was initially approved in 1993 for treatment of hairy cell leukemia and was known for its ability to selectively reduce lymphocyte count. Ex. 1015, 1751; Ex.1016, 419. By 2004, cladribine had been investigated in several MS clinical studies. Ex. 1016, 419.

65. In 1996, Sipe (Ex. 2030) and Beutler (Ex. 1014) each reported on a two-year, placebo-controlled, double-blind, crossover study of 51 patients with MS (mostly secondary progressive) in which patients received cladribine (intravenous) at 0.10 mg/kg per day for 7 days as four monthly courses for a total of 2.8 mg/kg or placebo in the first year. Ex. 2030, 345; Ex. 1014, 1716. While Sipe reported that "cladribine favorably alters the clinical course of progressive MS" (Ex. 2030, 346), and Beutler reported that "cladribine retards the progression of neurologic impairment of patients with chronic progressive MS" (Ex. 1014, 1719-20), Dr. Miller himself noted that "these results were not seen in the subsequent blinded, randomized, placebo-controlled trial [i.e., Rice]. Furthermore, studies of cladribine continue to show an enigmatic dissociation between positive effects on MRI and unconvincing clinical benefit." Ex. 2004, 341, 350; Ex. 2009, 22:20-25:2. Indeed, the authors of the Rice study reported that "clinical efficacy was not shown in this trial." Ex. 1018, 1153.

66. Likewise, the renowned MS specialist and former CEO of the Mayo Clinic, Dr. John Noseworthy, questioned the reliability of Beutler's results because "bone marrow toxicity …, herpetic infection[s] …, and reported protocol violations undermine the likelihood that the trial was sufficiently blinded to be convincing." Ex. 2031, 753, 821.

67. In 1999, Romine (Ex. 1031) reported on an 18-month, placebo-controlled, double-blind study to evaluate cladribine in RRMS patients. Ex. 1031, 35. Patients were given either placebo or 2.1 mg/kg cladribine by subcutaneous injection (0.07 mg/kg/day for 5 consecutive days as six monthly courses). *Id.*, 35-36. Romine reported that relapse rate fell dramatically in both the placebo and treatment groups during the first 6 months of the trial, but that thereafter the effect only continued in treated patients. *Id.*, 42. However, with respect to degree of disability, Romine "found no significant differences between the treatment groups in either EDSS or SNRS [i.e., Scripps Neurological Rating Scale] scores" over the length of the study. *Id.*, 40, 42.

68. The results of MS clinical studies on cladribine through 2004, as a whole, left skilled artisans in the field, including Dr. Miller and me, skeptical about the utility of cladribine for treating MS due to both (1) the reported lack of cladribine clinical efficacy and (2) safety concerns for long-term side effects of cladribine's lymphocytotoxic activity. *See* Ex. 2004, 341; Ex. 1018, 1153; Ex. 1015, 1753-54; Ex. 2031, 753; Ex. 2011, 3. For example, in a 2000 book chapter on "Treatment Issues" for MS—co-authored by Petitioner's declarant, Dr. Miller—he explained that "[i]n recently completed trials of oral myelin, cladribine, and sulfasalazine, these agents were found not to be of benefit" for treating MS and that "[a] trial of cladribine failed to show benefit in progressive disease." Ex.

2005, 45, 67. In a 2005 review paper that I authored on the "History of modern multiple sclerosis therapy," I noted that "[t]rials with both interferon alpha and gamma ***proved unsuccessful***, as did treatment with oral myelin, ***cladribine***, sulfasalazine and inhibitors of tumour necrosis factor." Ex. 2011, 3.

69. The following year, a review by Dr. Noseworthy, citing multiple pre-2004 trials by Sipe, Grieb, Beutler (Ex. 1014), Romine (Ex. 1031), and Rice (Ex. 1018), noted adverse effects (e.g., episodes of infection; bone marrow toxicity) and the lack of clinical benefit in some cladribine studies for MS. Ex. 2031, 753, 821, 855, 911, 913, 923. The results from these cladribine studies for MS failed to convince Dr. Noseworthy of cladribine's ability to treat MS. Instead, Dr. Noseworthy concluded that "[w]e ***remain to be convinced*** that cladribine is useful, and do not recommend its use in the management of patients with multiple sclerosis." *Id.*, 753.

70. Similarly, a 2008 review by Dr. Miller, referencing pre-2004 trials, expressed skepticism about using cladribine for MS given the lack of "promise" in treating MS and that studies "continue to show an enigmatic dissociation between positive effects on MRI and unconvincing clinical benefit." Ex. 2004, 341. Dr. Miller further characterized the "very long-lasting lymphopenia induced by" cladribine as a "drawback" and concluded that "it seems prudent to await the

results of a prospective, randomized, blinded trial of oral cladribine ***before recommending its use in patients with MS***." *Id.*

71. Accordingly, a POSA would have understood that the cladribine trials for MS through 2004 left skilled artisans skeptical about the utility of cladribine for the treatment of MS.

72. Additionally, a POSA would have understood that cladribine posed significant long-term safety concerns. *See*, *e.g.*, Ex. 1014, 1720 ("In the current study thrombocytopenia was noted in some patients receiving higher doses of the drug, and severe, transient marrow suppression occurred in one patient"). One review paper noted that in several Phase II/III studies, "the most common treatment emergent adverse events were due to the known ***pharmacological effects***" of cladribine "on bone marrow and ***lymphocytes***." Ex. 1015, 1753. And Romine explains that "[r]epeated treatment [with cladribine] raises long-term toxicity issues including: 1) susceptibility to opportunistic infection; 2) marrow stem cell depletion; and 3) an increase in the incidence of malignancy, known to occur in association with other long-term immunosuppressive treatments." Ex. 1031, 43-44.

73. Further, even Dr. Miller expressed concerns about the "profound and very long-lasting lymphopenia induced" by cladribine, which he characterized as a "drawback" of using cladribine in MS. Ex. 2004, 341. Accordingly, a POSA

would have understood that skilled artisans in the field had serious concerns about the safety of using cladribine to treat MS due to its pharmacological effects, including its "profound and very long-lasting" lymphocytotoxic effects. Ex. 1015, 1753; Ex. 2004, 341.

74. The mechanism by which cladribine exerted its therapeutic effect in MS patients was not known by 2004, nor is it currently fully elucidated. Ex. 1031, 42; Ex. 1016, 432; Ex. 2032, 1903; Ex. 2001, 20. At best, in 2004, cladribine's "potential activity in [MS] is based on the ***hypothesis*** that it acts by reducing the number of activated lymphocytes that can damage myelin." Ex. 1016, 432. Indeed, "[t]he mechanism of action of the beneficial effect of cladribine on MS is ***presumably*** related to the selective and sustained depletion of lymphocytes." Ex. 1031, 42. Thus, a POSA in 2004 would have understood that while cladribine induces a reduction in lymphocyte count as a pharmacological effect, it had not been established that cladribine's lymphocytic effect was the basis for its therapeutic effect, or what lymphocyte level (if any) was required to achieve cladribine's therapeutic effect in MS.

B. Alleged Prior Art

1. Bodor (Ex. 1022)

75. Bodor states that its "invention" "relates to a composition comprising a complex cladribine-cyclodextrin complex formulated into a solid oral dosage

form and to a method for enhancing the oral bioavailability of cladribine." Ex. 1022, 1:4-6. Bodor includes one paragraph relating to administering its cladribine-cyclodextrin complex using a flat, fixed dose; however, Bodor does not disclose any MS efficacy data of its cladribine formulation. *See id.*, 23:7-24.

76. Bodor also discloses bioavailability studies on its cladribine-cyclodextrin complex, finding that the 10 mg tablet had a bioavailability of 39.1-39.4%, as compared to intravenous administration. *Id.*, 38 (Table VIII).

2. Stelmasiak (Ex. 1013)

77. Stelmasiak discloses a cladribine study on RRMS patients that included only 10 patients and lacked a placebo-control group. Ex. 1013, 4. Stelmasiak explains that all patients received six cladribine courses given at monthly intervals, followed by two additional courses at month 9 and either month 12 or 15, in which each course consisted of five flat, fixed doses of cladribine taken once daily on consecutive days. *Id.*, 5. Stelmasiak further explains that six patients received cladribine subcutaneously via a 5 mg daily dose and four patients received cladribine orally via a 10 mg daily dose, but that "[t]hese dosing regimens produce equivalent area under the concentration-time curve" of cladribine. *Id.* A POSA would have understood that patients receiving cladribine subcutaneously received a flat 150 mg dose of cladribine over a 6-month period (5 mg/day x 5 days/month x 6 months = 150 mg) and two additional 25 mg doses at month 9 and

either month 12 or 15 (5 mg/day x 5 days/month x 1 month = 25 mg), while patients who received cladribine orally received a flat 300 mg dose of cladribine over a 6-month period (10 mg/day x 5 days/month x 6 months = 300 mg) and two additional 50 mg doses at month 9 and either month 12 or 15 (10 mg/day x 5 days/month x 1 month = 50 mg). That is, given a bioavailability of 50% as stated by Stelmasiak, the 300 mg oral flat dose for the first 6 months is equivalent to the 150 mg subcutaneous flat dosing in the initial 6 months. *See* Ex. 2052, ¶57. Similarly, given a bioavailability of 50% as stated by Stelmasiak, the 50 mg oral flat, fixed dose for one month in the subsequent dosing period is equivalent to the 25 mg subcutaneous flat, fixed dosing in the subsequent dosing period. *Id.*

78. Stelmasiak reports that a group of patients "respond[ed]" to treatment while others were "non-responders." Ex. 1013, 6. Stelmasiak explains that "[t]he treatment resulted in the reduction of lymphocyte counts to approx. 40% of the initial value at 6 months" and that "[n]eurological status of the patients (expressed semi-quantitatively according to the EDSS scale) showed a significant improvement between 6 and 15 month[s] of the study." *Id.*, 4. However, by month 24, at the end of the study, there was no difference between the final EDSS score and the starting baseline EDSS score based on average EDSS scores for all patients (*see id.*, 6 (Table 1)) and only a small improvement based on average EDSS scores for "responders." *Id.*, 6 (Figure 2). A POSA would have understood

that the initial "improvements" in EDSS scores were not maintained over the length of the study and, given the absence of a placebo group, the very small number of participants, and the varied administration regimens, these results would not have provided any meaningful conclusions as to cladribine's therapeutic efficacy in RRMS patients.

VII. THE '947 PATENT INVENTION

79. I have reviewed the '947 patent and in my opinion, the '947 patent provides a method of treating MS comprising a unique four-step oral dosing regimen. Ex. 1001, 19:13-30. The claims recite an induction period and a maintenance period during which cladribine is administered using a weight-based dosage (mg/kg), and two cladribine-free periods. *Id.* Specifically, the dosing regimen of claim 36 comprises:

> (i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
>
> (ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg;

(iv) a cladribine-free period wherein no cladribine is administered.

Ex. 1001, 19:13-30.

80. Claims 38, 39, and 41-46 of the ’947 patent depend from claim 36 and recite additional limitations, such as the length of the induction period, the length of the cladribine-free periods, the length of the maintenance period, the total cladribine dose of the induction period, and the daily dose of cladribine. *Id.*, 20:3-7, 20:11-25.

81. Example 1 of the ’947 patent embodies the challenged claims, disclosing a study in which patients in separate arms (i.e., Groups 2 and 3) receive a respective total induction period dose of 1.75 and 3.5 mg/kg cladribine followed by a 10- or 8-month cladribine-free period, respectively, and a total maintenance period dose of 1.75 mg/kg cladribine followed by another 10-month cladribine free period. *Id.*, 14:18-16:51. As demonstrated by the results of the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) Trial, the claimed dosing regimen provides a safe and effective method for treating MS, now approved by the FDA in MAVENCLAD®. Ex. 2033, 425-26. Specifically, CLARITY demonstrated that in

patients who received cladribine tablets (either 3.5 mg or 5.25 mg per kilogram), "[t]reatment with cladribine tablets significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks." *Id.*, 416. Thus, unlike other cladribine clinical studies that provided inconclusive results including showing a clinical-MRI paradox, cladribine tablets used in the reported unique dosing regimen significantly improved ***both*** clinical and MRI outcomes. *Id.*

82. Further, the subsequent CLARITY Extension Study unexpectedly demonstrated the benefits of the claimed methods were maintained several years after the treatment regimen had stopped. In the CLARITY Extension study, the cladribine recipients from CLARITY were re-randomized to receive cladribine or placebo and followed for another two years. Ex. 2035, 1594. Surprisingly, the Extension study demonstrated that those in the placebo arm, i.e., those who did not receive any further cladribine treatment, had maintained the efficacy improvements produced by their earlier cladribine treatment in the CLARITY study. *Id.*, 1603. Additionally, patients in the placebo arm had a lower incidence of lymphopenia, as compared to patients who continued receiving cladribine treatment for two additional years. *Id.*, 1600. Thus, the claimed dosing regimen unexpectedly provides a minimal dosing period that achieves durable clinical benefits with a lower incidence of lymphopenia, which can be viewed as a "sweet spot"

corresponding to the minimally required dosing period (two years) and achieving the same clinical efficacy as four-year dosing but with minimal side effects. *See id.*, 1603.

83. Notably, cladribine's long-term effectiveness was subsequently demonstrated in CLARITY-MS study—a long-term follow-up of patients from CLARITY/CLARITY Extension. Ex. 2036, 719, 728. The follow-up study surprisingly "indicated the sustained benefits of cladribine tablets in terms of no evidence of disease activity …, and for up to ***6 years*** from the baseline of CLARITY." *Id.*, 720. Further, the findings of the CLARITY-MS study "suggest the sustained long-term mobility and disability benefits of cladribine tablets" during the median ***10.9 years'*** follow-up period. *Id.*, 719.

VIII. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER BODOR AND STELMASIAK

84. Based on the above and for the reasons discussed below, it is my opinion that the challenged claims of the '947 patent (claims 36, 38, 39, and 41-46) would not have been obvious over Bodor and Stelmasiak, alone or in combination, to a person of ordinary skill in the art. Neither of the references, alone or in combination, teaches or suggests the claimed oral weight-based dosing, an induction period as claimed, a maintenance period, or the second cladribine-free period as claimed. Furthermore, a POSA would not have been motivated to modify Bodor's flat, fixed-dosing regimen in view of Stelmasiak's high-dose, flat,

fixed-dosing method to arrive at the claimed weight-based dosing method comprising the unique four-step oral dosing regimen discussed above (*see*, *e.g.*, ’947 patent, claim 36), or have had any reasonable expectation of success in doing so.

A. Neither Bodor Nor Stelmasiak Discloses Or Suggests All Limitations Of The Challenged Claims

1. Neither Bodor Nor Stelmasiak Discloses Or Suggests The Claimed Weight-Based Induction Or Maintenance Dosing

85. A POSA would have understood that both Bodor and Stelmasiak teach flat, fixed dosing.

86. Bodor teaches an orally-administered method for the treatment of MS using flat, fixed dosing rather than a weight-based dosage method. Bodor discloses that “for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” Ex. 1022, 23:15-20. Although the regimen may vary in the number of days of dosing over two months, i.e., 10 days, 12 days, or 14 days, a POSA would have understood that all patients, regardless of weight, receive the same 10 mg daily dosage of cladribine for that number of days and thus the dosage remains flat and fixed. Further, Bodor does not disclose any

relationship between the number of days of dosing and patient weight. As such, a POSA would have further understood that Bodor's total doses of 100, 120, and 140 mg doses are also ***flat*** and not weight-based.

87. I understand that the Board stated in its preliminary findings that Bodor uses weight-based dosing in "defining the terms 'therapeutically effective amount' and 'effective amount.'" Paper 10, 35. However, Bodor expressly defines these terms as "dosages effective to achieve the therapeutic result sought." Ex. 1022, 22:17-19. While Bodor references weight-based "therapeutically effective dosages" that have been reported in the literature for hairy cell leukemia and MS, those references are in the context of prior art subcutaneous dosing regimens (e.g., Beutler (Ex. 1014)), which would correspond to even higher oral doses if corrected for bioavailability. *Id.*, 22:19-26. A POSA considering the entirety of Bodor would not have understood this "definition" in Bodor to teach or suggest a method ***of treating MS*** that encompasses weight-based dosing. I have also reviewed Dr. Meibohm's Declaration and agree with his conclusion that Bodor only teaches flat, fixed dosing, despite referencing weight-based dosing in the prior art. Ex. 2052, ¶66-69. Additionally, a POSA would have understood that despite the reference to weight-based dosing in the prior art, Bodor chose flat, fixed dosing in describing its dosing regimen, as disclosed therein. *See* Ex. 1022, 23:15-24.

88. Further, a POSA would have understood that Bodor's examples confirm administration based on flat, fixed dosing. Example 4 of Bodor discloses that MS "[p]atients received randomly three different ***fixed*** oral doses (3.0 mg) and a fixed subcutaneous dose of 3.0 mg." *Id.*, 33:25-27. Example 5 of Bodor discloses that MS "[p]atients received randomly two different ***fixed*** oral doses (3.0 mg and 10.0 mg) and a fixed intravenous dose of 3.0 mg." *Id.*, 36:18-20. In my opinion, based on these examples, the specifically disclosed flat, fixed dosing regimen, and the absence of any disclosure of a relationship between the number of days of dosing/cumulative dose and patient weight, a POSA would have understood that nowhere does Bodor suggest administering its oral formulation of cladribine for treatment of MS based on patient weight.

89. Nevertheless, I understand that Petitioner's declarant, Dr. Miller, opined that a POSA would have understood that for a 70 kg adult, "Bodor's dose is equivalent to approximately 1.4 to 2 mg/kg." *See* Ex. 1002, ¶83. While I do not disagree with the mathematical calculation itself, I disagree that Bodor's flat, fixed dosing is "equivalent" to weight-based dosing of approximately 1.4 to 2 mg/kg just because there is an overlap for one very particular-weight patient, chosen with hindsight.

90. In my opinion, a POSA would not have considered Bodor's dosing regimen in the context of any patient weight. As discussed above, Bodor does not

disclose any relationship between the number of days of dosing/cumulative dose and patient weight. Further, there is no disclosure in Bodor of a patient weighing 70 kg, let alone of selecting a dose based on such a patient's weight. As such, there is nothing in Bodor that would have led a POSA to understand Bodor's flat, fixed dosing to be "equivalent" to weight-based dosing at approximately 1.4 to 2 mg/kg.

91. Further, a POSA would have understood that flat and weight-based dosing are fundamentally different dosing methods that would not result in equivalent dosing. When patients are administered a drug based on flat dosing, all patients, regardless of weight, receive the same amount of a drug. In contrast, when patients are administered a drug based on weight-based dosing, the prescriber determines the dose that each patient will get based on that individual's weight. Thus, there was no reason a POSA would have interpreted Bodor's flat, fixed dosing regimen as teaching that prescribers should select each patient's dose based on that individual's weight. Additionally, I have reviewed Dr. Meibohm's Declaration and agree with his opinions that (1) Bodor discloses flat, fixed dosing, not weight-based dosing; and (2) flat, fixed dosing and weight-based dosing are fundamentally different. Ex. 2052, ¶¶20, 66-69, 73.

92. Indeed, I understand that even Dr. Miller distinguished between weight-based dosing and fixed dosing for MS drugs. I have reviewed the transcript

and video corresponding to Ex. 2008 and Ex. 2007, respectively. In this video, Dr. Miller explained that before 2019, when FDA approved MAVENCLAD®, all MS drugs were administered using a "fixed dose." Ex. 2008, 4:21-5:1. Dr. Miller distinguished the "fixed dos[ing]" of those MS drugs, from MAVENCLAD®'s weight-based dosing regimen, which he characterized as "***unique***." *Id.*, 4:17-5:1. Specifically, Dr. Miller explained:

> The treatment regimen for MAVENCLAD® is rather ***unique*** … the dose of MAVENCLAD® is dependent on an individual's weight. ***This is the only MS medicine that we have that is not given in a fixed dose but rather the dose is determined by how much the individual weighs.***

Id.; Ex. 2007, 3:53-4:18.

93. I agree with Dr. Miller that MAVENCLAD®'s weight-based dosing regimen "is rather unique." I also agree with Dr. Miller that MAVENCLAD® is "the only MS medicine that we have that is not given in a fixed dose but rather the dose is determined by how much the individual weighs," i.e., by body weight. At the time of the '947 invention, none of the FDA-approved MS drugs was dosed by body weight. *Supra*, ¶53. Indeed, Dr. Miller ***distinguished*** between weight-based dosing and fixed dosing.

94. In view of the above, I see no reason why a POSA would have modified Bodor's flat, fixed dosing regimen to arrive at weight-based dosing method, or have had any motivation to do so.

95. Stelmasiak, like Bodor, also teaches flat, fixed cladribine dosing and thus does not remedy the deficiencies of Bodor.

96. As discussed above, Stelmasiak discloses that patients received 300 mg oral cladribine (i.e., flat, fixed dose of 10 mg/day for 5 days/month for six months), followed by 50 mg at month nine and 50 mg at month twelve or fifteen. Ex. 1013, 5; *supra* ¶77. Even though the reported weight distribution of Stelmasiak's patients was 52-75 kg, every patient receiving oral cladribine received the same cumulative dose of cladribine. Ex. 1013, 5. Stelmasiak thus teaches flat, fixed cladribine dosing and does not suggest weight-based dosing. Rather, Stelmasiak reports that some patients were "responders" while others were "non-responders" and explicitly states that "[t]here was ***no indication*** that a 'good response' is related to the actual cladribine dose per body weight." Ex. 1013, 6, 7. In other words, Stelmasiak teaches the effects of cladribine were not related to its dose per body weight. As such, in my opinion, Stelmasiak teaches away from adopting a weight-based dosing method and a POSA would not have been motivated to adopt the claimed weight-based dosing in view of Stelmasiak.

97. Nevertheless, even if one were to attempt to translate Stelmasiak's doses into weight-based doses based on the reported patient "body weight [of] 52-75 kg" (*id.*, 5), Stelmasiak would not have taught or suggested the claimed induction weight-based dose. Stelmasiak's initial oral dose of 300 mg over six months would correspond to 4.0-5.77 mg/kg (i.e., 300 mg ÷ 52 kg = 5.77 mg/kg; 300 mg ÷ 75 kg = 4.0 mg/kg); this is well above the claimed weight-based induction dose of about 1.7 to about 3.5 mg/kg. Thus, Stelmasiak also does not teach or suggest the claimed about 1.7 or about 1.7 to about 3.5 mg/kg total induction dosing. Stelmasiak does not teach or suggest any weight-based dosing, let alone the claimed about 1.7 to about 3.5 mg/kg induction dose, and instead teaches away from such weight-based dosing.

2. Neither Bodor Nor Stelmasiak Discloses Or Suggests A Maintenance Period As Claimed

a. Bodor Does Not Teach or Suggest Re-Treatment

98. A POSA would not have understood Bodor to teach re-treatment immediately after its 10-month cladribine-free period. Bodor's 10-month cladribine-free period follows the two-month cladribine dosing period. Ex. 1022, 23:15-20. Bodor does not state that re-treatment with cladribine should occur upon completion of the 10-month cladribine-free period (or otherwise). As discussed below, in view of the state of MS treatment in 2004, including safety concerns regarding cladribine treatment, the absence of any cladribine clinical studies

demonstrating a safe and efficacious dosing regimen, alternative MS treatments, and the basis on which FDA-approved disease-modifying drugs were dosed, a POSA considering Bodor would not have understood Bodor to teach re-administering cladribine at the end of the 10-month cladribine-free period.

i. Cladribine Treatment Raises Safety Concerns

99. A POSA reading Bodor would not have assumed that it would have been safe to re-treat patients with cladribine ***at the end of*** the 10-month cladribine-free period. Because of cladribine's known lymphocytotoxic activity, i.e., that it caused "prolonged, profound suppression of lymphocyte counts" (Ex. 1016, 420), a POSA would have understood that Bodor's 10-month cladribine-free period after a two-month dosing period likely relates to ***safety considerations***, i.e., to limit the potentially toxic effects of cladribine dosing. *See id.*, 430; *see also* Ex. 1001, 2:59-3:2, 3:22-30; Ex. 1014, 1720; Ex. 1013, 7 (Stelmasiak reports that in an earlier cladribine study, "dangerous marrow depression were reported in some multiple sclerosis patients."); Ex. 1023, 326 ("all patients on average displayed marked signs of marrow toxicity: a progressive, although moderate and reversible fall in hemoglobin concentration, a distinct macrocytosis and a moderate thrombocytopenia (these changes were not reversing after the treatment was discontinued), and a modest, but noticeable drop in granulocyte counts.").

100. Indeed, Dr. Miller acknowledges that after a cladribine dosing period, a POSA would have "followed" with a "drug-free period" "because cladribine toxicity was a concern." Ex. 1002, ¶103. Dr. Miller explains that "cladribine-free periods" are incorporated "into an MS treatment regimen to mitigate side effects associated with cladribine toxicity." *Id.* I agree with Dr. Miller that a POSA would have incorporated a cladribine-free period into an MS dosing regimen to mitigate side effects associated with cladribine toxicity. In my opinion, the cladribine-free period allows a physician to evaluate the condition of a patient, including safety markers such as lymphocyte levels, to consider potential safety risks. If lymphocyte levels remained suppressed beyond a safe range, a POSA would not have treated a patient with any further immunosuppressive therapy, cladribine or otherwise, due to safety concerns. As Dr. Miller explained in his book chapter, "[a]nother drawback to the use of cladribine is the profound and very long-lasting lymphopenia induced by the drug. This may preclude the use of other immunosuppressant agents and administration of cladribine almost invariably disqualifies a patient from consideration for other clinical trials." Ex. 2004, 341. *See also* Ex. 2008, 12:4-9 (Dr. Miller explaining that "some of the drugs that we – that the person might have been on … may have suppressed the lymphocyte count. And so we may need to wait to get that lymphocyte count back into the safe range[.]"). However, as of 2004, it was unclear how long cladribine-induced

lymphocyte suppression would last. For example, Selby discloses that "***one year*** after completion of cladribine … [t]he mean total lymphocyte, CD4 and CD8 counts had shown ***some recovery*** compared to the values at the end of therapy, but were still ***significantly below baseline*** level." Ex. 1047, 297. And Stelmasiak reports that "[t]he treatment resulted in the reduction of lymphocyte counts to approx. 40% of the initial value at 6 months, with a trend toward recovery ***evident only at 24 months***." Ex. 1013, 4.

101. Given the safety concerns arising from cladribine's lymphocytotoxic activity, and safety concerns associated with re-treatment, a POSA reading Bodor would not have assumed that it would be safe to re-treat patients with cladribine ***at the end of*** the 10-month cladribine-free period. *Infra*, ¶¶102-119. Accordingly, Bodor does not teach or suggest the claimed maintenance period after the 10-month cladribine-free period.

ii. Dosing of Approved Disease-Modifying Treatments For MS Was Based on Pharmacological Effects, Efficacy, And Safety

102. Dr. Miller opines that "a POSA would have thought to re-administer cladribine again after the specified cladribine-free period" (Ex. 1002, ¶87) and that "a POSA would have understood that a common strategy for treating MS involved administering a therapy for a period of time, stopping the therapy for a period of time, and retreating for a period of time." *Id.*, ¶59. These opinions appear to be

based on treatment with corticosteroids and cyclophosphamide. *See id.*, ¶¶54-58. However, I disagree with Dr. Miller's characterization that this "common strategy" would have informed treatment with cladribine.

103. ***First***, a POSA would have understood that in 2004, the strategy in MS treatment focused on DMAs, which were dosed continuously to maintain the drugs' pharmacological effects, while maximizing their efficacy and minimizing associated risks. *Supra*, ¶¶54-58. For example, frequent dosing of beta interferons is "***necessary to sustain the activity*** of intracellular molecular signalling pathways" (Ex. 2024, 9) and natalizumab is dosed 300 mg once every four weeks to maintain "maximal saturation … of α_4-integrin receptors on the surface of lymphocytes." Ex. 2020, 571, 573. And while "a pharmacological rationale for … an intermittent dosing schedule" of mitoxantrone relates to its "distribut[ion] into a deep tissue compartment from which it is slowly released," "[c]omplete blood counts, including platelets, should be ***monitored prior to each course***." Ex. 2025, 1879; Ex. 2018, 29-30. In other words, mitoxantrone can be dosed continuously so long as it is safe to do so. A POSA would have understood that MS drugs have different dosing schedules and that a given drug's dosing schedule is based on the drug's specific pharmacological effects, mechanism of action (if known), therapeutic benefits, and safety risks, rather than based on the purported "cyclical" nature of MS. *See* Ex. 1002, ¶54; Pet. 17, 54. Accordingly, a POSA would not

have simply "thought to re-administer cladribine again after the specified cladribine-free period" simply because "MS is a chronic disease that typically requires ongoing care and repeat treatment." *See* Ex. 1002, ¶87.

104. ***Second***, a POSA would have understood that treatments with corticosteroids and cyclophosphamide would not have informed treatment with cladribine. While MS is a chronic, progressive neurologic disorder with no cure, a POSA would have understood that whether a patient would need re-treatment depends not just on the disease state of the patient but also on the efficacy, mechanism of action, and safety of the particular drug. *See supra*, ¶¶54-58.

105. As discussed above, before the use of disease-modifying agents for MS, corticosteroids were used to reduce the severity of relapses but were "***not effective*** at reducing the relapse rate or the rate of disease progression." Ex. 2011, 4; *supra*, ¶48. Corticosteroids have not been proven to alter the natural course of MS, and were administered as needed to treat relapses when they occur. Ex. 2006, 273; Ex. 1016, 431; Ex. 2013, 176. A POSA would have understood that a drug used to reduce the severity of relapses and to hasten recovery, rather than to alter MS disease course, ***by nature*** would have to be re-administered during a patient's lifetime. A POSA would have further understood that such a treatment approach—i.e., a treatment that is administered as needed to treat relapses when they occur—does not inform treatment with disease-modifying agents such as cladribine, which

alter the MS disease course and which are designed to "slow disease progression ***over the long term.***" *See* Ex. 2006, 273, 279; Ex. 2005, 61. Thus, a POSA would not have looked to corticosteroid treatment to inform treatment with cladribine.

106. Dr. Miller also relies on a specific steroid treatment method—pulsed intravenous methylprednisone ("IVMP") treatment—to support his opinion that re-treatment is needed in MS patients. *See* Ex. 1002, ¶¶56-57. The only dosing regimen that Dr. Miller identifies for pulsed IVMP is one study's dosing of "1g/mo or 3 doses of 1 g/d every 3 months" in progressive MS patients. *Id.*, ¶56. However, Dr. Miller does not explain the rationale for this dose or why it would inform re-treatment with cladribine. Further, while Dr. Miller relies on Pirko (Ex. 1020) to disclose "neuroprotective or extended immunomodulatory effects" of IVMP and "delayed" formation of lesions (i.e., T1 black holes), Dr. Miller himself stated in his 2008 book chapter that "[a]dministration of regularly scheduled intermittent doses of pulse steroids has not been established as effective therapy for the prevention of clinical worsening in MS." Ex. 1002, ¶¶56-57; Ex. 2004, 342 (citing pre-2004 publications). Instead, "intravenous steroids have shown proven benefit in the management of ***acute exacerbations***." Ex. 2004, 342. That is, like the general corticosteroid treatment discussed above, IVMP appears to be effective for treating relapses when they occur, and a POSA would have understood that

such a treatment approach does not inform treatment with disease-modifying agents such as cladribine.

107. Dr. Miller also relies on cyclophosphamide dosing to show "re-treatment" in MS patients. Specifically, Dr. Miller relies on a 1993 publication by Weiner (Ex. 1021) that discloses administering progressive MS patients with induction doses of intravenous cyclophosphamide followed by "IV cyclophosphamide every 2 months for a 2-year period," which allegedly "is consistent with previous observations that the average time to reprogression following cyclophosphamide/ACTH induction is approximately 18 months." Ex. 1002, ¶58 (quoting Ex. 1021, 911, 913). While this cyclophosphamide dosing regimen suggests re-treatment based on disease progression, Dr. Miller does not provide any mechanistic or pharmacologic rationale as to how or why this dosing regimen would inform re-treatment with cladribine.

108. Further, Dr. Miller described in a 1997 publication that "[m]any trials have confirmed that the clinical benefits of cyclophosphamide therapy for MS are restricted to the ***short term*** and are marginal at best, with toxicity being a major problem" and concluded that "cyclophosphamide is an unlikely candidate for long-term therapy for patients with MS." Ex. 2037, 371. A study by the Canadian Cooperative Multiple Sclerosis Study Group provides the strongest evidence for cyclophosphamide's lack of efficacy. Ex, 2061, 441; *see also* Ex. 2006, 279. In

that study, 168 patients with progressive MS were randomized to receive intravenous cyclophosphamide and oral prednisone; oral cyclophosphamide, oral prednisone, and weekly plasma exchange; or placebo medications and sham plasma exchange. Ex. 2061, 441. However, "there were no significant differences among the groups" based on the primary analysis comparing rates of treatment failure using EDSS: 35% treatment failure with cyclophosphamide; 32% treatment failure with plasma exchange; and 29% treatment failure with placebo. *Id.* Further, there were no "differences in the proportions improved, stabilised, or worsened at each 6 month assessment or in the mean change in the EDSS at the final assessment." *Id.* The study authors stated that "this study fails to confirm previous reports that immunosuppressive treatments result in stabilisation or improvement in progressive MS." *Id.* In my opinion, there is no reason a POSA would have looked to the dosing of a drug with limited short term benefits to inform the dosing of cladribine, which causes prolonged suppression of lymphocytes.

109. Tellingly, neither the IVMP nor the cyclophosphamide dosing method includes an extended drug-free period, e.g., 8-10 months treatment-free period between induction and maintenance periods as claimed.

110. Accordingly, nothing in the art would have led a POSA to re-administer cladribine again after Bodor's 10-month cladribine-free period.

iii. The Art Did Not Suggest A Maintenance Period As Claimed

111. In my opinion, even if a POSA would have considered any re-treatment after Bodor's 10-month cladribine-free period, the art did not suggest repeating the treatment or resuming treatment immediately after the no treatment period ended.

112. ***First***, a POSA would have known that by 2004, most clinical trials studying cladribine for the treatment of MS used a single intravenous- or subcutaneous-dose dosing phase without any subsequent re-treatment phase. Ex. 1016, 425 (Table III, "Scripps pilot," "Scripps 2-year CPMS," "Scripps CPMS retreatment," "Multicentre North American CPMS," "Scripps 2-year RRMS").

113. ***Second***, a POSA would have recognized that any trials that intended to re-treat patients would have clearly specified the criteria for re-treatment at the outset. For the handful of cladribine trials for MS that re-treated patients, the published trial protocols expressly identified the re-treatment criteria to be met, and did not automatically or immediately re-treat patients after a period of non-treatment. For example, in the Rice study, patients in one treatment group were dosed with cladribine for two months, followed by six months of placebo. Ex. 1018, 1146. However, these patients were not re-treated with cladribine immediately after the six months of placebo. Instead, Rice discloses that "patients who ***fulfilled the hematologic dosing criteria*** were permitted to receive open-label

cladribine treatment … provided ***at least 12 months had elapsed*** since the last dose of cladribine and there was evidence of ***disease progression***." *Id.* A POSA would have understood that the "hematologic dosing criteria" include safety concerns about cladribine's hematologic toxicity. *See id.*, 1151-52 (Rice discussing lymphocyte levels in the "hematologic changes" sub-section within the "Safety evaluation" section). Similarly, Romine discloses that a subset of patients were re-treated "because of a ***recurrence of disease worsening***." Ex. 1031, 43. That is, not all patients received re-treatment after a cladribine-free period, and, for those that did, it was because they had a recurrence of symptoms. Given the re-treatment plans in Rice and Romine, at best, a POSA would have understood that any subsequent re-treatment would have been based on a combination of factors, such as evidence of disease progression, time course of therapeutic effects, and safety considerations, rather than automatically re-treating after a set period of time, which neither Rice nor Romine did.

114. ***Third***, a POSA would have been concerned about resuming cladribine treatment due to the safety and toxicity concerns associated with cladribine in particular. *See* Ex. 1031, 43-44. For example, Rice reports "significant overall lymphocytopenia" arising from decreased lymphocyte counts in patients treated with cladribine. Ex. 1018, 1151-52 (Rice discussing lymphocyte levels in the "hematologic changes" sub-section within the "Safety evaluation" section). A

POSA would have understood that Rice was concerned with lymphopenia, a decreased concentration of lymphocytes that can increase the risk of serious infections, and thus Rice allowed re-treatment only if patients "fulfilled the hematologic dosing criteria" and "***at least 12 months had elapsed*** since the last dose of cladribine and there was evidence of ***disease progression***." *Id.*, 1146.

115. That a POSA would have been concerned about the safety of cladribine re-treatment is consistent with Dr. Miller's acknowledgement that a POSA would have considered patient safety when assessing when to re-treat patients. For example, Dr. Miller opines that with respect to the "the length of time of the second cladribine-free period," "[a] POSA would have had the skill to monitor a patient's lymphocyte count and side effects associated with lymphocyte and myelosuppression" so as to "mitigate side effects." Ex. 1002, ¶104. As such, a POSA would have been concerned about the safety of re-treating a patient who had "significant overall lymphocytopenia" and would not have resumed treatment at the end of Bodor's 10-month cladribine-free period without, at a minimum, further indication that it was safe to do so, e.g., determining the extent of lymphocytopenia in the patients.

116. ***Fourth***, there was no consensus in the art regarding when re-treatment with cladribine would occur, if at all. Dr. Miller opines that "the general knowledge in the art recognized that 'the beneficial effect of a single course of

cladribine' is 'not permanent' and investigating 'retreatment with cladribine will be especially important.'" *See* Ex. 1002, ¶¶ 17, 59, 100. However, this does not suggest that a patient would in fact be re-treated with cladribine, or that any re-treatment would occur after Bodor's 10-month cladribine-free period. Dr. Miller appears to rely on Selby (Ex. 1047) to support his opinion that cladribine's effect is "not permanent" because "lymphocyte counts eventually rebounded after a cladribine-free period." *See* Ex. 1002, ¶95. However, Selby discloses that "***one year after*** completion of cladribine … [t]he mean total lymphocyte, CD4 and CD8 counts had shown ***some recovery*** compared to the values at the end of therapy, ***but were still significantly below baseline level***." Ex. 1047, 297. In my opinion, a POSA would have understood that Selby does not suggest that lymphocytes return to ***baseline levels*** one year after the last dose of cladribine. Instead, a POSA would have understood that Selby suggests it would be necessary to wait more than a year after the last cladribine dosing for the patient's lymphocyte level to further recover before considering any re-treatment and a POSA would not have resumed cladribine treatment after 8-10 months of no treatment as claimed.

117. Indeed, there were no cladribine dosing regimens that had been shown to be both safe and effective. Ex. 1031, 43-44; Ex. 1014, 1720; Ex. 1016, 430-431. As such, a POSA would not have known whether any further cladribine treatment would have been necessary or effective.

118. ***Fifth***, even if there was a need for further treatment, the art does not suggest that a POSA would have re-treated with cladribine. In my experience, if a patient experiences an inadequate treatment response to a DMA such as cladribine, some clinicians will switch the patient to an alternative MS therapy. Dr. Miller also agreed that "many people with MS start on a medication and then need to change medication, at some point, for one reason or another." Ex. 2009, 94:8-5; *see also* Ex. 2008, 11:17-19.

119. Thus, in view of the state of MS treatment in 2004, including cladribine clinical studies, a POSA considering Bodor would not have understood Bodor to teach re-administering cladribine at the end of the 10-month cladribine-free period or to do so using the claimed about 1.7 mg/kg maintenance dose.

b. Stelmasiak Does Not Teach Or Suggest A Maintenance Period As Claimed

120. In my opinion, Stelmasiak does not remedy the deficiencies of Bodor discussed above.

121. ***First***, Stelmasiak does not teach or suggest the claimed maintenance period, occurring about 8-10 months after the induction period. Stelmasiak teaches treatment after only two months of no treatment (at month nine). Ex. 1013, 5 ("Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months."). Additionally, the combination of Bodor

and Stelmasiak does not teach or suggest a maintenance period that occurs about 8-10 or about 10 months after the induction period as claimed.

122. Nevertheless, I understand that Petitioner argues that "a POSA would have retreated the patient with cladribine, as Stelmasiak taught," and that Stelmasiak and Bodor would have led a POSA to treat MS according to a "general treatment framework" that provides for "maintenance" after a 2-month induction period and 10 months of no treatment. Pet. 35-36; Ex. 1002, ¶105. However, as discussed above, by 2004, all FDA-approved MS drugs were dosed to maintain the pharmacologic effects of the drug, while maximizing its efficacy and minimizing associated risks. *Supra*, ¶¶54-58. Further, a POSA would have understood that whether a patient would need re-treatment would vary, depending not just on the disease state of the patient but also on the efficacy, mechanism of action, and safety of the particular drug. *See*, *e.g.*, Ex. 1018, 1146. In my opinion, Petitioner's suggestion that "a POSA would have done nothing more than follow[] the general immunosuppression framework common with MS therapies" oversimplifies the complexity of treating MS and ignores that different drugs act through different mechanisms of action, with different pharmacological effects and different safety risks. Here, Stelmasiak resumes treatment ***two months*** after the first treatment period, and thus does not teach or suggest a maintenance period that occurs about 8-10 or 10 months after the induction period as claimed.

123. ***Second***, Stelmasiak does not teach or suggest the claimed maintenance period lasting about 2-4 months, in which the total dose is about 1.7 mg/kg. Instead, Stelmasiak discloses a second dosing phase that lasts a single month—at month nine—in which ***one*** 50 mg oral course of cladribine is administered. Ex. 1013, 5. This second dosing phase is followed by a 2- or 5-month cladribine-free period. Stelmasiak thus teaches re-administering cladribine over a one-month period, but does not teach a maintenance period lasting about 2-4 months as claimed.

124. Further, as discussed above (*supra*, ¶¶95-97), Stelmasiak teaches ***flat*** dosing, i.e., the 300 mg oral cladribine administered during the initial treatment period followed by additional 50 mg doses. But even if one were to translate Stelmasiak's 50 mg treatment dose into mg/kg based on the reported patient weights of 52-75 kg, Stelmasiak's treatment course of 50 mg after a two-month cladribine-free period would correspond to 0.67-0.96 mg/kg, which is less than the claimed about 1.7 mg/kg maintenance dose. Thus, Stelmasiak does not teach or suggest the claimed about 1.7 mg/kg total maintenance dose.

c. A POSA Would Not Have Arrived At The Claimed Maintenance Period Based on Routine Optimization

125. I understand that Petitioner argues that the optimal cladribine dose and dosing length in a maintenance period could be determined through "routine optimiz[ation]." Pet. 40-43. Specifically, I understand that Petitioner argues that

"[a] POSA would have arrived at a suitable dose and length of administration, for example, by regularly measuring the patient's lymphocyte counts and evaluating the efficacy of a given dose based on the changed [sic] in the count." *Id.*, 42. I disagree that a POSA would have arrived at the claimed maintenance period dose and dosing length through routine optimization by evaluating the "efficacy" of a given dose or dosing length based on a change in lymphocyte count, or any other outcome measure.

126. ***First***, as explained above, a POSA would have understood that patient lymphocyte count is a metric of safety, not a metric of efficacy. *Supra*, ¶¶98-99, 113-115; *see also supra*, ¶¶119-124. While the Petition occasionally characterizes lymphocyte count (or change thereof) as a measure of cladribine's "efficacy" (Pet. 16-17, 42), the Petition otherwise refers to suppression of lymphocyte count as an "effect of cladribine," a "therapeutic effect," a "treatment response," or a "response" to cladribine. *Id.,* 2, 7, 16, 41. Dr. Miller likewise refers to lymphocyte suppression as a "treatment response" or "response to therapy" (Ex. 1002, ¶¶16, 31, 35, 38, 48, 106), with one reference to a change in lymphocyte count as a "therapeutic effect." *Id.*, ¶16. Notably, Dr. Miller does not associate lymphocyte count with "efficacy." In its preliminary findings, the Board appears to have credited these arguments and opinions, including that a POSA could have optimized cladribine dose and length to achieve therapeutic efficacy by

"measur[ing] … changes in a patient's lymphocyte counts." Paper 10, 29, 30, 40-41, 47, 49. However, as Dr. Miller admitted during his deposition, "[l]ymphocyte suppression is not a measure of efficacy," (Ex. 2009, 121:14-18), even though he testified that "a sustained reduction of lymphocytes … indicate[s] the treatment response," which "mean[s] the same thing as therapeutic effect." *Id*., 30:12-31:15. Further, during deposition, Dr. Miller also stated that "therapeutic effects" are the "results seen in the context of the therapy," and that "[t]he results of the therapeutic effect do include side effects." *Id.*, 37:3-40:3. In this context, Dr. Miller admitted that Stelmasiak's discussion of "lymphocyte counts … together with granulocyte counts and platelet counts" "refers to hematologic side effects," but stated that these effects "relate to therapeutic effects." In my opinion, Dr. Miller's testimony indicates that his use of the terms "treatment response" and "therapeutic effect" do not necessarily suggest any therapeutic efficacy, and instead include side effects. As such, a POSA would not have used lymphocyte count to evaluate the efficacy of any "optimization" to a dosing regimen.

127. ***Second***, a POSA would have understood that due to the complex nature of MS disease course, including that disability in MS evolves slowly over years, the therapeutic effects of any dosing schedule can likewise only be assessed over time. As Dr. Miller explains in a 2000 book chapter that he co-authored, assessing the efficacy of an MS drug in an "open trial in a few patients with known

disease … still take[s] ***many months to a year or longer*** because of the variable nature of MS." Ex. 2005, 49. Dr. Miller further explains that disease-modifying drugs "are designed to reduce the number and severity of attacks in the hope that they will slow disease progression ***over the long term***" (*id.*, 61 (emphasis in original)) and thus "it is not possible to evaluate the extent to which any of these drugs is working for any one individual ***at any particular point in time.***" *Id.*, 60. Further, relapses are random events that require long follow-up of large patient numbers to properly assess a therapeutic response. *See*, *e.g.*, Ex. 2014, 2-5; Ex. 2017, 4-7. Thus, in my opinion, Petitioner's "routine optimization" suggestion disregards the variable and complex nature of MS, including that "MS is a chronic disease in which changes occur relatively slowly in most people." *See* Ex. 2005, 49. As such, a POSA would have understood that the benefits of a disease-modifying drug can only be assessed over time and that it would require years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact clinical outcomes. In particular, a POSA would have understood that it could take years to determine how any single modification to any of the various dosing parameters of cladribine (i.e., the dose, dosing period, cladribine-free period, etc.) affects the safety and efficacy of a particular dosing regimen.

128. Further, as discussed below, there are numerous possible combinations of dose, dosing period length/number, and drug-free period

length/number that a POSA could have attempted to "optimize." *Infra*, ¶¶158-161. However, nothing in the prior art taught a POSA what specific combination (if any) of the different variables—dose, length and number of dosing periods or drug-free periods—would result in a safe and effective MS treatment method. *Infra*, ¶162. Thus, given the numerous possible modifications to the various dosing parameters, the long period of time required to ascertain the effects of these modifications, and the unpredictability of these effects, I disagree that any optimization suggested by the Petitioner would be "routine."

129. In sum, a POSA would have understood that (1) Bodor and Stelmasiak only teach flat, fixed dosing; (2) even if Stelmasiak's initial treatment dose were converted into weight-based doses as Petitioner suggests, it is well above the claimed weight-based induction dose of about 1.7 to about 3.5 mg/kg; (3) Bodor and Stelmasiak, even in combination, do not teach or suggest a maintenance period of about 2 months or 2-4 months after about 8-10 or 10 months of no treatment; (4) Stelmasiak's subsequent treatment dose, even if converted into mg/kg as Petitioner suggests, would not correspond to the claimed maintenance period dose; and (5) routine optimization would not have led a POSA to modify the prior art to arrive at the claimed dosing regimen. As such, Bodor and Stelmasiak, alone or in combination, do not teach or suggest "a maintenance period" of about 2-4 or 2 months occurring about 8-10 or 10 months after an

induction period and having a total dose of "about 1.7 mg/kg," as claimed in the '947 patent.

B. A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Challenged Claims With A Reasonable Expectation Of Success

130. According to Dr. Miller, "a POSA would have been motivated to administer Bodor's oral cladribine composition for two months, followed by 10 months of no cladribine therapy," at which point "a POSA would have been motivated to retreat with cladribine, followed by another break in cladribine therapy." Ex. 1002, ¶105. Dr. Miller opines that there would have been a reasonable expectation of success because "cladribine was known in the art to treat MS and the dosing regimen is similar to that of Stelmasiak." *Id.* However, doing so would (1) change Bodor and Stelmasiak's flat, fixed dosing to weight-based dosing; (2) effectively reduce the initial treatment length and dose of Stelmasiak, which was reported to result in only "partial" patient response; (3) effectively prolong Stelmasiak's initial drug-free period; and (4) effectively extend Stelmasiak's month-long treatment phase. As explained below, it is my opinion that a POSA would not have been motivated to combine the teachings of Bodor and Stelmasiak as Dr. Miller suggested, or have had any reasonable expectation of success in doing so.

1. A POSA Would Not Have Been Motivated To Arrive At The Claimed Dosing Methods Via Routine Optimization Or Have Had A Reasonable Expectation Of Success In Doing So

131. I understand that Petitioner argues that the claimed total induction dose of about 1.7-3.5 mg/kg would have been obvious because it "overlaps" with Bodor's purported dosing range of about 1.4-2 mg/kg. Pet. 39. However, in my opinion, there is no "overlap" between Bodor's doses and the claimed doses. As I discussed above, a POSA would have understood that Bodor and Stelmasiak expressly disclose flat, fixed dosing; neither discloses any weight-based dosing. *Supra*, ¶¶85-97. And while Dr. Miller is relying on the purportedly "average" human weight of 70 kg, there is no express or inherent disclosure in Bodor of a patient weighing 70 kg, let alone of selecting a dose based on such a patient's weight. Thus, in my opinion, Dr. Miller's example of a patient weighing 70 kg represents hindsight analysis, rather than the understanding of a POSA in 2004.

132. Bodor does not describe any information regarding the weight of patients to be treated, and instead uses flat, fixed doses for all subjects in its bioavailability studies and its described dosing regimen. Ex. 1022, 23:15-20; 33:25-27, 36:18-20. As described above, a POSA would have understood that flat and weight-based dosing are fundamentally different dosing methods that would not result in equivalent dosing. *Supra*, ¶91. Additionally, a POSA reading Bodor would have understood that Bodor was aware of and considered weight-based

dosing regimens of cladribine as reported in prior trials, (Ex. 1022, 22:27-23:6) but nevertheless chose to use flat, fixed dosing. *Supra*, ¶¶85-97. I have reviewed Dr. Meibohm's Declaration, and we both share the opinion that Bodor specifically teaches flat, fixed dosing, not the weight-based dosing as claimed; and that, in fact, Bodor was aware of and considered weight-based dosing regimens of cladribine as reported in prior trials, but nevertheless chose to specifically use flat, fixed dosing. Ex. 2052, ¶¶68-69.

133. Further, as I also discussed above, prior to this proceeding, even Dr. Miller distinguished cladribine's "unique" weight-based dosing from the flat, fixed dosing of ***all other*** MS drugs (Ex. 2007, 3:53-4:18; Ex. 2008, 4:21-5:1), which further demonstrates that a POSA would not have understood Bodor to teach or suggest consideration of patient weight in its dosing. *Supra*, ¶¶92-93. A POSA reading Bodor and Stelmasiak would not have been motivated to change the flat, fixed dosing method disclosed in each reference to arrive at the weight-based dosing method as claimed. I have reviewed Dr. Meibohm's Declaration and we both share this opinion. Ex. 2052, ¶¶66-75.

134. I understand that Petitioner further argues that the optimal cladribine dose and dosing length in a maintenance period could be determined through "routine optimization" because the maintenance dose and dosing length are "result-effective" variables and because Bodor states that cladribine doses can be "fine

tun[ed]." Pet. 41-42. More specifically, I understand that Petitioner argues that "cladribine's dose and length of administration are result-effective variables because they achieve a recognizable result" and thus "[a] POSA would have arrived at a suitable dose and length of administration, for example, by regularly measuring the patient's lymphocyte counts and evaluating the efficacy of a given dose based on the changed in the count." *Id.*, 41-42. I disagree that a POSA would have arrived at the claimed maintenance period dose and dosing length by evaluating the "efficacy" of a given dose or dosing length based on a change in lymphocyte count, or have had any reasonable expectation of success in doing so.

135. ***First***, regarding "fine tuning," a POSA would have understood that Bodor does not teach or suggest fine tuning a weight-based dosage or converting its flat, fixed dosing regimen to a weight-based dosing regimen. Instead, a POSA would have understood that because Bodor does not consider patient weight, Bodor's suggestion to fine tune is with respect to its daily flat dosage of 10 mg. *Supra*, ¶¶86-90. This is especially the case because a POSA would have understood that Bodor was aware of and considered weight-based dosing regimens of cladribine as reported in prior trials, but nevertheless chose to specifically use flat, fixed dosing. *Supra*, ¶132; Ex. 2052, ¶69.

136. ***Second***, in my opinion, a POSA would not have been motivated to optimize any alleged maintenance dosing or dosing length based on a patient's lymphocyte count, or have had any reasonable expectation of success in doing so.

137. As discussed above (*supra*, ¶126), a POSA would have understood that lymphocyte count, or changes thereof, is not a metric of therapeutic efficacy, as Petitioner and Dr. Miller suggest. *See, e.g.,* Pet. 16-17, 41, 42; Ex. 1002, ¶¶16-18. Indeed, Dr. Miller admitted during his deposition that "[l]ymphocyte suppression is not a measure of efficacy." Ex. 2009, 121:14-18. By 2004, the mechanism by which cladribine exerted its therapeutic effect in MS patients was unknown (and is currently still not fully elucidated). Ex. 1031, 42; Ex. 1016, 432; Ex. 2032, 1903; Ex. 2001, 20. At best, cladribine's "potential activity in [MS] is based on the ***hypothesis*** that it acts by reducing the number of activated lymphocytes that can damage myelin." Ex. 1016, 432. Indeed, "[t]he mechanism of action of the beneficial effect of cladribine on MS is ***presumably*** related to the selective and sustained depletion of lymphocytes." Ex. 1031, 42. Thus, while a POSA would have understood that cladribine induces a reduction in lymphocyte count as a pharmacological effect (Ex. 1016, 421), by 2004, it had not been established that this effect was the causal basis for any therapeutic effect of cladribine, or that any level or length of lymphocyte reduction would have led to

MS treatment efficacy, let alone that lymphocyte reduction was a metric of cladribine's therapeutic efficacy. *See*, *e.g.*, Ex. 2001, 20.

138. Nevertheless, Dr. Miller opines that "neurologists commonly ***assessed the therapeutic effect*** of cladribine by monitoring a patient's lymphocyte count, with a sustained reduction of lymphocytes, e.g. below 1000/μL, being characteristic of a treatment response." Ex. 1002, ¶16. As support, Dr. Miller cites to Ex. 1018, Ex. 1013, and Ex. 1014. *Id.* I have reviewed these references and in my opinion none of these references suggests that lymphocyte count, or a reduction in lymphocyte count, is a metric of therapeutic efficacy rather than safety.

139. Ex. 1018 corresponds to the Rice publication. Rice discloses a study by the Cladribine Clinical Study Group, of which I was a member. *See* Ex. 1018, 1145 (author list), 1154 (Appendix 1). Nowhere does Rice comment on efficacy based on lymphocyte count, or connect efficacy and lymphocyte count in any way. Instead, Rice discloses lymphocyte levels within the "hematologic changes" sub-section, which in turn falls within the "Safety evaluation" section. *See id.*, 1151-52. A POSA would have understood that monitoring of "hematologic changes" relates to safety concerns about cladribine's lymphocytotoxicity. And while the Rice publication notes that "[a] more marked, long-lasting, dose-related lymphocyte count reduction confirmed the ***pharmacologic activity*** of cladribine in

this study," (*id.*, 1153), this does not suggest that lymphocyte count reduction is a metric of cladribine's therapeutic efficacy.

140. Ex. 1013 corresponds to the Stelmasiak publication. Stelmasiak discusses "lymphocyte counts" in the context of "hematological side effects," alongside "Granulocyte counts" and "platelet counts." Ex. 1013, 5. Stelmasiak's Figure 1 shows that lymphocyte levels were ***lower*** at month 24 than month 3; however, Stelmasiak's Table 1 shows that the corresponding EDSS scores were ***worse*** at month 24 than month 3 (4.3±2.0 and 3.4±1.4, respectively). *Id.*, 5-6. Further, Stelmasiak shows that while "EDSS scores were significantly reduced during the treatment," the final EDSS score at month 24 returned to ***baseline*** levels, even though lymphocytes continued to be suppressed. *Id.*, 6. Stelmasiak also identified two "non-responders" who showed lymphocyte "reduction of approximately the same magnitude as in some of the 'responders,'" further demonstrating that a reduction in lymphocyte count does ***not*** correlate with cladribine efficacy. *Id.* In view of these results, a POSA would have understood that neither lymphocyte count nor a change in lymphocyte count measures cladribine's therapeutic efficacy.

141. Lastly, Ex. 1014 corresponds to Beutler's 1996 publication. Like Rice and Stelmasiak, Beutler discloses lymphocyte evaluation as part of its "[h]ematologic evaluation." Ex. 1014, 1717 (explaining that "[l]ymphocyte subset

evaluation was done monthly during the course of drug administration" as part of its "[h]ematologic evaluation"). Beutler also discusses "[c]hanges in lymphocyte subsets" in its section on "Toxicity and adverse events[.]" *Id.*, 1719.

142. Thus, a POSA would have understood that, as of 2004, the art consistently showed that lymphocyte count was a metric of safety, not a metric of therapeutic efficacy for cladribine treatment.

143. While Dr. Miller has relied in part on Rice to support his opinion that lymphocyte count is a metric of "therapeutic effect," he has elsewhere criticized Rice for its lack of treatment "promise" and "unconvincing clinical benefit." In his 2008 book chapter reviewing "Escape therapies and management of multiple sclerosis" in "Multiple Sclerosis: A Comprehensive Text," Dr. Miller reviewed "a variety of drugs or procedures that have been studied for the treatment of MS," including cladribine. Ex. 2004, 333. As Dr. Miller admitted during deposition, his review of cladribine is based on two studies, a 1996 publication by Sipe et al. titled, "Development of cladribine treatment in multiple sclerosis" (Ex. 2030) and the 2000 Rice publication (Ex. 1018). Ex. 2004, 341, 350; Ex. 2009, 22:2-25:2. In his concluding "Summary and Recommendations" on cladribine, Dr. Miller states:

> Initial trials with cladribine [i.e., Sipe] ***showed promise*** in the treatment of SPMS ***but these results were not seen*** in the subsequent blinded, randomized, placebo-controlled trial [i.e., Rice]. Furthermore, studies

> of cladribine continue to show an enigmatic dissociation between positive effects on MRI and ***unconvincing clinical benefit***. Another ***drawback*** to the use of cladribine is the profound and very long-lasting ***lymphopenia induced by the drug*** … At this point, it seems ***prudent to await the results*** of a prospective, randomized, blinded trial of oral cladribine ***before recommending its use in patients with MS***.

Ex. 2004, 341.

144. In this same excerpt, Dr. Miller warned that cladribine-induced lymphopenia, i.e., lymphocyte reduction, is a "drawback" of cladribine treatment—even though his declaration in this matter repeatedly states that lymphocyte suppression is a "treatment response" or a metric of "therapeutic effect," based on studies such as Rice. *See id.*; Ex. 1002, ¶¶16, 35, 38, 48.

145. I understand that the Board noted in its preliminary findings that "[p]rior studies may not have universally pointed to cladribine's promise or efficacy but much of the reporting in the literature did." Paper 10, 49. However, Dr. Miller's prior statements, and the review papers of other skilled artisans in the field, including myself, suggest otherwise.

146. For example, the renowned MS specialist, Dr. John Noseworthy, published a 2006 book chapter reviewing "Disease-modifying treatments in multiple sclerosis," which included a review of cladribine. Ex. 2031, 729, 753.

Dr. Noseworthy's review of cladribine is based on at least four cladribine studies, all pre-2004: (1) Sipe et al. (1994); (2) Beutler et al. (1996); (3) Romine et al. (1999); and (4) Rice et al. (2000). Ex. 2031, 753, 821, 911, 913, 923. Dr. Noseworthy concluded his review of cladribine by stating, "We ***remain to be convinced*** that cladribine is useful, and ***do not recommend*** its use in the management of patients with multiple sclerosis." *Id.*, 753.

147. As for myself, I noted in a 2005 review paper on the "History of modern multiple sclerosis therapy" that "[t]rials with both interferon alpha and gamma ***proved unsuccessful***, ***as did treatment with*** oral myelin, ***cladribine***, sulfasalazine and inhibitors of tumour necrosis factor." Ex. 2011, 3. All of the references cited in my 2005 review paper were from 2004 or earlier.

148. Thus, based on at least my review, Dr. Miller's review, and Dr. Noseworthy's review of pre-2004 cladribine MS studies, a POSA would have understood that the pre-2004 cladribine MS clinical studies failed to demonstrate an effective clinical outcome for cladribine in treating MS.

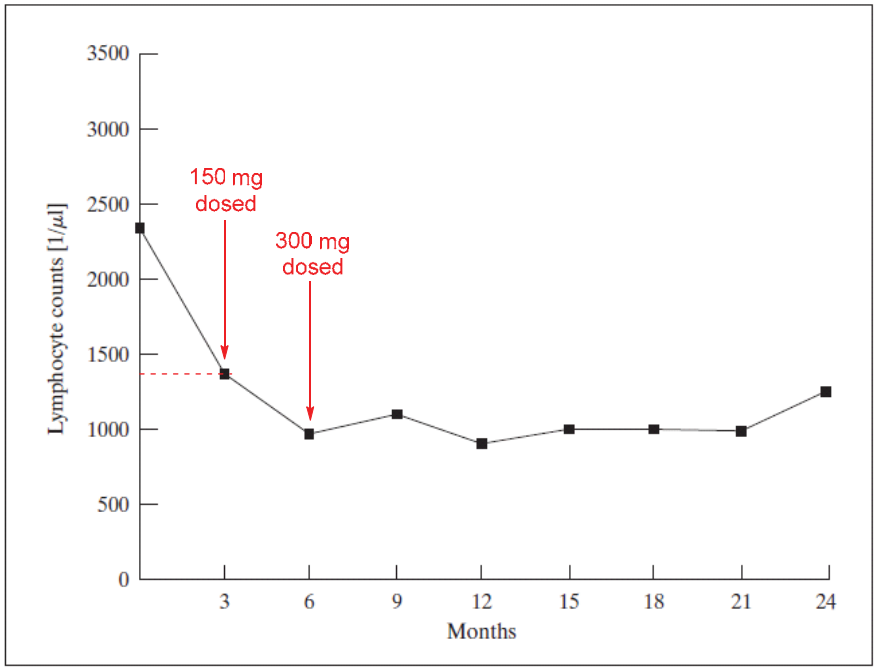
149. ***Third***, even if a POSA would have assumed that lymphocyte suppression is a measure of efficacy, it is not clear from the Petition ***what level*** of lymphocyte suppression would have been sufficient to show efficacy. Dr. Miller frequently states that "a decrease in the lymphocyte count to 1 x 10^9/L (or 1000/μL) or below constitutes 'suppression'" but also vaguely notes that during

induction and maintenance, lymphocyte count should be "below a given ***threshold***" and "suppressed to the ***threshold***" without identifying the threshold. Ex. 1002, ¶¶40, 59. During deposition, Dr. Miller agreed that "if a treatment is given and then the lymphocyte level is below normal range, that constitutes suppression," where "1,000 [cells/μL] is usually given as the lower limit of normal." Ex. 2009, 31:16-20, 32:9-12. In this context, I understand that the Board noted in its preliminary findings that "it is not evident that a sustained reduction to below 1000 cells/μL would be necessary before a therapeutic effect is observed." Paper 10, 47. But in the absence of ***any guidance*** as to a threshold lymphocyte level that would correspond to a therapeutic effect, especially in view of Stelmasiak's data showing the continued suppression of lymphocyte counts as EDSS scores returned to baseline in cladribine-treated patients, a POSA would not have been able to optimize cladribine dose or dosing length based on lymphocyte count, as Petitioner and Dr. Miller now suggest. Pet. 42; Ex. 1002, ¶¶89-93, 99-106, 108-110. Indeed, Dr. Miller admitted during his deposition that "[l]ymphocyte suppression is not a measure of efficacy." Ex. 2009, 121:14-18.

150. And to the extent that lymphocyte levels must be ***suppressed*** to or below a threshold of 1000 cells/μL, as Dr. Miller defines suppression (Ex. 1002, ¶¶32, 40, 90; Ex. 2009, 31:16-32:12), to show efficacy, a POSA would not have expected Bodor's dosing regimen to meet this threshold. This is at least because

the Stelmasiak study shows that even a dose of 150 mg oral cladribine did not suppress lymphocytes to or below a threshold of 1000 cells/μL. As shown in the annotated version of Stelmasiak's Figure 1 below, administration of 150 mg of oral cladribine at month three resulted in suppression of lymphocytes to a level ***above*** 1000 cells/μL (~1350 cells/μL). Ex. 1013, 5. Based on Dr. Miller's definition of suppression, i.e., that lymphocyte levels drop to below 1,000 cells/μL (Ex. 2009, 31:16-32:12), a POSA would have expected that Bodor's maximum cladribine dose of 140 mg, which is ***lower*** than Stelmasiak's 150 mg dose, would have been even less likely to reduce lymphocytes to a level below 1000 cells/μL, and thus according to Petitioner's argument likely would have been insufficient to result in an effective MS treatment. This is especially so in view of the lower bioavailability (39-43%) reported in Bodor, which I discuss further below. *See also* Ex. 2052, ¶¶81-85.

Figure 1. Average lymphocyte counts during and after treatment with cladribine.



151. ***Fourth***, even if a POSA would have assumed that the change in lymphocyte count were a measure of efficacy (which Dr. Miller and I agree it is not (*see* Ex. 2009, 121:14-18)), a POSA would not have been motivated to optimize cladribine dosing "by adjusting the ***daily dose*** administered." Pet. 42.

152. In my opinion, the art does not suggest that any change in daily lymphocyte count would provide any meaningful information on cladribine dosing. For example, lymphocyte count was not measured on a daily basis in the prior art of record. *See*, *e.g.*, Ex. 1018, 1146 ("MRI scans were obtained at ***baseline and months 6 and 12***, as were total lymphocyte count and lymphocyte subset counts … During the first year of the post-double-blind follow-up phase, … lymphocyte

counts were assessed ***quarterly***"); Ex. 1014, 1717 ("Lymphocyte subset evaluation was done ***monthly*** during the course of drug administration and less frequently thereafter"). While lymphocyte counts may fluctuate from day-to-day, such fluctuations would not provide sufficient information to evaluate the extent to which the change in dose or dosing length was beneficial for a patient, especially in view of the "marked and sustained reduction in lymphocyte counts [that] appears to occur ***regardless*** of the total cladribine dose." Ex. 1016, 422. Because cladribine induces a "prolonged, profound suppression of lymphocyte counts" (*id.*, 420), a POSA would not have been able to determine whether any change in lymphocyte count was a result of an adjustment in daily dose, or whether it was a result of the dose ***prior*** to adjustment. For at least these reasons, a POSA would not have been motivated to optimize cladribine dosing "by adjusting the daily dose administered" by measuring the lymphocytes counts.

153. However, even if changes in daily lymphocyte counts were measured, a POSA would not have had confidence in lymphocyte count as a metric of efficacy, at least because Stelmasiak's results show a lack of correlation between lymphocyte count and EDSS scores, i.e., the data showed the continued suppression of lymphocyte counts as EDSS scores retuned to baseline for cladribine-treated patients. *See* Ex. 1013, 5-6.

154. Additionally, I understand that Petitioner and Dr. Miller suggest that ***both*** cladribine dosage and dosage duration can be optimized based on their effects on lymphocyte levels. Pet. 40-43; Ex. 1002, ¶¶89-93. But for the reasons discussed above regarding lymphocyte count as a metric of safety and not efficacy, a POSA would not have "optimized" dose and or dosing length based on lymphocyte count.

155. ***Fifth***, I also understand that the Petition does not appear to limit the "recognizable result" to a change in lymphocyte count. *See* Pet. 41 ("The prior art, therefore, teaches that cladribine's dose and length of administration are result-effective variables because they achieve a recognizable result—'the therapeutic effect,' which can be measured by, ***e.g.***, the change in a patient's lymphocyte count"); *id.*, 42 ("A POSA would have arrived at a suitable dose and length of administration, ***for example***, by regularly measuring the patient's lymphocyte counts and evaluating the efficacy of a given dose based on the changed in the count."). And while Dr. Miller uses "e.g.," occasionally (Ex. 1002, ¶91, 95, 117, 118), he also expressly relies primarily on a change in lymphocyte count as the "recognizable result." *See* Ex. 1002, ¶¶91, 95, 109, 117, 118.

156. Nevertheless, I understand that Petitioner suggests that cladribine's dose and dosing length are result-effective variables that could be modified to achieve immunosuppression and therapeutic efficacy based on a metric ***other than***

changes in lymphocyte count. However, I did not find any other metric of efficacy that could be used to optimize cladribine's dose and dosing length identified in the Petition. *See* Pet. 41. While Dr. Miller did note that Rice discloses "a small, dose-dependent, median percent decrease in T2 lesion volume" (cleaned up) (Ex. 1002, ¶91), Rice also reported that "clinical efficacy was not shown" in its study. Ex. 1018, 1153; *see also* Ex. 2004, 341 ("studies of cladribine continue to show an enigmatic ***dissociation*** between positive effects on MRI and ***unconvincing clinical benefit***.").

157. But regardless of which "recognizable result" a POSA would have looked to for optimization, a POSA would have understood that due to the complex nature of MS disease course, including that disability in MS evolves slowly over years, the therapeutic effects of any dosing schedule can only be assessed ***over time***. *See* Ex. 2005, 49 (Dr. Miller explaining that assessing the efficacy of an MS drug in an "open trial in a few patients with known disease … still take[s] ***many months to a year or longer*** because of the variable nature of MS."); *id.* 60-61 (Dr. Miller explaining that disease-modifying drugs "are designed to reduce the number and severity of attacks in the hope that they will slow disease progression ***over the long term***" and thus "it is not possible to evaluate the extent to which any of these drugs is working for any one individual ***at any particular point in time.***"). As such, a POSA would have understood that it would require

years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact outcome measures, including clinical efficacy measures or MRI; and that for each adjustment in dose and/or dosing length, a separate dosing schedule would need to be studied to assess the impact of such a change, which would take years. Thus, in my opinion, Dr. Miller's suggestion that a POSA would have arrived at the claimed method by routine optimization, including by "***easily*** … adjusting the daily dose" (Ex. 1002, ¶117) ignores the variable and complex nature MS, including that "MS is a chronic disease in which changes occur relatively slowly in most people." *See* 2005, 49. A POSA would have understood that the benefits of a disease-modifying drug can only be assessed over time and that it would require years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact clinical outcomes.

158. Lastly, Dr. Miller's routine optimization suggestion also ignores the numerous possible combinations of dose, dosing period length/number, and drug-free period length/number that a POSA could have "optimized." Dr. Miller opines that a POSA would have "used Bodor's [2/10]-month [treatment/no treatment] period as a starting point" for both the maintenance period and the subsequent cladribine-free period, "knowing that it could be routinely optimized." Ex. 1002, ¶¶102, 104. However, as discussed above, a POSA would not have even started with Bodor's treatment regimen at least because Bodor's maximum cladribine dose

of 140 mg is lower than Stelmasiak's 150 mg dose and has lower bioavailability than Stelmasiak's dosage form, which likely would have been insufficient to reduce lymphocytes to a level below 1000 cells/μL or would further reduce the "partial" efficacy reported by Stelmasiak. *Supra,* ¶150. Nor would a POSA have simply resumed treatment after Bodor's 10-month cladribine-free period (rather than before/after the 10-months, if at all) without at least considering the disease state of the patient, the need for further treatment, the efficacy of the treatment, and safety signals such as lymphocyte counts. *Supra,* ¶¶103, 113-115. As I noted before, even Dr. Miller opines that with respect to the "the length of time" of a "cladribine-free period," "[a] POSA would have had the skill to monitor a patient's lymphocyte count and side effects associated with lymphocyte and myelosuppression" so as to "mitigate side effects." Ex. 1002, ¶104. To the extent a POSA would have modified the teaching of Bodor and re-treated after Bodor's 140 mg dose, a POSA could have considered a shorter cladribine-free period, such as the 2- or 5-month cladribine-free period disclosed in Stelmasiak (Ex. 1013, 5), or the at least 12-month minimum cladribine-free period disclosed by Rice (Ex. 1018, 1146), or any other length of the cladribine-free period (e.g., 3, 4, 6, 7, 8, 9, or 11 months). For at least these reasons, I disagree "it would have been logical for a POSA to have used Bodor's [2/10]-month treatment period as a starting point."

159. Further, despite opining that "the length of cladribine administration was recognized as a result-effective variable" that could be optimized based on a patient's lymphocyte count while using Bodor's 2-month treatment as a good "starting point" for routine optimization, Dr. Miller concludes that "[a] POSA would have thought to re-administer cladribine for two months during the retreatment (or maintenance) period" simply "because a POSA would have known that Bodor teaches that a treatment cycle of two months of cladribine therapy followed by 10 months of no cladribine therapy is an appropriate dosing regimen to treat MS." Ex. 1002, ¶102. Rather than "optimize" the length of the maintenance period, Dr. Miller opts to "lower the total dose of cladribine administered during the maintenance period" because Stelmasiak administers 50 mg at month nine, compared to the initial 300 mg over six months. *Id.*, ¶108. But Stelmasiak's "lower" dose is simply one treatment course, as compared to six consecutive treatment courses in the initial treatment period. Ex. 1013, 5. If a POSA "starting" with Bodor would have looked to Stelmasiak for guidance on a maintenance period dose, as Dr. Miller opines, a POSA would have at least considered using one course of treatment, as Stelmasiak did, to "lower" the dose, which Dr. Miller himself suggests but subsequently ignores. *See* Ex. 1002, ¶102 ("a POSA would have known how to optimize the length of cladribine administered to optimize a patient's lymphocyte count (e.g., by administering

cladribine for a shorter period of time to reduce the amount delivered).”). Further, if a POSA would have started with Stelmasiak’s 300 mg oral dose as an induction period dose, ***any*** dose less than 300 mg would have satisfied Dr. Miller’s requirement that the maintenance period dose be lower than the induction period dose.

160. Similarly, despite opining that “the length of the cladribine-free period is a result-effective variable” that could be optimized based on “monitor[ing] a patient’s lymphocyte count and side effects associated with lymphocyte and myelosuppression” to “mitigate side effects while maximizing lymphocyte suppression,” Dr. Miller simply concludes that “a POSA would have been motivated” to use a 10-month second cladribine-free period. *See* Ex. 1002, ¶105 (illustration of “how a POSA would have been motivated to treat MS in view of Bodor and Stelmasiak in light of the general knowledge in the art”). Dr. Miller does not even address how a 10-month cladribine-free period, rather than a shorter or longer period, would have “mitigate[d] side effects while maximizing lymphocyte suppression,” especially in view of the alleged “lower” maintenance dose preceding this cladribine-free period and in view of cladribine’s “prolonged, profound suppression of lymphocyte counts.”

161. Thus, Dr. Miller’s routine optimization suggestion ignores the numerous possible combinations of dose, dosing period length/number, and drug-

free period length/number that a POSA could have "optimized." For example, a POSA could have considered (1) an induction period dose between Bodor's 140 mg and Stelmasiak's 300 mg initial dose (160 different doses); (2) an induction period length between Bodor's two-month treatment length and Stelmasiak's six-month treatment length (at least 5 different dosing lengths); (3) a cladribine-free period between Stelmasiak's two-month cladribine-free period and Bodor's ten-month cladribine-free period (9 different cladribine-free periods); (4) a maintenance period dose between Stelmasiak's 50 and 300 mg initial dose (at least 250 different doses); (5) a maintenance period length between Stelmasiak's one-month and six-month treatment length (at least six different dosing lengths).

162. Importantly, as of 2004, nothing in the prior art taught a POSA what specific combination (if any) of the different variables—dose, length and number of dosing periods or drug-free periods—would result in a safe and effective MS (including RRMS or early SPMS) treatment method. Indeed, despite the various cladribine clinical trials before 2004 using different dosing regimens, there was skepticism regarding using cladribine for treating MS. Ex. 2005, 45 ("In recently completed trials of oral myelin, cladribine, and sulfasalazine, these agents were found not to be of benefit" for treating MS), *id.*, 67 ("A trial of cladribine failed to show benefit in progressive disease."); Ex. 2031, 753 ("We ***remain to be convinced*** that cladribine is useful, and do not recommend its use in the

management of patients with multiple sclerosis."); Ex. 2004, 341 (noting that "studies of cladribine continue to show an enigmatic ***dissociation*** between positive effects on MRI and ***unconvincing clinical benefit***."). Further, given that "[a] marked and sustained reduction in lymphocyte counts appears to occur ***regardless*** of the total cladribine dose" (Ex. 1016, 422) and the dissociation between outcome measures in cladribine studies, a POSA would not have known how the combination of these variables would impact the treatment efficacy of MS, which as described above, could take years to evaluate.

163. Thus, given (1) the numerous possible combinations of dosing parameters a POSA could have considered; (2) the lack of guidance as to which combination would be safe or effective; (3) the lack of any guidance as to what level of lymphocyte reduction or length of lymphocyte reduction (if any) would be effective in treating MS; and (4) the "many months to a year or longer" needed to evaluate the extent to which any of the possible combinations would be effective, other than through hindsight analysis, a POSA would not have been motivated to arrive at the claimed dosing methods via routine optimization or have had a reasonable expectation of success in doing so.

2. A POSA Would Not Have Been Motivated To Adopt Weight-Based Dosing Or Have Reasonably Expected To Arrive At The Claimed Weight-Based Dosing Regimen

164. As I discussed above (*supra*, ¶¶85-97), a POSA would have understood that both Bodor and Stelmasiak teach flat, fixed dosing. Neither Bodor nor Stelmasiak would have motivated a POSA to shift from their respective flat dosing method to a weight-based dosing method.

165. Bodor referenced and considered weight-based dosing in the art but ultimately selected flat, fixed dosing for its method. Ex. 1022, 22:17-23:24. Stelmasiak, like Bodor, teaches flat, fixed cladribine dosing, but further teaches the effects of cladribine were unrelated to its dose per body weight. Stelmasiak reports that "[t]here was no indication that a 'good response' is related to the actual cladribine dose per body weight" and that "there was no correlation between the depth of lymphocyte nadir, or the magnitude of lymphocyte count reduction from the initial value, and the drug dose expressed per kg of body weight[.]" Ex. 1013, 6, 7. That is, Stelmasiak teaches the effects of cladribine were not related to its dose per body weight. In my opinion, Stelmasiak thus teaches away from weight-based dosing and a POSA would not have been motivated to shift from flat, fixed dosing to adopt weight-based dosing.

166. For at least these same reasons, i.e., that Stelmasiak teaches the effects of cladribine are not related to the dose per body weight, a POSA would not have

had a reasonable expectation of success in modifying Bodor and Stelmasiak to arrive at the weight-based dosing of the challenged claims.

3. A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed Induction Doses Or Have Had A Reasonable Expectation Of Success In Doing So

167. As I discussed above (¶¶150, 158), a POSA would not have started with Bodor's treatment regimen at least because Bodor's maximum cladribine dose of 140 mg is lower than Stelmasiak's 150 mg dose (after three months) and thus would have been less likely to reduce lymphocytes to a level below 1000 cells/μL, under Dr. Miller's theory that lymphocyte suppression to such a level is required for an MS "therapeutic effect." *See*, *e.g.*, Ex. 1002, ¶16; Ex. 2009, 31:16-32:12. Nevertheless, Dr. Miller opines that "[a] POSA would not have expected Bodor's cladribine tablets to provide the same in vivo lymphocyte profile as Stelmasiak and Grieb report because of Bodor's 'improved cladribine absorption' and 'higher bioavailability.'" Ex. 1002, ¶110. I also understand that Petitioner identifies "oral drug delivery," "increased bioavailability," and "lowered interpatient variation" as reasons for a POSA "to use Bodor's form to treat MS." Pet. 34. However, in my opinion, a POSA would have understood that Stelmasiak's oral cladribine formulation has higher bioavailability than Bodor's. I have reviewed Dr. Meibohm's Declaration and he also shares the opinion that Stelmasiak's oral cladribine formulation has higher bioavailability than Bodor's. Ex. 2052, ¶¶81-83.

168. I have reviewed Dr. Meibohm's Declaration and agree with his opinion that Stelmasiak and Liliemark (as cited by Stelmasiak) describe the same cladribine PBS (pH=7.4) formulation. I note that even Dr. Miller admits that "a POSA would have understood [Stelmasiak's solution] was the same dosage form disclosed by Liliemark." Ex. 1002, ¶110. I also agree with Dr. Meibohm's opinion that Stelmasiak's formulation has 50% bioavailability, because Stelmasiak reports that its 10 mg oral dosage would generate the same exposure as its 5 mg subcutaneous dosage, and Liliemark reported that the same cladribine PBS (pH=7.4) formulation, when dosed subcutaneously, resulted in 100% bioavailability. Ex. 1013, 5; Ex. 2052, ¶¶57, 62-63. Additionally, I agree with Dr. Meibohm's opinion that despite the small difference in concentration between the Stelmasiak and Liliemark's cladribine-PBS solution (1 mg/mL vs. 2 mg/mL), a POSA would have understood that the bioavailability of the oral formulation used in Stelmasiak was the same as reported in Liliemark, i.e., about 50%, because such a small difference in concentration would not cause a significant difference in bioavailability. *See* Ex. 2052, ¶¶64-65.

169. This is consistent with the disclosure of Grieb (Ex. 1023), which is co-authored by Stelmasiak, and has substantially the same disclosure. Grieb also discloses that the same saline-based oral cladribine formulation has 50% bioavailability. Ex. 1023, 324 ("The drug was prepared as isotonic saline solution

… for subcutaneous injections."), *id.*, 325 (AUC "is practically of the same size when the dose is given … subcutaneously, or when a doubled dose is given orally (oral bioavailability is approximately 50%)"). A POSA would have understood Stelmasiak and Grieb's saline-based oral cladribine formulation has 50% bioavailability, as determined from the AUC ratio of the administration forms.

170. I have reviewed Dr. Meibohm's Declaration in which he describes Bodor and Stelmasiak's relative AUC approach to determine bioavailability (*see* Ex. 1013, 5; Ex. 1023, 325) and determined Bodor's tablets have 39.1-43.1% bioavailability. Ex. 2052, ¶¶42-43, 45-47. Bodor's Example 4 ("Clinical Study: Relative Bioavailability") shows the AUC ratio of Bodor's "Tablet 1" relative to the subcutaneous reference formulation ranged from 41.9-43.1% and Example 5 ("Clinical Study: Dose Response and Absolute Bioavailability") shows the AUC ratio of Bodor's 10.0 mg tablets relative to an intravenous reference formulation ranged from 39.1-39.4%. Ex. 1022, 36 (Table VI), 38 (Table VIII). Ex. 2052, ¶¶42-43, 45-47.

171. I have reviewed Dr. Meibohm's opinions and agree with his opinion that a POSA considering the bioavailability data reported by Bodor and Stelmasiak in view of Liliemark would have understood that Bodor's oral cladribine formulation has lower bioavailability than Stelmasiak's oral formulation because

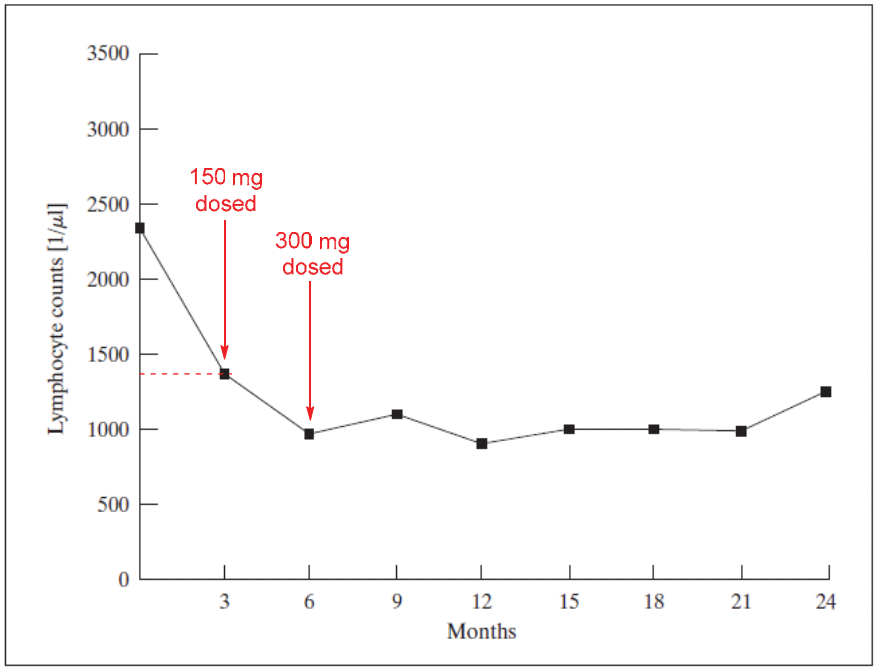
Bodor's formulation has 39.1-43.1% bioavailability, which is ***less*** than the 50% bioavailability of Stelmasiak's formulation. Ex. 2052, ¶¶81-83.

172. A POSA considering the oral cladribine formulations of Bodor and Stelmasiak, which differ in that Bodor's formulation has lower bioavailability, would not have been motivated to start with Bodor's oral cladribine dose of 100-140 mg administered over two months in an induction period, especially in view of the absence of any efficacy data in Bodor. Ex. 2052, ¶¶85-89. Stelmasiak reported "significantly reduced" EDSS scores of 3.4±1.5 and 2.9±1.7 at months 3 and 6, respectively, which correspond to cladribine doses of 150 mg and 300 mg, respectively. Ex. 1013, 6 (Table 1). Here, the higher dose (300 mg) resulted in a better EDSS score than the lower dose (150 mg). *Id*. While Bodor's maximum dose of 140 mg is close to Stelmasiak's 150 mg dose, Bodor's formulation has ***lower*** bioavailability than Stelmasiak's formulation. As such, a POSA would not have expected Bodor's 140 mg dose to have the same effect as Stelmasiak's 150 mg dose. Based on my review of Dr. Meibohm's declaration, I understand he agrees with this opinion. *See* Ex. 2052, ¶¶86-89.

173. Further, I understand that the Petition asserts that "the primary ***goal*** of [MS] treatment is to reduce signs or symptoms of MS, example.g., [*sic*] ***decrease lymphocyte count***, reduce relapse rate, and ***postpone disease progression***." Pet. 17 (emphasis added). However, Stelmasiak reports that the lymphocyte count reached

a nadir of 968 cells/μL at month 6 only after administering 300 mg as compared to ~1350 cells/μL at month 3 after administering 150 mg was administered (as shown in the annotated version of Stelmasiak's Figure 1 below). In other words, Stelmasiak's 300 mg dose not only results in lower lymphocyte counts but also in better EDSS scores than its 150 mg dose. Thus, in view of Petitioner's argument that "decreas[ing] lymphocyte count" and "postpon[ing] disease progression" are goals of MS treatment (Pet. 17), and in view of Bodor's lower bioavailability, a POSA if anything would have expected Bodor's lower dose of 140 mg and two-month dosing period to be less effective than Stelmasiak's dosing regimen at "decreas[ing] lymphocyte count" and "postpon[ing] disease progression." Ex. 2052, ¶¶84-89.

Figure 1. Average lymphocyte counts during and after treatment with cladribine.



174. But even if a POSA would have viewed Stelmasiak's 150 mg dose after 3 months to be efficacious, Stelmasiak reported that three out of ten patients were "non-responders," i.e., their relapse rate did not change and their EDSS scores were worse than baseline after 18 months of treatment. Ex. 1013, 6 (Figure 2). If anything, a POSA would have wanted to further increase Stelmasiak's 150 mg dose to try to improve efficacy, rather than decrease its dose to Bodor's 100-140 mg dose.

175. Accordingly, a POSA would not have been motivated to start with Bodor's oral cladribine dose of 100-140 mg administered over two months in an

induction period, or have had a reasonable expectation of success in doing so. *See also* Ex. 2052, ¶¶84-89.

176. Lastly, a POSA also would not have been motivated to modify the teachings of Bodor and Stelmasiak to arrive at the claimed induction dose. I have reviewed Dr. Meibohm's declaration and he agrees that a POSA also would not have been motivated to modify the teachings of Bodor and Stelmasiak to arrive at the claimed induction dose. Ex. 2052, ¶¶73-77, 83-85, 89-90. Stelmasiak reports a patient weight range of 52-75 kg. Ex. 1013, 5. Even if one were to convert Stelmasiak's 300 mg initial dose into mg/kg based on the reported patient weight range, that would correspond to 4.0-5.77 mg/kg—this is significantly higher than the claimed induction period doses of about 1.7-3.5 or 1.7 mg/kg. *See id*. And here, Stelmasiak's dosing regimen did not ultimately result in ***any change in EDSS score*** at the end of the study (month 24) for the study population, despite Stelmasiak reporting "significant improvement" of "[n]eurological status of the patients (expressed semi-quantitatively according to the EDSS scale) … between 6 and 15 month of the study" (*id.*, 4). *Id*., 6 (Table 1) (showing baseline EDSS score before treatment at 4.3±1.8 and final EDSS score at month 24 at 4.3±2.0). Given the ultimate lack of efficacy in improving disability using Stelmasiak's dosing regimen, a POSA would not have been motivated to ***lower*** Stelmasiak's dose to

arrive at the claimed induction period dose of about 1.7-3.5 or 1.7 mg/kg, or have had a reasonable expectation of success in doing so. *See* Ex. 2052, ¶¶86-89.

177. Therefore, in my opinion, a POSA considering Bodor and Stelmasiak would not have been motivated to start with Bodor's oral cladribine dose of 100-140 mg administered over two months in an induction period, which would effectively reduce both Stelmasiak's dose and dosing period, to arrive at the claimed induction period dose of about 1.7-3.5 or 1.7 mg/kg, or have had a reasonable expectation of success in doing so. Ex. 2052, ¶¶73-77, 84-85, 86-89.

4. A POSA Would Not Have Been Motivated To Immediately Re-Treat Patients After Bodor's 10-Month Cladribine-Free Period Or Have Had A Reasonable Expectation Of Success In Doing So

178. I understand that Dr. Miller opines that a POSA would have been motivated to re-treat patients with cladribine "after [Bodor's] 'ten months of no treatment'" because "clinical studies [indicate] that patients may relapse during or after cladribine therapy" and because Stelmasiak allegedly reports a "a very marked" reduction in relapse rate and improvement in EDSS scores "***after*** the retreatment." Ex. 1002, ¶¶100-101. I also understand that Petitioner argues that a POSA would have resumed treatment after Bodor's cladribine-free period because this was "the general immunosuppression framework common with MS therapies: an induction period, followed by a drug-free period, and followed by a further retreatment (maintenance) period." Pet. 36. However, as I discussed above, Bodor

does not teach or suggest re-treatment at any time, including immediately after its 10-month cladribine-free period. *Supra*, ¶¶98-119. I disagree that Stelmasiak or the art cited by Dr. Miller would have motivated a POSA to re-treat with cladribine after Bodor's 10-month cladribine-free period. *See supra*, ¶¶98-124.

179. ***First***, as I discussed above, the art did not teach such a "general immunosuppression framework" as the Petition alleges. *Supra*, *e.g.*, ¶¶54-58, 102-110, 113, 122. For example, as described above, by 2004, the art shows that approved disease-modifying treatments for MS were dosed continuously to maintain the drug's pharmacological effects, rather than based on the purported "cyclical" nature of MS. *Supra*, ¶¶54-58. Thus, in my opinion, a POSA would not have understood there to be a "general immunosuppression framework common with MS therapies," which includes an induction period, a drug-free period, and a re-treatment period. *See* Pet. 36; *see also* Pet. 17.

180. Further, in the context of cladribine, if a POSA were to consider re-treatment, a POSA would have looked to the studies in which cladribine was re-treated, e.g., Rice and Romine. Rice set forth three requirements before a patient could receive re-treatment: "patients who fulfilled the hematologic dosing criteria were permitted to receive open-label cladribine treatment … provided at least 12 months had elapsed since the last dose of cladribine and there was evidence of disease progression." Ex. 1018, 1146. Similarly, Romine discloses re-treating a

subset of patients "because of a recurrence of disease worsening." Ex. 1031, 43. Based on Rice and Romine, a POSA would have understood that any re-treatment with cladribine would have been based on a patient's need for further treatment, while taking in consideration cladribine's mechanism of action and pharmacologic effects, as measured by the patient's safety biomarkers, e.g., hematologic criteria. Tellingly, Rice teaches an 8-month regimen that includes a 2-month cladribine-dosing period followed by a 6-month placebo-dosing (drug-free) period. Ex. 1018, 1145, 1146. However, re-treatment, if any, does not restart immediately following the 8-month regimen, but instead is subject to the three separate requirements discussed above, including "at least 12 months had elapsed since the last dose of cladribine." *Id*., 1146.

181. Thus, based on how cladribine and other disease-modifying therapies were readministered, a POSA would not have been motivated to automatically and immediately resume treatment after Bodor's 10-month cladribine-free period, but would have considered re-treatment—if at all—only when there is a showing of patient need for further treatment and when it was safe to do so. *Supra*, ¶¶54-58, 102-110, 113.

182. ***Second***, that some "patients may relapse during or after cladribine therapy" does not suggest that a POSA "would have been motivated to retreat the relapsing patients with cladribine after [Bodor's] 'ten months of no treatment.'"

See Ex. 1002, ¶100. The occurrence of relapses during or after cladribine therapy could suggest an inadequate treatment response to cladribine, at which point some clinicians will switch the patient to an alternative MS therapy.

183. ***Third***, a POSA looking to Stelmasiak would have understood that, at best, Stelmasiak only teaches the "maintenance" of EDSS scores and lymphocyte levels when cladribine is re-administered at month 9 (after 2 months of no treatment) and either month 12 or 15 (after either 2 or 5 months of no treatment). Ex. 1013, 5 (Figure 1), 6 (Table 1); *see also* Ex. 1002, ¶108 ("a dose of 50 mg at months 9 and 12 or 15 ***maintained*** the reduction in lymphocytes for another 6-9 months"). But Stelmasiak does not teach "maintaining" efficacy levels after 10 months of no treatment. Instead, Stelmasiak's results indicate that during 9 months of no treatment (months 16-24), ***EDSS scores worsened*** for both "responders" and "non-responders," eventually returning to baseline for both groups and nearly returning to baseline for "responders." Ex. 1013, 6 (Table 1, Figure 2). Further, after 6 months of no treatment (months 16-21), lymphocyte levels began to increase, even though they remained below baseline levels. *Id*., 5 (Figure 1). And while Dr. Miller opines that a POSA would have simply "***believed*** Bodor's dosing regimen to have a sufficient immunosuppressive effect to ***treat MS***" (Ex. 1002, ¶99), there are ***no data*** in Bodor to support efficacy of Bodor's treatment regimen. Instead, if anything a POSA would have understood from Stelmasiak's results that

Bodor's oral formulation and treatment regimen would have been less likely to be effective, especially since Stelmasiak used a higher dose of an oral cladribine formulation having higher bioavailability but still did not report maintaining efficacy over a 9-month cladribine-free period.

184. Thus, as described above, if anything a POSA would have expected Bodor's 100-140 mg dose to be less effective than Stelmasiak's initial three months of treatment using 150 mg cladribine dose with higher bioavailability than Bodor's formulation. *Supra*, ¶¶150, 158. At least because Stelmasiak suggests its treatment efficacy cannot be maintained after a 9-month cladribine-free period, a POSA would not have had a reasonable expectation of success in re-treating patients after Bodor's 10-month cladribine-free period.

5. A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed 1.7 Mg/Kg Maintenance Dose Or Have Had A Reasonable Expectation Of Success In Doing So

185. I understand that the Board indicated the challenged claims do not require that the total maintenance dosing be lower than the total induction dosing. Paper 10, 17. Nevertheless, I understand that Dr. Miller opines that "[a] POSA would have been motivated to administer a lower total dose of cladribine in the maintenance period compared to the total dose in the induction period [of Bodor, i.e., 100-140 mg]." Pet. 39 (citing Ex. 1002, ¶108). According to Dr. Miller, "a POSA would have understood that a lower dose of cladribine was sufficient to

maintain the lymphocyte suppression effected during the induction period" because Stelmasiak's "50 mg at months 9 and 12 or 15 maintained the reduction in lymphocytes for another 6-9 months." Ex. 1002, ¶108. However, the "lymphocyte suppression effected" by Stelmasiak's 50 mg dose, i.e., the immunosuppressive effect (Pet. 38), is based on a ***higher*** initial dose (300 mg), as compared to Bodor's maximum 140 mg dose, and which reportedly "significantly reduced" EDSS scores and lymphocyte levels. Ex. 1013, 5-6. And as I discussed in the previous section (*supra*, ¶¶183-184), Stelmasiak only teaches the "maintenance" of EDSS and lymphocyte levels when cladribine is readministered after a 2- or 5-month drug-free period (at month 9 and 12 or 15). *Id*. But these effects were not "maintained" during 9 months of no treatment (months 16-24)—Stelmasiak's results indicate that by month 18 (after at least 3 months of no treatment), EDSS scores were worsening, and by month 24 (after 9 months of no treatment), EDSS scores returned to baseline before treatment, even though lymphocyte levels started to increase but otherwise remained below baseline levels. Ex. 1013, 5 (Figure 1), 6 (Table 1).

186. As described above, compared to Stelmasiak, if anything a POSA would have expected Bodor's maximum dose of 140 mg dose using a formulation having ***lower*** bioavailability to be less effective than Stelmasiak's 150 mg dose (with higher bioavailability). *Supra*, ¶¶150, 158, 167-175. In other words, a

POSA would not have expected Bodor's 140 mg dose to have the same immunosuppressive effect as Stelmasiak's 150 mg dose. As such, a POSA would not have known what level of immunosuppression, if any, would be maintained with further treatment and would not have had any motivation to select the claimed about 1.7 mg/kg weight-based dose by looking to a cladribine dose that was the same as or lower than the initial induction dose.

187. But regardless of whether a POSA would have looked to a dose that was the same as or lower than the induction dose for any alleged maintenance dosing, a POSA would not have had any teaching or guidance from Bodor or Stelmasiak as to what cladribine dose would have been required to maintain any treatment effects of Bodor's treatment method comprising using 100-140 mg cladribine. In view of the various possible re-treatment doses a POSA could have considered (e.g., 50 mg, 300 mg, or any value between 50 and 300 mg, or more than 300 mg or less than 50 mg), it would require years to determine which maintenance dose from among the numerous options was "optimal," all without any clear guidance from the prior art or any level of predictability as to which re-treatment dose would have resulted in a safe and effective MS treatment method. *Supra*, ¶¶157-162.

188. Thus, in my opinion, a POSA would not have been motivated to modify Bodor's treatment method based on Stelmasiak to arrive at the claimed

method for treating MS comprising a total induction period dose of about 1.7 or 1.7-3.5 mg/kg and a maintenance period about 8-10 or 10 months after the induction period, lasting about 2 or 2-4 months with a total dose of about 1.7 mg/kg, or have had any reasonable expectation of success in doing so.

C. The Dependent Claims Would Not Have Been Obvious Over Bodor And Stelmasiak

189. I understand that claims 38, 39, and 41-46 depend from claim 36 and thus include every limitation from claim 36. For at least the same reasons as discussed above, it is my opinion that dependent claims 38, 39, and 41-46 would not have been obvious over Bodor and Stelmasiak, alone or in combination.

190. Based on the additional reasons discussed below, claim 39, which further recites "wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg," i.e., that the total induction period dose and the total maintenance period dose are the same dose of "about 1.7 mg/kg," would not have been obvious over Bodor and Stelmasiak.

191. I understand that Dr. Miller opines that claim 39 would have been obvious because a POSA would have understood that "Bodor's dose is equivalent to approximately 1.4 to 2 mg/kg, which encompasses the dose of 'about 1.7 mg/kg.'" Ex. 1002, ¶124. However, for the reasons discussed above in *supra*, ¶¶85-94, Bodor does not teach or suggest any weight-based dosing for its method, nor would a POSA have understood Bodor to teach or suggest as such. Further,

Dr. Miller does not opine that a POSA would have been motivated to use the same dosing for maintenance and induction, or that a POSA would have had a reasonable expectation of success in doing so. Instead, the only opinion provided by Dr. Miller regarding the same dosing for maintenance and induction is in a footnote stating that "[a] POSA ***may*** also have considered administering cladribine in the maintenance period at the same total dose as in the induction period[.]" Ex. 1002, ¶89, n.3. But I understand that this opinion is inconsistent with Dr. Miller's proposed construction of the term "maintenance period," which he defined as "a defined length of time in which cladribine is administered at a lower dose than the cladribine dose administered in an induction period." *Id*., ¶70.

192. Here, in my opinion, none of Bodor, Stelmasiak, or any other reference cited by the Petition or Dr. Miller's declaration teaches or even suggests a cladribine dosing regimen having an induction period and a maintenance period using the same cladribine doses. The only reference relied on by the Petition in its Ground to teach re-treatment is Stelmasiak, which clearly requires a second cladribine treatment dose (50 mg) significantly different from the initial treatment dose (300 mg). Thus, it is my opinion that a POSA would have had no motivation to repeat the same initial treatment dose in a subsequent re-treatment phase, nor would a POSA have had any reasonable expectation that such a cladribine

treatment protocol would be safe and effective. Therefore, claim 39 would not have been obvious over Bodor and Stelmasiak for these additional reasons.

IX. OBJECTIVE INDICIA SUPPORT THE NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS OF THE ’947 PATENT

193. I understand that objective indicia of non-obviousness are relevant to the determination of whether patent claims are non-obvious. In my opinion, the non-obviousness of challenged claims of the ’947 patent is further demonstrated by at least: (1) the skepticism of others, (2) the unexpected durable efficacy and safety of the claimed dosing regimen, and (3) the satisfaction of a long-felt unmet need for a short-course, oral therapy for MS.

A. Skepticism Of Others

194. I understand that evidence of skepticism of the claimed invention can weigh in favor of the non-obviousness of an invention. This is because doubt or disbelief by skilled artisans about the likely success of a solution suggests that they would not have combined or modified references to achieve the claimed invention. In my opinion, that is the case here.

195. As evidenced by multiple reports, skilled artisans expressed skepticism that cladribine could be used to treat MS. For example, Petitioner’s own declarant, Dr. Miller, expressed skepticism that cladribine would be useful for treating MS. In his 2000 book chapter on “Treatment Issues” for MS, Dr. Miller explained that “[i]n recently completed trials of oral myelin, cladribine, and

sulfasalazine, these agents were found not to be of benefit" for treating MS and that "[a] trial of cladribine failed to show benefit in progressive disease." Ex. 2005, 45, 67. Then, in his 2008 book chapter reviewing "Escape therapies and management of multiple sclerosis" in "Multiple Sclerosis: A Comprehensive Text," Dr. Miller reviewed "a variety of drugs or procedures that have been studied for the treatment of MS," including cladribine trials conducted before 2004. Ex. 2004, 333. Dr. Miller's review of cladribine is based on two pre-2004 studies, a 1996 publication by Sipe et al. titled, "Development of cladribine treatment in multiple sclerosis" (Ex. 2030) and the 2000 Rice publication (Ex. 1018). Ex. 2004, 341, 350; Ex. 2009, 22:2-25:2. In his concluding "Summary and Recommendations" on cladribine, Dr. Miller stated:

> Initial trials with cladribine [i.e., Sipe] ***showed promise*** in the treatment of SPMS ***but these results were not seen*** in the subsequent blinded, randomized, placebo-controlled trial [i.e., Rice]. Furthermore, studies of cladribine continue to show an enigmatic dissociation between positive effects on MRI and ***unconvincing clinical benefit***. Another drawback to the use of cladribine is the profound and very long-lasting lymphopenia induced by the drug … At this point, it seems ***prudent to await the results*** of a prospective, randomized, blinded trial of oral cladribine ***before recommending its use in patients with MS***.

Ex. 2004, 341. During deposition, Dr. Miller confirmed that "it would be preferable or prudent to await the results … of the prospective trial" before recommending oral cladribine for use in patients with MS. Ex. 2009, 26:15-27:8.

196. Based on his review of the pre-2004 cladribine trials, Dr. Miller expressed skepticism that cladribine would be useful to treat MS given that previous studies showed "unconvincing clinical benefit" and that the lymphopenia induced by cladribine is a "drawback," as demonstrated by Rice and other pre-2004 studies. Ex. 2004, 341.

197. But even before Dr. Miller expressed skepticism of cladribine in 2008, other skilled artisans also expressed skepticism in using cladribine to treat MS. For example, in 2006, the renowned MS specialist and former CEO of the Mayo Clinic, Dr. John Noseworthy, published a 2006 book chapter reviewing "Disease-modifying treatments in multiple sclerosis," which included a review of pre-2004 cladribine trials. Ex. 2031, 729, 753. Dr. Noseworthy's review of cladribine is based on at least four cladribine studies, all pre-2004: (1) Sipe et al. (1994); (2) Beutler et al. (1996); (3) Romine et al. (1999); (4) Rice et al. (2000). *Id.*, 753, 821, 911, 913, 923. Dr. Noseworthy concluded his review of cladribine by stating, "We ***remain to be convinced*** that cladribine is useful, and do not recommend its use in the management of patients with multiple sclerosis." *Id.*, 753. Thus, Dr. John

Noseworthy not only expressed skepticism that cladribine would be useful for treating MS, but also expressly recommended against its use in MS patients. *Id.*

198. I also expressed skepticism of cladribine's utility for treating MS based on my review of pre-2004 cladribine trials. I noted in a 2005 review paper on the "History of modern multiple sclerosis therapy" that "[t]rials with both interferon alpha and gamma ***proved unsuccessful***, ***as did treatment with*** oral myelin, ***cladribine***, sulfasalazine and inhibitors of tumour necrosis factor." Ex. 2011, 3. All of the references cited in my 2005 review paper were from 2004 or earlier.

199. Notably, there was skepticism of the safety of the cladribine dosing regimen even after the CLARITY trial reported its positive results based on significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity. *See* Ex. 2033, 416. In 2011, FDA issued a complete response letter requesting the study sponsor, EMD Serono, "provide an improved understanding of safety risks and the overall benefit-risk profile either through additional analyses or by additional studies." Ex. 2038, 1. FDA's complete response letter cited concerns over higher cancer risks associated with MAVENCLAD®, despite "conclud[ing] that substantial evidence of Cladribine Tablets' effectiveness was provided by the CLARITY[] study." *Id.* Thus, despite multiple outcome measures in the CLARITY trial supporting the efficacy of oral

cladribine for the treatment of MS, FDA still expressed concerns about using cladribine to treat MS. In my opinion, such concerns are tied directly to the CLARITY dosing regimen, which encompasses a commercial embodiment of the challenged claims of the ’947 patent, and provide further evidence that the claimed dosing regimen was nonobvious.

B. Unexpected Results

200. I understand that unexpected results also weigh in favor of the non-obviousness of the claimed invention. The challenged claims of the ’947 patent are directed to an oral MS dosing regimen comprising (i) an induction period having a total cladribine dose of about 1.7-3.5 mg/kg and lasting about 2-4 months; (ii) a cladribine-free period lasting from about 8 months to about 10 months; (iii) a maintenance period having a total cladribine dose of about 1.7 mg/kg and lasting about 2-4 months; and (iv) a cladribine-free period. In my opinion, Patent Owner’s MAVENCLAD® product practices the method recited in the challenged claims and has offered unexpected durable efficacy and safety in treating MS.

201. FDA approved MAVENCLAD® in 2019 on the basis of the results from the 96-week CLARITY Trial (ClinicalTrials.gov number NCT00213135), in combination with 10 years of safety data that overcame FDA’s initial concerns of increased cancer risks associated with MAVENCLAD®. Ex. 2040, 1; Ex. 2060, 1-2. The FDA News Release stated:

> The efficacy of Mavenclad was shown in a clinical trial in 1,326 patients with relapsing forms of MS who had least one relapse in the previous 12 months. Mavenclad significantly decreased the number of relapses experienced by these patients compared to placebo. Mavenclad also reduced the progression of disability compared to placebo.

Ex. 2040, 1.

202. Specifically, CLARITY showed that "[t]reatment with cladribine tablets significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks" in patients with RRMS. Ex. 2033, 416. In CLARITY, 1,326 patients had been assigned to one of three arms "to receive one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo." *Id.*, 417. In the first

48-week treatment period,[4] those in the 3.5 mg/kg arm received 0.875 mg/kg per course for two courses plus placebo for two courses, for a total of 1.75 mg/kg, while those in the 5.25 mg/kg arm received 0.875 mg/kg/course for four courses, for a total of 3.5 mg/kg. Ex. 2041, 1. In the second 48-week period, both cladribine groups received two courses of cladribine, at 0.875 mg/kg per course, for a total of 1.75 mg/kg. Ex. 2033, 418; Ex. 2041, 1. "***Both*** the regimens of ***3.5 mg and 5.25 mg per kilogram*** appeared to be ***equally efficacious***," as "each dose showed significant benefits in rate of relapse, disability progression, and magnetic resonance imaging (MRI) measures." Ex. 2033, 425; Ex. 2035, 1594.

203. In an extension of the CLARITY study ("CLARITY Extension"), the duration of the therapeutic benefit from CLARITY and the effects of an additional two years of treatment with cladribine tablets beyond the two-year dosing regimen from the original CLARITY trial were studied. Patients who had received

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[4] The '947 patent specification states that "'[a] month' refers to a period of time of or about 28, about 29, about 30 or about 31 days" and that "'[a] week' refers to a period of time of or about 5, about 6 or about 7 days." Ex. 1001, 4:43-46. A POSA would have understood that a month is about 28 days, which is about four weeks. Thus a POSA would have understood that a "48-week" period is about 12 months or a year.

cladribine during the CLARITY study received either placebo or an additional cumulative 3.5 mg/kg dose of cladribine over years three and four. Ex. 2035, 1594. The CLARITY Extension study unexpectedly showed that patients who had received a total cladribine dose of 3.5 or 5.25 mg/kg over two years in CLARITY, followed by two years of placebo in the extension study, continued to experience the benefits of the two-year dosing regimen from the original CLARITY trial, with "no evidence of increased clinical activity (i.e. disease rebound) after treatment discontinuation …, as reported for other therapies in MS with a direct effect on lymphocytes." *Id.*, 1603. Thus, the efficacy improvements from the CLARITY study were ***maintained*** in patients later treated with placebo in the Extension study, for at least two years after the initial two years of treatment.

204. Further, for those who continued to receive an additional 3.5 mg/kg of cladribine during the extension study, not only was there "no significant incremental benefit from additional treatment with cladribine tablets in Years 3 and 4," but the incidence of lymphopenia (Grade ≥3) was higher than for the placebo group, which received cladribine treatment only in the first two years of the 4-year study. *Id.*, 1599 (Table 2), 1603. In other words, continued treatment with cladribine, after the initial two-year treatment, did not provide any clinical improvement in efficacy but increased the risk of adverse events.

205. Thus, the two-year dosing regimen from the original CLARITY trial resulted in "***durable***" clinical efficacy that was comparable to the four-year cladribine regimen, but with an improved safety profile. *Id.*, 1594, 1603. As the study authors explained, "the response achieved at the end of CLARITY in the proportion of patients free from relapses or sustained disability progression was ***maintained*** in the Extension." *Id.*, 1603. The durability of the two-year dosing regimen from CLARITY was unexpected. As Dr. Kottil Rammohan, MD, professor of clinical neurology and director of the MS Division and Multiple Sclerosis Center of Excellence at the University of Miami, explained in an interview with NeurologyLive, a platform that provides direct access to expert insight in neurology: "What became clear, with both the lapse in going into the extension immediately and also about the extension, was this drug [i.e., cladribine] has a ***durability*** of effect that was ***unexpected***." Ex. 2042, 3.

206. The long-term efficacy and durability of the effect of cladribine tablets in patients from CLARITY/CLARITY Extension was confirmed in the CLASSIC-MS study. Ex. 2036, 719. This study evaluated long-term mobility and long-term disability status in patients who participated in CLARITY, with or without subsequent enrollment to CLARITY Extension. *Id.*, 720-721. The CLASSIC-MS study found "sustained long-term mobility and disability benefits of cladribine tablets" during the median ***10.9 years'*** follow-up period, with "favorable

outcomes ... observed in the subgroup of patients exposed to a cladribine tablets dose of 3.5 mg/kg over 2 years." *Id.*, 719, 728. For example, "[f]or patients receiving cladribine tablets 3.5 mg/kg over 2 years, the ARR [i.e., annual relapse rate] during the time period since LPSD [i.e., last parent study dose] was 0.13," with the proportion of patients in this exposed cohort who were relapse-free approximately two times higher than that observed in the cohort of never-exposed patients (i.e., 46.9% versus 26.8%). *Id.*, 724, 727 (Table 3).

207. Thus, the CLARITY trial demonstrated that the claimed dosing regimen yielded significant benefits in rate of relapse, disability progression, and MRI measures, with the benefits in relapse rate and disability progression maintained for more than 10 years. The CLARITY Extension trial also showed that the claimed dosing regimen provides a minimal dosing period that achieves durable clinical benefits with a lower incidence of lymphopenia, which can be viewed as a "sweet spot" corresponding to the minimally required dosing period (two years) and achieving the same clinical efficacy as four-year dosing but with minimal side effects. *See* Ex. 2035, 1603. The optimal cladribine dosing length of two years is also surprising in view of Stelmasiak, which showed that EDSS scores of the RRMS patients treated with cladribine returned to baseline by the end of the 24-month study.

208. Lastly, as discussed further below, the unexpected durable efficacy of MAVENCLAD® and the unique dosing regimen are tied directly to the claimed features of the ’947 patent invention, specifically the dosing regimen embodied by MAVENCLAD® and the CLARITY trial comprising: (i) an induction period lasting from about 2-4 months, wherein the total dose of cladribine administered is from about 1.7-3.5 mg/kg; (ii) a cladribine-free period lasting from about 8-10 months; (iii) a maintenance period lasting from about 2-4 months, wherein the total dose of cladribine administered is about 1.7 mg/kg; followed by (iv) a cladribine-free period. *See infra*, ¶¶218-226.

C. Long-Felt Need

209. I understand that evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of the claimed invention. This is because a long-felt need reasonably would have been resolved if its solution were obvious. At the time of the filing of the ’947 patent, there was a long-felt need for a safe, effective, and convenient oral therapy for MS.

210. As of 2004, FDA-approved MS drugs were DMAs and were all injectables—none was approved for oral administration. *Supra*, ¶53. Drugs that are administered via injection are less convenient than those administered orally.

211. As of 2004, FDA-approved MS drugs were also dosed continuously “without an intended interruption in dosing” as the effects of the drugs “are closely

related to their short half-lives and pharmacokinetic and pharmacodynamic profiles." Ex. 2032, 1923; *supra*, ¶¶54-57. For example, the interferons Betaseron®, Avonex®, and Rebif® are administered 0.25 mg every other day, 30 mcg/week, and 44 mcg three times/week, respectively. Ex. 2014, 12; Ex. 2015, 3; Ex. 2016, 17; Ex. 2024, 9; Ex. 2020, 571, 573; Ex. 2025, 1879, 1883. Notably, even though oral therapy for MS had been approved by 2019, these products still required frequent dosing. *See* Ex. 2060, 1.

212. In contrast, MAVENCLAD® is given in two short courses of tablets in the first and second year for two years. Ex. 2001, 5, 6. Unlike other DMAs, the effects of cladribine "persist long after the drug is eliminated from the body[.]" Ex. 2032, 1923. Today, "[c]ladribine tablets [i.e., MAVENCLAD®] are postulated to be an immune reconstitution therapy," i.e., cladribine causes a transient reduction in lymphocytes "followed by a recovery period during which cells gradually repopulate and immune function is restored." *Id*. It has been hypothesized that the "reconstituted lymphocyte population is … less autoreactive towards the CNS component, resulting in prolonged efficacy, as demonstrated in the cladribine tablets clinical studies[.]" *Id*. Surprisingly, "there was no rebound or return of clinical or MRI activity ***even after*** recovery of lymphocyte counts[.]" *Id*.

213. Potentially due to the unique mechanism of action of hypothesized for cladribine, cladribine tablets provide the durable efficacy observed in CLARITY Extension. *Id*., 1924. This unexpected durability of oral cladribine tablets, now approved as MAVENCLAD®, provides a short-duration dosing regimen that "allows for reduced treatment and management burden for patients and providers," (*id*., 1924), which "facilitate[s] treatment adherence, a significant challenge for patients with MS." Ex. 2035, 1603.

214. Since MAVENCLAD®'s approval, over 56,000 people have been treated globally. Ex. 2070, 2. As an MS therapy, MAVENCLAD® has benefitted many patients, including those who have tried another MS drug that they could not tolerate or that has not worked well enough.

215. Dr. Rammohan described the impact of MAVENCLAD®'s dosing regimen as follows:

> It's huge. I mean, from a patient standpoint, once they invest in the initial 5 days, and then the second 5 days, their commitment for a year is over. A year later, you commit yourself for another 5 days and another 5 days, and that's the end of the treatment. To be able to do that and not to have to worry about, "Did I miss my drug? Did I take it?" You can go on vacation. You can leave your home for 6 months

> or even a year and you don't have any problems. That convenience for them is really, really big.

Ex. 2042, 4.

216. Thus, unlike other FDA-approved MS treatments that generally required continuous dosing (¶¶54-58, *supra*), MAVENCLAD®'s "unique dosing regimen has offered patients a more convenient method of medication administration" that provides "the benefit of a short commitment to the treatment and a long-lasting possibility to offer relief." Ex. 2042, 1, 4. Indeed, even Dr. Miller stated that the MAVENCLAD®'s dosing regimen is "unique." Ex. 2007, 3:53-4:18; Ex. 2008, 4:17-5:1. In my opinion, this is further evidence that the claimed dosing regimen was anything but obvious.

D. Nexus

217. The non-obviousness of the '947 patent invention is demonstrated by the unexpected durable efficacy and safety of the claimed dosing regimen, the skepticism of others, and the satisfaction of a long-felt need for a safe, effective, and convenient oral therapy. *Supra*, ¶¶194-216. I understand that, in order for them to be relevant to the analysis, there must be a nexus between these objective indicia and the claimed invention and that the objective indicia must be reasonably commensurate with the scope of the claims. Further, I understand that there is a

nexus between objective indicia and the claims when the evidence of objective indicia is the direct result of the unique characteristics of the claimed invention.

218. As I have explained throughout this declaration, the unique characteristic of the claimed invention is the four-step method of treating MS using orally-administered cladribine, comprising (i) an induction period lasting from about 2-4 months, wherein the total dose of cladribine administered is from about 1.7-3.5 mg/kg; (ii) an 8- to 10-month cladribine-free period; (iii) a maintenance period lasting from about 2-4 months, wherein the total dose of cladribine administered is about 1.7 mg/kg; and (iv) a second cladribine-free period. *See*, *e.g.*, *supra*, ¶¶84-124. As I explain below, each of the objective indicia is tied to the unique four-step method of treating MS, as claimed.

219. The unexpected results of CLARITY are plainly tied to the unique features of the ’947 patent invention: the durable efficacy and safety of the claimed dosing regimen as studied in CLARITY is a direct result of the two-year dosing regimen, in which ***both*** the ***3.5 mg/kg and 5.25 mg/kg*** two-year regimens were “***equally efficacious***” and comparable to the four-year cladribine regimen, but with an ***improved safety*** profile. Ex. 2033, 425; Ex. 2035, 1594, 1599 (Table 2), 1603. Specifically, both the 3.5 mg/kg two-year regimen (which corresponds to the about 1.7 mg/kg total dose for each of the induction and maintenance periods as claimed) and 5.25 mg/kg two-year regimen (which corresponds to the about 3.5 mg/kg total

dose for the induction dose and the about 1.7 mg/kg total dose for the maintenance dose as claimed) showed significant benefits in rate of relapse, disability progression, and magnetic resonance imaging (MRI) measures, but two additional years of cladribine treatment provided "no significant incremental benefit" while leading to a greater incidence of Grade ≥ 3 lymphopenia. Ex. 2033, 425-426; Ex. 2035, 1594, 1599 (Table 2), 1603.

220. In my opinion, the CLARITY dosing regimen is embodied by the commercial MAVENCLAD® product. For example, MAVENCLAD® is a tablet indicated for the treatment of relapsing forms of multiple sclerosis (MS). Ex. 2001, 1. The cumulative dosage for MAVENCLAD® is 3.5 mg/kg administered orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). *Id*. In the first treatment course, there are two cycles of treatment. *Id*., 5. In the first cycle, which can start any time, 1 or 2 cladribine tablets are administered once daily over 4 or 5 consecutive days. *Id*., 6. The second cycle starts 23 to 27 days after the last dose of the first cycle. *Id*. Over the two cycles of the first treatment course, 1.75 mg/kg of MAVENCLAD® tablets is administered. *Id*., 1, 5. The second treatment course starts at least 43 weeks after the last dose of the first course. *Id*., 5. Similarly, in the first 48-week treatment period of the dosing regimen used in CLARITY, "drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets … given once daily for the first 4

or 5 days of a 28-day period," wherein patients in the 3.5-mg group received two courses of cladribine. Ex. 2033, 417-418. Specifically, during this first treatment period of CLARITY, patients in the 3.5 mg arm received "cladribine at a low dose (0.875 milligram per kilogram per course [mg/kg/course] for two courses," i.e., 1.75 mg/kg. Ex. 2041, 1.

221. The second treatment course of MAVENCLAD® starts at least 43 weeks after the last dose of the first course and also has two cycles. Ex. 2001, 5. In the first cycle of the second treatment course, 1 or 2 cladribine tablets are administered once daily over 4 or 5 consecutive days. *Id*., 6. The second cycle of the second treatment course starts 23 to 27 days after the last dose of the first cycle. *Id*. Over the two cycles of the second treatment course of MAVENCLAD®, 1.75 mg/kg of MAVENCLAD® tablets is administered. *Id*., 1, 5. Similarly, in the second 48-week treatment period of the dosing regimen used in CLARITY, patients in the 3.5-mg group received two courses of cladribine. Ex. 2033, 418. Specifically, during this second treatment period of CLARITY, patients in the 3.5 mg arm received "cladribine at a low dose (0.875 mg/kg/course for two courses)," i.e., 1.75 mg/kg. Ex. 2041, 1.

222. In my opinion, the CLARITY dosing regimen embodies the claims of the '947 patent. For example, claim 36 recites "an induction period lasting from about 2 months to about 4 months," which covers the two and four 28-day-courses

of cladribine in the two dosing arms (3.5 mg/kg and 5.25-mg/kg cumulative doses, respectively) during the first 48-week treatment period. Ex. 2033, 417-418. Claim 36 also recites "the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg," which covers the 1.75 mg/kg and 3.5 mg/kg dose administered during the two and four 28-day-courses of cladribine, respectively, in the two dosing arms in the CLARITY trial. *Id*.; Ex. 2041, 1. Claim 36 also recites "a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered," which covers the time after the four and two 28-day-courses of cladribine, but before the second 48-week treatment period begins. Ex. 2033, 417-418; Ex. 2041, 1, 5. Claim 36 further recites "a maintenance period lasting from about 2 months to about 4 months," which covers the two 28-day-courses of cladribine in each dosing arm (3.5 mg/kg and 5.25-mg/kg cumulative doses, respectively) during the second 48-week treatment period. Ex. 2033, 418; Ex. 2041, 1, 5. Claim 36 further recites "wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg," which covers the 1.75 mg/kg dose administered during the two 28-day-courses of cladribine in each dosing arm during the second 48-week treatment period. Ex. 2033, 418; Ex. 2041, 1. Lastly, claim 36 recites "a cladribine-free period wherein no cladribine is administered," which covers the

time after the two 28-day-courses of cladribine during the second 48-week treatment period.[5] Ex. 2033, 418; Ex. 2041, 1, 5.

223. As further illustrated in the claim charts below, the CLARITY trial and **MAVENCLAD®** both practice at least claims 36 and 39 of the '947 patent.

Claim 36 ('947 Patent)	**CLARITY Trial**	**MAVENCLAD®**
36. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:	"Cladribine provides immunomodulation through selective targeting of lymphocyte subtypes. We report the results of a 96-week phase 3 trial of a short-course **oral tablet therapy** in patients with relapsing–remitting **multiple sclerosis**" Ex. 2033, 416. "In the **Cladribine Tablets Treating Multiple Sclerosis Orally** (CLARITY) study, we investigated the **efficacy** and safety of cladribine in a 96-week, phase 3, double-blind, placebo-controlled, multicenter trial involving patients with relapsing-remitting **multiple sclerosis**." Ex. 2033, 417.	"MAVENCLAD® (**cladribine**) tablets, for **oral** use" Ex. 2001, 1. "INDICATIONS AND USAGE [¶] MAVENCLAD is a purine antimetabolite indicated for the **treatment of relapsing forms of multiple sclerosis (MS)**, to include relapsing-remitting disease and active secondary progressive disease, in adults." Ex. 2001, 1.
(i) an induction period lasting	"Eligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative	"DOSAGE AND ADMINISTRATION … Cumulative dosage of 3.5

[5] The '947 patent specification states that "'A month' refers to a period of time of or about 28, about 29, about 30 or about 31 days." Ex. 1001, 4:45-46.

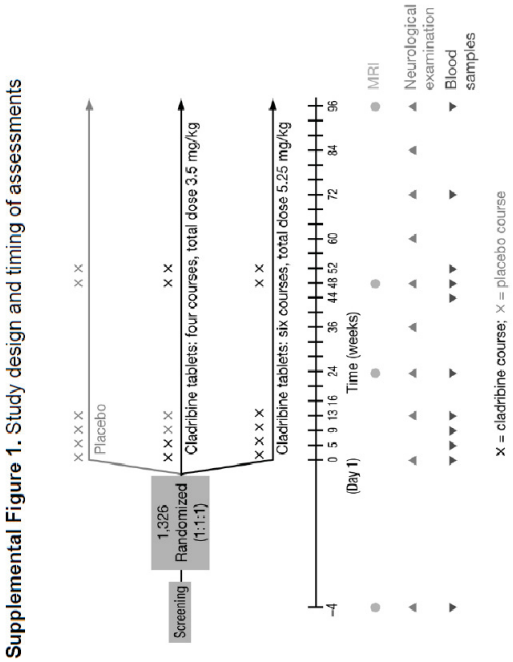
Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;	doses of cladribine over 96 weeks (either **3.5 mg or 5.25 mg per kilogram of body weight**) or matching placebo … The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of **a 28-day period**. [¶] **In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group);** or four courses of placebo (in the placebo group), **starting at day 1 and at weeks 5, 9, and 13** (8 to 20 days of treatment)." Ex. 2033, 417-418. "This is a randomized, double-blind, three-arm, placebo-controlled, multi-center study. The study includes a pre-study evaluation period (up to 28 days prior to the start of treatment); an initial treatment period from Week 1 to 48; and a re-treatment period during Week 49 to 96. [¶] During the **initial treatment period** (Week 1 to 48), eligible subjects are equally randomized by a central randomization system to receive either **a) cladribine at a low dose (0.875**	mg/kg administered orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles." Ex. 2001, 1. "2.2 Recommended Dosage [¶] The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into **2 yearly treatment courses** (**1.75 mg per kg per treatment course**) (see Table 1). Each treatment course is divided into 2 treatment cycles: Administration of First Treatment Course • **First Course/First Cycle: start any time.** • **First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle**. Administration of Second Treatment Course • **Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.**

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	milligram per kilogram per course [mg/kg/course] for two courses plus placebo for two courses); **b) cladribine at a high dose (0.875 mg/kg/course for four courses)**; or c) placebo (four courses). During the re-treatment period (Weeks 49 to 96), subjects received either a) cladribine at a low dose (0.875 mg/kg/course for two courses); or b) placebo (two courses)." Ex. 2041, 1. "Drug: Cladribine 3.5 mg/kg [¶] Cladribine tablet will be administered as **cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Weeks 1, 5,** 48, and 52 and placebo matched to cladribine tablet will be administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment	• Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle." Ex. 2001, 5. "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days[.]" Ex. 2001, 6.

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	period of 96 weeks."[6] Ex. 2041, 5. "Drug: Cladribine 5.25 mg/kg [¶] Cladribine tablet will be administered as **cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13**, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks." Ex. 2041, 5.[7] "Cladribine tablets: four courses, total dose 3.5 mg/kg" Ex. 2034, 1.	

[6] A POSA would have recognized that weeks "48" and "52" are typographical errors and should instead be weeks "49" and "53" at least because Ex. 2041 states that "[t]he study includes a pre-study evaluation period (up to 28 days prior to the start of treatment); an initial treatment period from Week 1 to 48; and a re-treatment period during Week ***49*** to 96." *See* Ex. 2041, 1. A POSA would have understood that the first 28-day course of the second treatment period starts at week 49 and that the second 28-day course of the second treatment period starts at week 53.

[7] *Supra*, n.6.

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	"Cladribine tablets: six courses, total dose 5.25 mg/kg." Ex. 2034, 1.  	

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	Ex. 2034, 1.[8]	
(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;	"**In the first 48-week treatment period**, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), **starting at day 1 and at weeks 5, 9, and 13** (8 to 20 days of treatment). **In the second 48-week period**, both cladribine	"DOSAGE AND ADMINISTRATION … Cumulative dosage of 3.5 mg/kg administered orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles." Ex. 2001, 1.

[8] Supplemental Figure 1 of Ex. 2034 shows "cladribine course[s]" at weeks 48 and 52 for the 3.5 mg/kg and 5.25 mg/kg dosing arms. However, a POSA would have recognized that weeks "48" and "52" are typographical errors and should instead be weeks "49" and "53." First, Ex. 2034 states that "Additional Study Details" can be found in "ClinicalTrials.gov identifier: NCT00213135." Ex. 2034, 1. Second, Ex. 2041, which is the study record for NCT00213135, states that "[t]he study includes a pre-study evaluation period (up to 28 days prior to the start of treatment); an initial treatment period from Week 1 to 48; and a re-treatment period during Week ***49*** to 96." Ex. 2041, 1. A POSA would have understood that the first 28-day course of the second treatment period starts at week 49 and that the second 28-day course of the second treatment period starts at week 53.

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix)." Ex. 2033, 418.[9] "This is a randomized, double-blind, three-arm, placebo-controlled, multi-center study. The study includes a pre-study evaluation period (up to 28 days prior to the start of treatment); an initial treatment period from Week 1 to 48; and a re-treatment period during Week 49 to 96. [¶] **During the initial treatment period** (Week 1 to 48), eligible subjects are equally randomized by a central randomization system to receive either a) cladribine at a low dose (0.875 milligram per kilogram per course [mg/kg/course] for two	"Administration of Second Treatment Course • **Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.** • Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle." Ex. 2001, 5.

[9] A POSA would have recognized that "weeks 48 and 52" is a typographical error and should instead be "weeks 49 and 53." Here, Ex. 2033 expressly references "Fig. 1 in the Supplementary Appendix." Ex. 2033, 418. As explained in note 8, *supra*, a POSA would have recognized that weeks "48" and "52" in Supplemental Figure 1 are typographical errors and should instead be weeks "49" and "53."

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	courses plus placebo for two courses); b) cladribine at a high dose (0.875 mg/kg/course for four courses); or c) placebo (four courses). **During the re-treatment period (Weeks 49 to 96),** subjects received either a) cladribine at a low dose (0.875 mg/kg/course for two courses); or b) placebo (two courses)." Ex. 2041, 1.	
(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg;	"**In the second 48-week period**, **both cladribine groups received two courses of cladribine**, and the placebo group received two courses of placebo, **starting at weeks 48 and 52** (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix)." Ex. 2033, 418.[10] "**During the re-treatment period** (Weeks 49 to 96), subjects received either a) **cladribine at a low dose (0.875 mg/kg/course for two courses**); or b) placebo (two courses)." Ex. 2041, 1.	"2.2 Recommended Dosage [¶] The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (**1.75 mg per kg per treatment course**) (see Table 1). Each treatment course is divided into 2 treatment cycles: Administration of Second Treatment Course … • Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle**.** • **Second Course/Second Cycle: administer 23 to 27 days after the last dose of**

[10] *Supra*, n.9.

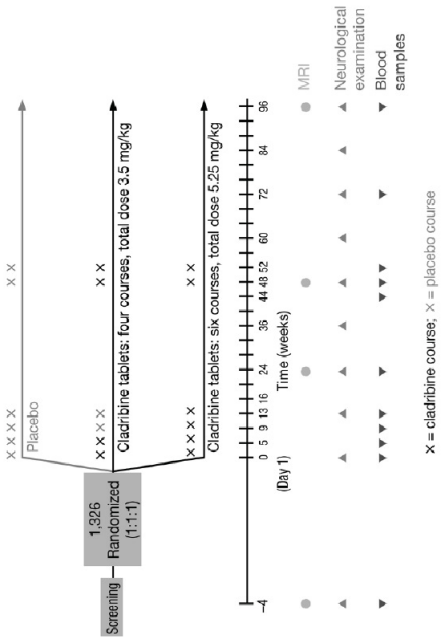
Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
		Second Course/First Cycle." Ex. 2001, 5. "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days[.]" Ex. 2001, 6.
(iv) a cladribine-free period wherein no cladribine is administered.	"This is a randomized, double-blind, three-arm, placebo-controlled, multi-center study. The study includes a pre-study evaluation period (up to 28 days prior to the start of treatment); an initial treatment period from Week 1 to 48; and a re-treatment period during Week 49 to 96." Ex. 2041, 1. "**In the second 48-week period**, **both cladribine groups received two courses of cladribine**, and the placebo group received two courses of placebo, **starting at weeks 48 and 52** (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix)." Ex. 2033, 418.[11] "**During the re-treatment period** (Weeks 49 to 96), subjects received either a) **cladribine at a low dose (0.875 mg/kg/course**	"2.2 Recommended Dosage [¶] The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course) (see Table 1). Each treatment course is divided into 2 treatment cycles: Administration of Second Treatment Course … • **Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.** • **Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle**." Ex. 2001, 5.

[11] *Supra* n.9.

Claim 36 ('947 Patent)	CLARITY Trial	MAVENCLAD®
	for two courses); or b) placebo (two courses)." Ex. 2041, 1.	"Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days[.]" Ex. 2001, 6. "Following the administration of 2 treatment courses, **do not administer additional MAVENCLAD treatment during the next 2 years.**" Ex. 2001, 6.

Claim 39 ('947 Patent)	CLARITY Trial	MAVENCLAD®
39. The method according to claim 36,	*See* claim 36 above.	*See* claim 36 above.
wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.	"Eligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine over 96 weeks (either **3.5 mg** or 5.25 mg **per kilogram of body weight**) or matching placebo … The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of **a 28-day period**. [¶] **In the first 48-week treatment period,**	"DOSAGE AND ADMINISTRATION … Cumulative dosage of 3.5 mg/kg administered orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles." Ex. 2001, 1. "2.2 Recommended Dosage [¶] The recommended cumulative dosage of

	patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment)." Ex. 2033, 417-418. "During the **initial treatment period** (Week 1 to 48), eligible subjects are equally randomized by a central randomization system to receive either **a) cladribine at a low dose (0.875 milligram per kilogram per course [mg/kg/course] for two courses** plus placebo for two courses); b) cladribine at a high dose (0.875 mg/kg/course for four courses); or c) placebo (four courses). During the re-treatment period (Weeks 49 to 96), subjects received either a) cladribine at a low dose (0.875 mg/kg/course for two courses); or b) placebo (two courses)." Ex. 2041, 1. "Drug: Cladribine 3.5 mg/kg [¶] Cladribine tablet will be administered as **cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Weeks 1, 5,** 48, and 52 and placebo matched to cladribine tablet will be administered at Week 9 and 13	MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into **2 yearly treatment courses** (**1.75 mg per kg per treatment course**) (see Table 1). Each treatment course is divided into 2 treatment cycles: Administration of First Treatment Course • **First Course/First Cycle: start any time.** • **First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle**." Ex. 2001, 5.

	resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks." Ex. 2041, 5.[12] "Cladribine tablets: four courses, total dose 3.5 mg/kg" Ex. 2034, 1. **Supplemental Figure 1.** Study design and timing of assessments  Ex. 2034, 1.[13]	

224. The unexpected results are also tied to the unique features of the '947 patent invention, as embodied by the commercial MAVENCLAD® product. That

[12] *Supra*, n.6.

[13] *Supra*, n.8.

is, the durable efficacy and safety of the claimed dosing regimen as studied in CLARITY is a direct result of the 3.5 mg/kg cumulative two-year dosing regimen, which showed significant benefits in rate of relapse, disability progression, and magnetic resonance imaging (MRI) measures, and was comparable to the four-year cladribine regimen but with an ***improved safety*** profile. Ex. 2033, 425; Ex. 2035, 1594, 1599 (Table 2), 1603.

225. In my opinion, the FDA-approved method of administering the commercial MAVENCLAD® product to treat MS also embodies the claims of the '947 patent. For example, claim 36 recites "an induction period lasting from about 2 months to about 4 months," which covers the two treatment cycles during the first treatment course of MAVENCLAD®. Ex. 2001, 1, 5. Claim 36 also recites "the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg," which covers the 1.75 mg/kg dose administered during the two treatment cycles in the first course of treatment MAVENCLAD®. *Id*. Claim 36 also recites "a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered," which covers the "at least 43 weeks" between the first treatment course and the second treatment course. *Id*., 5. Claim 36 further recites "a maintenance period lasting from about 2 months to about 4 months," which covers the two treatment cycles during the second treatment course MAVENCLAD®. *Id*. Claim 36 further recites

"wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg," which covers the 1.75 mg/kg dose administered during the two treatment cycles in the second treatment course of MAVENCLAD®. *Id*. Lastly, claim 36 recites "a cladribine-free period wherein no cladribine is administered," which covers the remaining time in the second treatment course after the two treatment cycles. *Id*.

226. As illustrated in the claim charts above, the FDA-approved method of administering MAVENCLAD® practices at least claims 36 and 39 of the '947 patent.

227. Likewise, the skepticism expressed by Dr. Miller regarding the utility of cladribine to treat MS is based on pre-2004 earlier cladribine studies, and was only eventually overcome with the approval of MAVENCLAD® applying the unique features of the claimed dosing regimen.

228. The skepticism expressed by FDA regarding cladribine for the treatment of MS before it eventually approved MAVENCLAD® is also directly linked to the claimed dosing regimen. FDA's complete response letter cited concerns over higher cancer risks associated with MAVENCLAD®, despite "conclud[ing] that substantial evidence of Cladribine Tablets' effectiveness was provided by the CLARITY[] study." Ex. 2038, 1. As discussed above, the CLARITY trial practices at least claims 36 and 39 of the '947 patent. *See supra*,

¶¶222-223. The skepticism regarding cancer risks arising from the CLARITY trial is tied to the dosing regimen used in the CLARITY trial. *See* 2033, 424 ("The occurrence of neoplasms (including those that were found to be benign, malignant, or unspecified) was reported as a serious adverse event in 1.4% of patients in the cladribine 3.5-mg group and in 0.9% of those in the cladribine 5.25-mg group, as compared with no patients in the placebo group.").

229. Thus, the non-obviousness of the '947 patent invention is demonstrated by the unexpected durable efficacy and safety of the claimed dosing regimen and the skepticism of others, each of which has a nexus to the claimed invention.

X. CONCLUSION

230. As discussed above, it is therefore my opinion that the challenged claims are patentable.

231. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

232. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: December 21, 2023

By: Fred D Lublin

Fred. D. Lublin, M.D.

APPENDIX A

Materials Considered

Exhibit No.	Description
	Paper 2, Petition for Inter Partes Review, U.S. Patent No. 7,713,947
	Paper 10, Institution Decision
1001	U.S. Patent No. 7,713,947 (De Luca, G., et al., "Cladribine Regimen for Treating Multiple Sclerosis," U.S. Patent No. 7,713,947 B2 (filed June 18, 2007; issued May 11, 2010)
1002	Declaration of Aaron Miller, MD
1006	Noseworthy, J.H., et al., "Multiple Sclerosis," *The New England Journal of Medicine*, 343(13):938-952 (2000)
1007	Neuhaus, O., et al., "Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection," *TRENDS in Pharmaceutical Sciences*, 24(3):131-138 (2003)
1008	Weiner, H.L., et al., "Immunotherapy of Multiple Sclerosis," *Annals of Neurology*, 23(3):211-222 (1988)
1009	Wingerchuk, D.M., et al., "Biology of Disease, Multiple Sclerosis: Current Pathophysiological Concepts," *Laboratory Investigation*, 81(3):263-281 (2001)
1010	Kurtzke, J.F., "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)," *Neurology*, 33:1444-1452 (1983)
1012	Whitaker, J.N., "Rationale for Immunotherapy in Multiple Sclerosis," *Annals of Neurology*, 36:S103-S107 (1994)
1013	Stelmasiak, Z., et al., "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis," *Medical Science Monitor*, 4(1):4-8 (1998)
1014	Beutler, E., et al., "The treatment of chronic progressive multiple sclerosis with cladribine," *Proceedings of the National Academy of Sciences*, USA 93:1716-1720 (1996)
1015	Tortorella, C., et al., "Cladribine Ortho Biotech Inc," *Current Opinion in Investigational Drugs*, 2(12):1751-1756 (2001)

Exhibit No.	Description
1016	Langtry, H.D., et al., "Cladribine, A Review of its Use in Multiple Sclerosis," *BioDrugs*, 9(5):419-433 (1998)
1017	Rudick, R.A., et al., "Management of Multiple Sclerosis," *The New England Journal of Medicine*, 337(22):1604-1611 (1997)
1018	Rice, G.P.A., et al., "Cladribine and progressive MS, Clinical and MRI outcomes of a multicenter controlled trial," *Neurology*, 54:1145-1155 (2000)
1019	Barkhof, R., et al., "Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis," *Neuroradiology*, 36:382-387 (1994)
1020	Pirko, I. and Rodriguez, M., "Pulsed Intravenous Methylprednisolone Therapy in Progressive Multiple Sclerosis: Need for a Controlled Trial," *Archives of Neurology*, 61:1148-1149 (2004
1021	Weiner, H.L., et al., "Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: Final report of the Northeast Cooperative Multiple Sclerosis Treatment Group," *Neurology*, 43:910-918 (1993)
1022	Bodor, N. and Dandiker, Y., "Oral Formulations of Cladribine," International Publication No. WO 2004/087101 A2 (filed March 26, 2004; published October 14, 2004)
1023	Grieb, P., et al., "Effect of Repeated Treatments with Cladribine (2-Chlorodeoxyadenosine) on Blood Counts in Multiple Sclerosis Patients," *Archivum Immunologiae Experimentalis*, 43:323-327 (1995)
1024	Schultz, T.W., et al., "Cyclodextrine Cladribine Formulations," U.S. Patent No. 6,194,395 B1 (filed February 25, 1999; issued February 27, 2001)
1026	Beutler, E., "Use of Substituted Adenine Derivatives for Treating Multiple Sclerosis," U.S. Patent No. 5,506,214 B2 (filed February 18, 1993; issued April 9, 1996)
1031	Beutler, E., "Use of Substituted Adenine Derivatives for Treating Multiple Sclerosis," U.S. Patent No. 5,506,214 B2 (filed February 18, 1993; issued April 9, 1996)
1033	Bloom, P.M., "Treatment of Multiple Sclerosis with Lymphocytapheresis and Chemo-Immunosuppression," U.S. Patent No. 4,964,848 (filed June 27, 1988; issued October 23, 1990)

Exhibit No.	Description
1036	Lassmann, H., et al., "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy," *TRENDS in Molecular Medicine*, 7(3):115-121 (March 2001)
1037	Lublin, F. D., et al., "Defining the clinical course of multiple sclerosis: Results of an international survey," *Neurology*, 46:907-911 (1996)
1038	Casanova, B., et al., "High clinical inflammatory activity prior to the development of secondary progression: a prospective 5-year follow-up study," *Multiple Sclerosis*, 8:59-63 (2002)
1042	Shurkovich, S., et al., "Randomized study of antibodies to INF-γ and TNF-α in secondary progressive multiple sclerosis," *Multiple Sclerosis*, 7:277-84 (2001)
1043	Khoury, S. J., "Multiple Sclerosis: What Have We Learned From Magnetic Resonance Imaging Studies?," *Archives of Internal Medicine*, 158:565-73 (1998)
1044	Roitt, I. M., "Essential Immunology, Sixth Edition," Blackwell Scientific Publications, 1-29 (1988) (Excerpt)
1045	Filippi, M., et al., "The effect of cladribine on T1 'black hole' changes in progressive MS," *Journal of Neurological Sciences*, 176:42-44 (2000)
1046	Romine, J. S., et al., "Cladribine: Use in Therapy of Multiple Sclerosis," *Biodrugs*, 7(5):386-93 (1997)
1047	Selby, R., et al., "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis," *Canadian Journal of Neurological Sciences*, 25:295-99 (1998)
1048	Liliemark, J., "The Clinical Pharmacokinetics of Cladribine," *Clinical Pharmacokinetics*, 32(2):120-31 (1997)
1049	Barkhof, F., et al., "Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis," *Neuroradiology*, 36:382-387 (1994)
1050	Chumlea, W.C., "Total body water data for white adults 18 to 64 years of age: The Fels Longitudinal Study," *Kidney International*, 56:244-252 (1999)
2001	MAVENCLAD® (Cladribine) Package Insert (2022)

Exhibit No.	Description
2004	H. El-Moslimany et al., *Escape Therapies and Management of Multiple Sclerosis* in C. S. Raine MULTIPLE SCLEROSIS A COMPREHENSIVE TEXT 333 (2008)
2005	A. E. Miller et al., *Treatment Issues* in R. C. Kalb MULTIPLE SCLEROSIS: THE QUESTION YOU HAVE – THE ANSWERS YOU NEED 43 (2d ed. 2000)
2006	M. J. Tullman et al., *Immunotherapy of Multiple Sclerosis – Current Practice and Future Directions*, 39 J. REHAB. RES. DEV. 273 (2002)
2007	Video: A. Miller, *What You Need to Know About Mavenclad®* (https://www.nationalmssociety.org/Treating-MS/Medications/Mavenclad) (2019)
2008	Transcript of Video, A. Miller, *What You Need to Know About Mavenclad®* (2019)
2009	Deposition Transcript of Dr. Aaron Miller (December 12, 2023)
2010	J. E. Joy et al., Multiple Sclerosis: Current Status and Strategies for the Future, 17 (2001)
2011	F. Lublin, *History of Modern Multiple Sclerosis Therapy*, 252 (SUPPL 3) J. NEUROL. III/3 (2005)
2013	D. S. Goodin et al., *Disease Modifying Therapies in Multiple Sclerosis*, 58 NEUROLOGY 169 (2002)
2014	Betaseron® (Interferon beta-1b) Package Insert (1993)
2015	Avonex™ (Interferon beta-1a) Package Insert (1996)
2016	Rebif® (Interferon beta-1a) Package Insert (2003)
2017	Copaxone® (glatiramer acetate) Package Insert (2001)

Exhibit No.	Description
2018	Novantrone® (mitoxantrone) Package Insert (2000)
2019	Tysabri® (natalizumab) Package Insert (2004)
2020	R. A. Rudick et al., *Natalizumab: α_4-Integrin Antagonist Selective Adhesion Molecule Inhibitors for MS*, 4 EXPERT REV. NEUROTHER. 571 (2004)
2021	R. A. Rudick et al., *Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis*, 354 NEW ENG. J. MED. 911 (2006)
2024	L. Durelli, *Dose and Frequency of Interferon Treatment Matter*, 250 J. NEUROL. (SUPPL 4) IV/9 (2003)
2025	D. S. Alberts et al., *Disposition of Mitoxantrone in Cancer Patients*, 45 CANCER RES. 1879 (1985)
2026	M. Caporro et al., *Two Decades of Subcutaneous Glatiramer Acetate Injection: Current Role of the Standard Dose, and New High-Dose Low-Frequency Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis Treatment*, 8 PATIENT PREFER. ADHERENCE 1123 (2014)
2030	J. C. Sipe et al., *Development of Cladribine Treatment in Multiple Sclerosis*, 1 MULT. SCLER. 343 (1996)
2031	J. Noseworthy et al., *Disease-Modifying Treatments in Multiple Sclerosis* in A. Compston MCALPINE'S MULTIPLE SCLEROSIS 729 (4th ed. 2005)
2032	K. Rammohan et al., *The Development of Cladribine Tablets for the Treatment of Multiple Sclerosis: A Comprehensive Review*, 80 DRUGS 1901 (2020)
2033	G. Giovannoni et al., *A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis*, 362 NEW ENG. J. MED. 416 (2010)

Exhibit No.	Description
2034	G. Giovannoni et al., Supplementary Appendix to *A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis*, 362 NEW ENG. J. MED. 416 (2010)
2035	G. Giovannoni et al., *Safety and Efficacy of Cladribine Tablets in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized Extension Trial of the CLARITY Study*, 24 MULT. SCLER. J. 1594 (2018)
2036	G. Giovannoni et al., *Long-Term Follow-Up of Patients with Relapsing Multiple Sclerosis from the CLARITY/CLARITY Extension Cohort of CLASSIC-MS: An Ambispective Study*, 29 MULT. SCLER. J. 719 (2023)
2037	A. Miller et al., *Current and Investigational Therapies Used to Alter the Course of Disease in Multiple Sclerosis*, 90 SOUTH. MED. J. 367 (1997)
2038	*Merck Receives Complete Response Letter From FDA on Cladribine Tablets New Drug Application*, FIERCEBIOTECH.COM (March 2, 2011) (https://www.fiercebiotech.com/biotech/merck-receives-complete-response-letter-from-fda-on-cladribine-tablets-new-drug-application) Accessed on November 24, 2023
2040	FDA News Release: *FDA Approves New Oral Treatment For Multiple Sclerosis* (March 29, 2019) (https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-treatment-multiple-sclerosis) Accessed on November 25, 2023
2041	ClinicalTrials.gov publication and Record History, NCT00213135 *A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS) (CLARITY)* (2014) (https://clinicaltrials.gov/study/NCT00213135; https://clinicaltrials.gov/study/NCT00213135?tab=history&a=13) Accessed on November 25, 2023

Exhibit No.	Description
2042	M. Hoffman, K. Rammohan Interview: *Short-Term Dosing Regimen Gives Cladribine an Advantage in MS*, NEUROLOGYLIVE (July 1, 2020) (https://www.neurologylive.com/view/shortcommitment-dosing-regimen-gives-cladribine-an-advantage-in-ms) Accessed on November 10, 2023
2052	Declaration of Bernd Meibohm, Dr.rer.nat.
2059	Copaxone® (glatiramer acetate) Package Insert (2014)
2060	A. Liu, *Better 8 Years Late Than Never: Merck KGaA Nabs FDA Nod for MS Drug Mavenclad*, FIERCEPHARMA.COM (April 1, 2019) (https://www.fiercepharma.com/pharma/better-8-years-late-than-never-merck-kgaa-nabs-fda-nod-for-ms-drug-mavenclad) Accessed on December 18, 2023
2061	The Canadian Cooperative Multiple Sclerosis Study Group, *The Canadian Cooperative Trial of Cyclophosphamide and Plasma Exchange in Progressive Multiple Sclerosis*, 337 Lancet 441 (1991)
2070	SAFETY & SIDE EFFECTS Learn about the possible risks of MAVENCLAD (https://www.mavenclad.com/en/home/why-mavenclad/safety-and-side-effects.html#:~:text=It) (last updated November 2022) Accessed on December 18, 2023

APPENDIX B

CURRICULUM VITAE

FRED DAVID LUBLIN, M.D.

Born:		September 28, 1946; Philadelphia, Pa.
Married:		Barbara H. Swartz, June 11, 1969 Children: Alex L. (Aug. 6, 1972) Derek M. (May 5, 1976)
Citizenship:		U.S.A.
Address:	Office	Corinne Goldsmith Dickinson Center for Multiple Sclerosis Department of Neurology Icahn School of Medicine at Mount Sinai 5 East 98th Street; Box 1138 New York, NY 10029-6574
	Phone	(212) 241-6854
	FAX	(212) 423-0440
	E-Mail	fred.lublin@mssm.edu
	Orchid ID	0000-0001-5722-0475
	Home	40 East 94th Street; #4L New York, NY 10128
Education:		A.B. - June 1968, Temple University, Phila., Pa. M.D. - June 1972, Jefferson Medical College, Phila., Pa.

Professional Training:

Internship:	Internal Medicine, Bronx Municipal Hospital - Albert Einstein Medical Center, Bronx, N.Y. July 1, 1972 - June 30, 1973
Residency:	Neurology, New York Hospital - Cornell Medical Center, N.Y., N.Y. July 1, 1973 - June 30, 1976
Externship:	National Hospital for Nervous Diseases, Queen Square, London. April 10, 1972-May 29, 1972.

Academic Appointments:

Instructor in Neurology,
Cornell Medical College
July 1, 1975 - June 30, 1976

Instructor in Neurology,
Jefferson Medical College
July 1, 1976 - June 30, 1978

Research Associate in Biochemistry
(Immunology) Jefferson Medical College
July 1, 1976 - June 30, 1978

Assistant Professor of Neurology,
Jefferson Medical College of Thomas Jefferson University
July 1, 1978 - June 30, 1982

Assistant Professor of Biochemistry,
Jefferson Medical College of Thomas Jefferson University
July 1, 1978 - June 30, 1983

Associate Professor of Neurology,
Jefferson Medical College of Thomas Jefferson University
July 1, 1982 - June 30, 1986

Associate Professor of Biochemistry & Molecular Biology
Jefferson Medical College of Thomas Jefferson University
July 1, 1983 - October 31, 1996

Professor of Neurology, Jefferson Medical
College of Thomas Jefferson University
July 1, 1986 - October 31, 1996

Director, Division of Neuroimmunology,
Department of Neurology, Jefferson Medical College
of Thomas Jefferson University
January 1, 1987 (inception) - October 31, 1996

Vice-Chairman, Department of Neurology
Jefferson Medical College of Thomas Jefferson University
June 1, 1987 - June 30, 1995

Member, The Jefferson Cancer Center of the
Jefferson Cancer Institute, Jan. 1994 - October 31, 1996

Acting Chairman, Department of Neurology
Jefferson Medical College of Thomas Jefferson
University, July 1, 1995- June 30, 1996

Professor of Neurology, MCP Hahnemann University
(formerly Allegheny University of the Health
Sciences), November 1, 1996 – April 30, 2000

Vice-Chairman for Clinical Affairs, Neurology
MCP Hahnemann University (formerly Allegheny
University of the Health Sciences), November 1, 1996
- April 30, 2000

Director, Multiple Sclerosis Center at MCP
Hahnemann University (formerly Allegheny
University of the Health Sciences), November 1, 1996
(inception) - April 30, 2000

Director, Neurological Clinical Trials Center of
MCP Hahnemann University (formerly Allegheny
University of the Health Sciences)
November 1, 1996 (inception) - April 30, 2000

Member, Center for NeuroVirology and
NeuroOncology, MCP Hahnemann University
(formerly Allegheny University of the Health Sciences)
November 1, 1996 – September 30, 1999

Professor of Neurology, Mount Sinai School of
Medicine, April, 2000 – Present

Director, Corinne Goldsmith Dickinson Center
For Multiple Sclerosis, Mount Sinai School of
Medicine, April 1, 2000 – Present

Saunders Family Professor of Neurology, Mount Sinai
School of Medicine, September 2004 - Present

Hospital Appointments:

Assistant Neurologist - New York Hospital
July 1, 1973 - June 30, 1975

Neurologist - New York Hospital
July 1, 1975 - June 30, 1976

Attending Neurologist - Thomas Jefferson University Hospital, July 1, 1976 - October 31, 1996

Co-Director, Multiple Sclerosis Comprehensive Clinical Center, Thomas Jefferson University Hospital, November 1984 (inception) - October 31, 1996

Attending Neurologist, Medical College of Pennsylvania Hospital; Hahnemann University Hospital (formerly Allegheny University Hospitals), November 1, 1996 – April 30, 2000

Neurology Chief of Service, Medical College of Pennsylvania Hospital (formerly Allegheny University Hospitals-MCP), November 1, 1996 - April 30, 2000

Attending Neurologist, Mount Sinai Medical Center, April 2000 – Present

Medical Director, Multiple Sclerosis Neuropsychology Program, Mount Sinai Hospital; July 1, 2018 - Present

Medical Licensure:

New York, 1973:	M.D. 116580
Pennsylvania, 1976:	M.D. 17745E
New Jersey, 2020:	25MA10975400

Certification:

Diplomat, American Board of Medical Examiners, 1973; #31240112
Certified in Neurology - American Board of Psychiatry and Neurology, October 1977

Awards and Honors:

Temple University:
Honors

Phi Eta Sigma National Honor Fraternity, 1965
President's Scholar, 1968
Magna Cum Laude, 1968

Jefferson Medical College Honors:

Lange Medical Publications Prize, 1969, 1970, 1971
Roche Award, 1970
Alpha Omega Alpha, 1971 (President)
Henry M. Phillips Prize, 1972
William Potter Memorial Prize, 1972
Alumni Prize, 1972
Summa Cum Laude, 1972

Professional Honors:

Teacher-Investigator Development Award-
National Institute of Neurological and
Communicative Disorders and Stroke.
July 1, 1978.

Established Investigator - National Multiple
Sclerosis Society, June 1987.

Who's Who in Frontiers of Science and Technology

The Best Doctors in America: 1994-2018;
Neurology: Infectious and Demyelinating Diseases

President, Philadelphia Neurological Society, 1991-92

Sally Harrington Goldwater Lecturer and Visiting
Professor: Barrow Neurological Institute, Phoenix, AZ;
March 1993

Chairman, Advisory Committee on Clinical Trials of
New Drugs in Multiple Sclerosis; National Multiple
Sclerosis Society, Jan. 1994- December 1999

Advisor, National Institute of Allergy and Infectious
Diseases/NIH Advisory Council, Sept. 1994

Chairman, Professional/Clinical Advisory Committee,
Delaware Valley Chapter, National Multiple Sclerosis
Society, July 1995 – October 1999.

Milestone Award, National Multiple Sclerosis Society,
Delaware Valley Chapter, November 1996

Hope Award, National Multiple Sclerosis Society,
Delaware Valley Chapter, November 1, 1999

McEwan Visiting Professorship & Lecture in
Neurology, Univ. of Toronto, November 11-12, 1999

Chairman, Research Programs Advisory Committee,
National Multiple Sclerosis Society, Jan. 2000 – Jan.
2004

Best Doctors: New York Magazine, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2015, 2021, 2022, 2023

America's Top Doctors (book series): 1st Edition, 2nd Edition, 3rd Edition, 4th Edition, 5th Edition, 6th Edition, 7th Edition, 8th Edition, 9th Edition, 10th Edition, 11th Edition, 12th Edition, 13th Edition, 14th Edition; Castle Connolly America's Top Doctors (digital guide): 2016, 2017, 2018, 2019, 2020, 2021

Top Doctors: New York Metro Area (book series): 6th Edition, 7th Edition, 8th Edition, 9th Edition, 10th Edition, 11th Edition, 12th Edition, 13th Edition, 14th Edition, 15th Edition, 16th Edition, 17th Edition, 18th Edition; (digital guide): 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023

Attending of the Year Award, Mount Sinai Medical Center Neurology Residents, June 2001

Teacher of the Year Award, Mount Sinai Medical Center Department of Neurology, June 2003

National Multiple Sclerosis Society Volunteer Hall of Fame, Nov. 2003

Fellow, American Academy of Neurology, July 2004

Saunders Family Professor of Neurology, invested September 2004

John N. Whitaker Lecture in MS- University of Alabama, Birmingham. April 3, 2007

MS Charcot Lecture, Embassy of France, Washington, DC. May 22, 2007

Chairman, Clinical Advisory Committee- New York City Chapter, National Multiple Sclerosis Society
June 2008 – Dec 2014

Award of Appreciation for Outstanding Teaching, Mount Sinai Medical Center; Neurology Residents, June 2008

George A. Schumacher Lectureship (Inaugural) in Neurology, University of Vermont College of Medicine November 13, 2008

William S. Fields Lecturer, University of Texas Health Sciences Center at Houston, December 14, 2012

Award of Appreciation for Outstanding Academic Teaching, Mount Sinai Medical Center Neurology Residents, June 2013

Honorary Member, French Society of Neurology, (Société Française de Neurologie) 2017

2018 Clifford H. Goldsmith Award Recipient Mount Sinai Medical Center, March 2018

Award for Recognition of Leadership and Dedication in Applying Medical Education to Improve Care of Patients with Multiple Sclerosis. AcademicCME, Advanced Curriculum for Multiple Sclerosis; February 28, 2019

June Halper Lifetime Achievement Award, Consortium of Multiple Sclerosis Centers May 30, 2019.

Presidential Lecture, Consortium of MS Centers Annual Meeting; “Use and Abuse of the McDonald Diagnostic Criteria, May 30, 2019.

Hope Award, National Multiple Sclerosis Society Dinner of Champions, September 13, 2021

The Bernard J Alpers Lecture, Thomas Jefferson University; Targeting Progressive Multiple Sclerosis: Implications for All Neurodegenerative Disorders. May 19, 2022

Cullman Family Award for Excellence in Physician Communication; Mount Sinai Health System; September 2022

Professional Organizations,
Advisory Boards and Societies:

American Neurological Association (Fellow, 2013)
American Academy of Neurology (Fellow, July 2004)
Assoc. for Research in Nervous and Mental Diseases
Alpers Society for Clinical Neurology
Research Group on Neuroimmunology of the
World Federation of Neurology
International Brain Research Organization
International Society of Neuroimmunology
(Charter member)

Philadelphia Neurological Society
Second Vice-President, 1989 -1990
First Vice-President, 1990 -1991
President, 1991-1992
Councillor, 1992-1995

Member, Medical Advisory Board,
Myasthenia Gravis Foundation,
Delaware Valley Chapter, 1982-1990

Member, Professional/Clinical Advisory Committee,
Greater Delaware Valley Chapter,
National Multiple Sclerosis Society, 1985-2000
Vice-Chairman, 1/93 - 6/95
Chairman, 7/95-10/99

Member, Committee on Drug Development,
National Multiple Sclerosis Society, 1983-1987

Member, Advisory Committee on Clinical Trials of New
Drugs in Multiple Sclerosis; National
Multiple Sclerosis Society, 1987-2020
Chairman, Jan. 1994-December 1999

Chairman, Computer Database Committee,
National Multiple Sclerosis Society, 1986-1997

Member, Advisory Committee on Health Care
Delivery and Policy, National Multiple Sclerosis
Society, 1992-1995; 1998-2001

Member, Medical Advisory Board, National Multiple Sclerosis Society, 1988-1991; 1993-2014

Member, Executive Committee of the Medical Advisory Board, National Multiple Sclerosis Society, 1988-2007, 2009 – Sep 2012

Member, International Medical Advisory Board, International Federation of Multiple Sclerosis Societies, (MSIF) 1988-2021

Member, Commission of European Communities Concerted Action in Multiple Sclerosis
European Charcot Foundation

Member, Neurological Disorders Program Project B Committee, National Institute of Neurological Disorders and Stroke, NIH, July 1990 -June 1994

Member, Advisory Committee on Health Care Delivery and Policy, National Multiple Sclerosis Society, 1992-1995; 1998-2001

Advisor, National Institute of Allergy and Infectious Diseases/NIH Advisory Council, Sept. 1995

Ad Hoc Reviewer for NIH, NSF, Veterans Administration, National Multiple Sclerosis Society, Canadian MS Society, Italian MS Society.

Member, Working Group for American Academy of Neurology Quality Standards Subcommittee Guideline Project on Multiple Sclerosis, 1993 - 1996

Member, Research Programs Advisory Committee, National Multiple Sclerosis Society, Jan 1998- Jan. 2004
Chairman Jan. 1, 2000 – Jan. 2004

Member, Multiple Sclerosis Council for Clinical Practice Guidelines, 1997- 2003

Member, U.S. Linomide MS Study Group Executive Committee, 1994-1998

Member, Berlex Laboratories Secondary Progressive MS Study Steering Committee, 1995-1996

Member, Teva Marion Partners Copaxone in Primary Progressive MS Study Advisory Committee, 1997 - 2003

Coordinating Investigator, A Safety Trial of Adding COPAXONE (glatiramer acetate) Injections to Patients with Relapsing-Remitting Multiple Sclerosis (MS) receiving AVONEX (interferon beta-1a), (CombiRx) 1998-2002

Member, International MS Data Center Oversight Committee of the Sylvia Lawry Center for MS Research; International Federation of Multiple Sclerosis Societies; Vice-Chair Clinical Trials Working Group; 1999 – 2005
Member, Advisory Committee, Oral Copaxone in MS Clinical Trial. Teva, August 1999- 2003

Member, Board of Trustees, Greater Delaware Valley Chapter of the National MS Society
November 1999- October 2002

Examiner in Neurology, The American Board of Psychiatry and Neurology - 1986; 1993

Pennsylvania Carrier Advisory Committee- PA Blue Shield Medicare; Neurology Representative, 1992-95

Dystel Award Subcommittee, American Academy of Neurology, May 2001 – April 2009

Chair, Data Safety & Monitoring Board, Biogen-Idec Antegren (Tysabri) Phase III Trials.

Member, Data Safety Monitoring Board, Teriflunomide Phase 2 in Relapsing MS, Aventis.

Member, Data Safety & Monitoring Board, Novartis FTY720 Phase II trial.

Member, Data Safety & Monitoring Board, Pfizer Ponezumab (PF-04360365), Phase I & II in Alzheimers Disease.

Member, Data Safety & Monitoring Board, MBP8298 Phase 3 SPMS, BioMS Technology.

Chair, Data Monitoring Committee, MEDI-551 in Relapsing MS, Medimmune.

Chair, Data Monitoring Committee, Ublituximab Phase 2 relapsing MS, TG Therapeutics.

Chair, Data Monitoring Committee, MEDI-551 (Inebilizumab) in NMO, Medimmuine/Viela Bio.

Member, IGIV-C in MS International Steering Committee Bayer, Nov. 2000 – 2007

Member, Clinical Advisory Committee- New York City Chapter, National Multiple Sclerosis Society
July 2002 – Present.
Chairman- June 2008 – Dec 2014

Chair, Mount Sinai School of Medicine Clinical Research Center Scientific Advisory Committee
March 2010 – March 2015

Deputy Medical Officer, National Multiple Sclerosis Society, July 2003 – Present

Member, National Board of Directors,
National Multiple Sclerosis Society,
Jan 2004 – July 2015

Executive Committee- MS-Core, 2004-2010

Chair, American Academy of Neurology Dystel Award Subcommittee, April 2005 – April 2009

Member, MSSM General Clinical Research Center Advisory Committee, October 2006 – March 2015

Member, Board of Directors, New York City/Southern NY Chapter, NMSS, 2008-2014

Member, Executive Committee of the Multiple Sclerosis International Federation International Medical & Scientific Board, 2007- 2013

Councilor, American Academy of Neurology MS Section Executive Committee, 2013 – 2016

Member, Board of Directors, MS Hope for a Cure Feb 2007 – March 2020

Member, Mount Sinai Neurology NIH/NINDS R25 Advisory Committee, 2023

Member, Ponesimod Advisory Committee, Actelion 2007- 2023

Chair, SPI2 Biotin in Progressive MS Phase 3 Study, Steering Committee, MedDay Pharmaceuticals

Chair, Data Monitoring Committee, Receptos/Celgene/BMS RCP-01 (ozanimod)

Chair, Data Monitoring Committee, Laquinimod Phase 2/3 studies, Relapsing and PP MS, Teva.

Chair, Data Monitoring Committees, Inebilizumab Phase 3 Myasthenia Gravis and IgG4-Related Disease, Viela Bio/ Horizon Therapeutics. 2020-Present

Member, Scientific Advisory Board, Avotres Jan 2020 – Present.

Member, Immunic Scientific-Medical Advisory Board Nov 2020 – Present.

Member, Scientific Advisory Board, Entelexo Biotherapeutics; Sep 2021- Present

Member, Scientific Advisory Board, Neuralight; October 2021 – Present

Member, Labcorp Neurology Advisory Board; September 2021- Present

Member, Setpoint Medical MS Advisory Board;
January 2022- Present

Chair, NINDS MS Common Data Elements Working Group, Sept 2010- Present

Member, NINDS Common Data Elements Steering Committee, 2010- present

World health Organization (WHO) Advisory Group for the Revision of ICD-10 Diseases of the Nervous System-Demyelinating Diseases Working Group, 2010

Chairman, Proof of Concept Clinical Trial Strategies Working Group of the International Progressive MS Collaborative Working Group; Jan 2012 – 2015

Chair, Progression and Progressive MS Working Group 1; International Advisory Committee on Clinical Trials in MS Progression and Progressive MS Initiative ad hoc committee; National MS Society/ECTRIMS; 2020

Member, International Progressive MS Alliance's Scientific Steering Committee, MSIF Representative December 2021- December 2023.

Member, International Advisory Committee on Clinical Trials in Multiple Sclerosis; MS Progression Framework – Implementation and Policy Considerations Working Group
March 2022- Present

Chair, Data Monitoring Committee
Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Inebilizumab in Pediatric Subjects with Neuromyelitis Optica Spectrum Disorder; Horizon Therapeutics,
2022- Present

Member, MS Quality of Care Alliance
Sponsor- Novartis; 2022- Present

Member, Scientific Advisory Board,
Lapix Therapeutics, 2023- Present

Member, ENSURE Steering Committee
Immunic, 2023- Present

Editorial Boards:

Multiple Sclerosis Journal (inception 1995 - Aug 2011)
Neurology (2004-2007)
MS Update
Neurology News
Neura: Perspectives on CNS Disease Management
Mount Sinai Journal of Medicine- 2007- 2013

Co-Chief Editor, Multiple Sclerosis and Related Disorders, 2011 (inception) – December 31, 2017

Journal and Manuscript Review:

Annals of Neurology, Neurology, Science, Brain, Lancet, Laboratory Investigation, Journal of Neuroimmunology, Annals of Internal Medicine, Pediatrics, Journal of the Neurological Sciences, Clinical Therapeutics, Multiple Sclerosis Journal, Journal of NeuroVirology, Archives of Neurology, BioDrugs, Acta Neurologica Scandinavica; Lancet Neurology, Multiple Sclerosis and Related Disorders; New England Journal of Medicine; JAMA Neurology

Research Grants:

Basic Research Support Grant- National Institutes of Health; Small Grants Program. F.D. Lublin, Principal Investigator. Investigation of Immunologic Reactivity of Lymphocytes Isolated from the Central Nervous System and Its Environs. November1, 1976 - October 31, 1977

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS): Teacher Investigator Development Award - F.D. Lublin. Studies of Cellular Immune Responses Within the CNS. July 1, 1978 - June 30, 1983

National Multiple Sclerosis Society Research Grant - F.D. Lublin, Principal Investigator. Studies of Delayed, Relapsing Experimental Allergic Encephalomyelitis in Mice. April 1, 1981 - January 31, 1985

National Multiple Sclerosis Society Research Grant - F.D. Lublin, Principal Investigator. NMSS-Industry Drug Screening Program. September 1, 1983 - September 30, 1993

National Multiple Sclerosis Society Research Grant - F.D. Lublin, Principal Investigator. Study of Brain Transplants in Genetic Analysis of EAE. July 1, 1985 - March 30, 1989

Triton Biosciences Inc. Research Study- F.D. Lublin, Co-Investigator. Double Blind Placebo Controlled Phase I Study to Evaluate the Safety of IFN-B_{SER} Given Subcutaneously in Patients with Relapsing-Remitting Multiple Sclerosis. April 1986 -March 1993

National Multiple Sclerosis Society Research Grant - F.D. Lublin, Principal Investigator. Maintenance of a Colony of Recombinant Inbred Strains of Mice. October1, 1987 - September 30, 1988

National Institutes of Health-NINCDS
Research Grant - NS 23081. F.D. Lublin,
Principal Investigator. Study of Brain Transplants in
Genetic Analysis of EAE.
July 1, 1986 - June 30,1990

Triton Biosciences Inc/ Berlex Labs. Research Study-
F.D. Lublin, Co-Investigator. Double Blind
Placebo Controlled Phase III Study to Evaluate the
Efficacy of IFN-B_{SER} Given Subcutaneously
in Patients with Relapsing- Remitting Multiple
Sclerosis. July 1988 - Dec 1993

National Multiple Sclerosis Society Research
Grant - F.D. Lublin, Principal Investigator.
Study of Brain Transplants in Genetic
Analysis of EAE. April 1, 1989 -
September 30, 1992

National Multiple Sclerosis Society Grant -
F.D. Lublin, Principal Investigator. Establishment
of an MS COSTAR Computer Support Center.
July 1, 1990 – Sep 30, 1999

Athena Neurosciences/Bio-Pharm Clinical Services -
F.D. Lublin, Principal Investigator.
A Multi-Center, Double Blind, Randomized, Placebo Controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity due to Multiple Sclerosis.
Feb 1, 1992 - Jan 31, 1993

National Multiple Sclerosis Society Research Grant
F.D. Lublin, Principal Investigator.
Superantigen Modulation of the T Cell Response in
EAE. April 1, 1992-Sep 30, 1993

Commonwealth of Pennsylvania- Legislative Initiative
Grant- F.D. Lublin, Principal Investigator. Role of the
Blood-Brain Barrier in Autoimmune Disease of the
Brain. July 1, 1992 - June 30, 1993

Athena Neurosciences/Bio-Pharm Clinical Services -
F.D. Lublin, Principal Investigator.
A Multi-Center, Open-Label, Long Term Study to
Evaluate the Safety of Tizanidine Tablets in Patients
Suffering from Spasticity due to Multiple Sclerosis.
Sep 1, 1992- Aug 31, 1996

National Multiple Sclerosis Society Research Grant
F.D. Lublin, Principal Investigator.
Cellular Localization of Genetic Susceptibility to EAE.
April 1, 1993 - March 31, 1996

National Multiple Sclerosis Society
Aaron Miller, Principal Investigator
F.D. Lublin, Co-Investigator
A Double-Blind, Randomized, Placebo-Controlled
Trial of Influenza Immunization in Multiple Sclerosis.
Sep. 23, 1993 - Sep. 22, 1994

National Multiple Sclerosis Society Research
Grant - F.D. Lublin, Principal Investigator.
Effects of Bee Venom on EAE.
Nov. 1, 1994 – Sep. 30, 1999

Vespa Laboratories
F.D. Lublin, Principal Investigator.
Effects of Bee Venom on EAE.
Nov. 1, 1994 – Sep. 30, 1999

Berlex Laboratories
F.D. Lublin, Principal Investigator
Phase II, Open Label, Randomized Study to Evaluate
Masking Techniques in Patients with Multiple Sclerosis
Receiving Betaseron Therapy.
Jul. 14, 1994 - Jul. 13, 1995

Berlex Laboratories
F.D. Lublin, Principal Investigator
Betaseron Outcome Study- Six Month Analysis
May 5, 1995 - May 4, 1999

The R.W. Johnson Pharmaceutical Research Institute
F.D. Lublin, Co-Investigator
Leustatin (Cladribine) Clinical Trial in Chronic, Non-Remitting, Progressive Multiple Sclerosis (Phase III)
August 1994 - January 2001

Berlex Laboratories
F.D. Lublin, Co-Investigator,
Steering Committee Member
Phase III, Double-Masked, Placebo-Controlled Study To Evaluate the Safety and Efficacy of Two Doses of Betaseron in Patients with Secondary Progressive Multiple Sclerosis. August 1995 - Oct. 1996

Pharmacia-Upjohn
F.D. Lublin, Principal Investigator and Steering Committee Member.
A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Roquinimex (Linomide) in Relapsing-Remitting and Secondary Progressive Multiple Sclerosis
December 1995 - December 1998

Neurocrine Biosciences
F.D. Lublin, Principal Investigator
Double-Blind, Randomized, Placebo-Controlled Evaluation of the Safety, Tolerability, and Pharmacokinetics of NBI-5788 in Patients with Multiple Sclerosis. August 1996 - May 1999

NIH/NINDS
Program Project: Viral Model for Tumor Pathogenesis In Brain. K. Khalili, Principal Investigator
Project 3. Immunobiology of Viral-Induced Tumors in Experimental Animals
F.D. Lublin, Project Leader
September 30, 1996 - June 30, 1999

ICOS Corporation
F.D. Lublin, Principal Investigator (for all sites)
Phase II Study of HU23F2G in Acute Exacerbations of Multiple Sclerosis
November 1996 - January 1999

Athena Neurosciences
F.D. Lublin, Principal Investigator
An Open-Label Study to Assess the Long-Term Safety of Zanaflex (Tizanidine HCL) in Patients Treated With 28 to 36 Mg/Day.
Nov. 1997 - Mar. 1999

Biogen, Inc.
F.D. Lublin, Principal Investigator
A randomized, Double-Blind, Placebo-Controlled Study To Evaluate the Efficacy of Avonex in the Treatment of Secondary Progressive Multiple Sclerosis (MS).
March 1998- March 2001

Biogen, Inc. & Teva Marion Partners
F.D. Lublin, National Coordinator
A Safety Trial of Adding Copaxone (Glatiramer Acetate) Injections to Patients with Relapsing-Remitting Multiple Sclerosis Receiving Avonex (Interferon β-1a) Therapy (CombiRx)
January 1, 1999 – December 2000

Teva Marion Partners
F.D. Lublin, P.I.
A Multi-National, Multi-Center, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy, Tolerability and Safety of Glatiramer Acetate for Injection In Primary Progressive Multiple Sclerosis Patients.
March 16, 1999 – December 31, 2002

Teva Marion Partners
F.D. Lublin, P.I
Copaxone Responsivity in Treatment-Naïve and Interferon Non-Responders in MS.
December 1, 2000 – July 2002

NIH/NINDS R21 NS41986
F.D. Lublin, P.I.
Combination Therapy in Multiple Sclerosis
Clinical Trial Planning Grant
July 1, 2001 – June 30, 2002

Pfizer
A 12 Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Hydrochloride (E2020-A001-405) in the Treatment of Cognitive Impairment in Patients with Multiple Sclerosis
F.D. Lublin, P.I.
March 2001-March 2002

Immunex/Amgen
Registry to Evaluate Novantrone Effects in Worsening MS (RENEW): Prospective, Open-Label Tolerability and Safety Monitoring Study of Novantrone in a selected cohort of Multiple Sclerosis Patients
F.D. Lublin, P.I.
March 2001- 2005

Biogen
A Multicenter, Phase IV, Randomized, Open-Label Study to Compare the Efficacy of Two Therapies (Acetaminophen and Prednisone) in the Management of Flu-Like Symptoms Associated with AVONEX® (Interferon beta-1a) Treatment in Patients with Relapsing Multiple Sclerosis
F.D. Lublin, P.I.
May 2001-August 2002

Wyeth-Ayerst
Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Safety, Tolerability, and Magnetic Resonance Imaging Study of J695 in Patients with Multiple Sclerosis
F.D. Lublin, P.I. June 2001—July 2002

Bristol Myers Squibb
A Phase II, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Preliminary Efficacy, Pharmacokinetics and Immunogenicity of BMS-1 88667 Administered to Subjects with Relapsing-Remitting Multiple Sclerosis
F.D. Lublin, P.I.
Sept 2001-Nov. 2003

Immunex/Amgen
An Open Label Study of the Safety and Efficacy of Combination Therapy with Mitoxantrone (Novantrone) and Either Interferon-b1a (Avonex) or Glatiramer Acetate
F.D. Lublin, P.I.
Sept 2001- 2005

Serono
A Randomized Multicenter, Parallel Group, Open-label Study Comparing the Tolerability of Rebif Injection with and without the use of Rebiject Mini in Relapsing-Remitting Multiple Sclerosis
F.D. Lublin, P.I.
November 2001- July 2002

National Multiple Sclerosis Society
Oral Megadose Corticosteroid Therapy of Acute Exacerbations in MS (OMEGA)
F.D. Lublin, P.I.
October 2002 – July 2013

Bayer
Randomized, Double-blind, Placebo-Controlled Study to Compare the Effects of Different Dose Regimens of IGIV-Chromatography (IGIV-C), 10% Treatment on Relapses in Patients with Relapsing-Remitting Multiple Sclerosis
F.D. Lublin, P.I.
September 2002 – 2008

Acorda Therapeutics
Double-Blind, Placebo-Controlled, 20-Week, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine-SR in Subjects with Multiple Sclerosis
F.D. Lublin, P.I.
November 2002 – 2008

TEVA Neuroscience
A Multi-Centered, Randomized, Two-Arm, Open Label Study to Evaluate the Safety, Tolerability, and Efficacy of Induction Treatment with Mitoxantrone (Novantrone®) Preceding Treatment with Glatiramer Acetate (Copaxone®) versus Chronic Treatment with Glatiramer Acetate Alone in Relapsing Forms of Multiple Sclerosis NC-100; 9/01/2002- 2007

NIH/NINDS U01 NS045719
Fred D. Lublin, PI
Combination Therapy in Multiple Sclerosis
Sep. 30, 2003 – Nov 30, 2008

Acorda Therapeutics
MSF203 EXT- Open-Label Extension Study to Evaluate the Safety, Tolerability and Activity of Oral Fampridine-SR in Subjects with Multiple Sclerosis who Participated in the MS-F203 Trial
F.D. Lublin, P.I.; 09/01/2005-2009

Acorda Therapeutics
MSF204 - Double-Blind, Placebo-Controlled, 21-Week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR in Subjects with Multiple Sclerosis
F.D. Lublin, P.I. 3/01/2007-2009

Acorda Therapeutics
MSF204 EXT- Open-Label Extension Study to Evaluate the Safety, Tolerability and Activity of Oral Fampridine-SR in Subjects with Multiple Sclerosis who Participated in the MS-F204 Trial
F.D. Lublin, P.I. 7/01/2007-2009

Sanofi-Aventis
An international, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two-year treatment with teriflunomide 7 mg once daily and 14 mg once daily versus placebo in patients with a first clinical episode suggestive of multiple sclerosis. TOPIC
Fred D. Lublin, Principal Investigator
Feb 2007 – Sep 2012

New York State MS Consortium
The Establishment of a Patient Registry and initiation of related projects of The New York State Multiple Sclerosis Consortium (NYSMSC)
Fred D. Lublin, Principal Investigator
Feb 2006 –Dec, 2012

NIH/NINDS U02 NS045719 (Lublin)
Continuation of Combination Therapy in Multiple Sclerosis (CombiRx-Phase III)
Fred D. Lublin, Principal Investigator
12/01/2008-11/30/2014

PDA-001
Celgene Cellular Therapeutics
A Phase 1B, Randomized, Placebo Controlled, Multiple Dose Study to Evaluate the Safety of Intravenous Infusion of Human Placenta-Derived Cells (PDA001) for the Treatment of Adults with Multiple Sclerosis
Fred D. Lublin, Principal Investigator (Study & Site)
Jan, 2011 – Sep, 2013

NMSS
Maintaining and Further Developing the CombiRx Participant Cohort at Study Sites
Fred D. Lublin, Principal Investigator
April 2012- June, 1014

Teva Pharmaceuticals
Laquinimod Disease Progression Planning Project
Fred D. Lublin, Principal Investigator
July, 2013 – June 2014

NMSS RG 5120A3/1 (Co-PI; Inglese)
Multimodal Longitudinal Imaging in Progressive MS
April 2014 - 2018

NMSS
Institutional Clinician Training Award
Fred D. Lublin, Principal Investigator
July 2014 – June 2019

Teva Neuroscience(Co-PI; Inglese, PI)
Structural, Metabolic and Functional Characterization of Progressive MS at High and Ultra-high Field MRI
January 2015 - Present

International Progressive MS Alliance- NMSS Collaborative Network Award Planning Grant
Fred D. Lublin, Principal Investigator
Prospectively Defining Secondary Progressive MS
October 2015 – October 2016

Actelion
Ponesimod / ACT-128800 (PI: LublinAC-058B302, POINT, Multicenter, randomized, double-blind, parallel-group, add-on, superiority study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate (Tecfidera®)
05/2017-1/1/2019

NIH
R01NS099527 (PI- Inglese; PI- Lublin)
07/1/2017-06/30/2022
Examining the role of brain sodium content in multiple sclerosis using MRI

NIH
R01NS100811 (PI- Inglese; PI- Lublin)
09/30/2017-07/31/2022
MRI predictors of disease and disability progression in African Americans with multiple sclerosis

NMSS
Institutional Clinician Training Award
Fred D. Lublin, Principal Investigator
July 2019 – June 2024

Brainstorm Cell Therapeutics
Fred D. Lublin, PI
Phase 2 study to evaluate the safety and efficacy of repeated administration of NurOwn (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors in Progressive Multiple Sclerosis.
Dec 2019 – Present

Biogen
Brain atrophy in DMF-treated vs untreated RRMS patients: retrospective real world data.
Fred D. Lublin, PI
Dec 2019 – Dec 2020

Biogen
A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment
Fred D. Lublin, PI
Jan 2020 – Dec 2022

BIBLIOGRAPHY

ORIGINAL ARTICLES

1. Duckett, S., Cracco, J., Lublin, F. and Scott, T. Electron Microscopical Diagnosis of Lipidosis with the Use of Rectal Biopsy. American Journal of Diseases of Children 127:704-705, 1974.

2. Lublin, F.D., Tsairis, P., Streletz, L.J., Chambers, R.A., Riker, W.F., Van Poznak, A. and Duckett, S.W. Myokymia and Impaired Muscular Relaxation With Continuous Motor Unit Activity. Journal of Neurology, Neurosurgery and Psychiatry 42:557-562, 1979.

3. Lublin, F.D., and Maurer, P.H. Separation and Properties of Lymphocytes Obtained from the Central Nervous System. Journal of Clinical and Laboratory Immunology 4:195-198, 1980.

4. Lublin, F.D., Maurer, P.H., Berry R.G., and Tippett, D. Delayed, Relapsing Experimental Allergic Encephalomyelitis in Mice. Journal of Immunology 126:819-822, 1981.

5. Berry, R.G., Chambers, R.A., and Lublin, F.D. Syringoencephalomyelia (Syringocephalus). Journal of Neuropathology & Experimental Neurology 40:633-644, 1981.

6. Lublin, F.D. Delayed Relapsing Experimental Allergic Encephalomyelitis in Mice, Role of Adjuvants and Pertussis Vaccine. Journal of the Neurological Sciences 57:105-110, 1982.

7. Check, J.H., Lublin, F.D., Mandel, M.D. Clomiphene as an Anticonvulsant Drug. Archives of Neurology 29:784, 1982.

8. Bakri, Y.N., Lee, J.H., Lewis, G.C., Lublin, F.D., and Danoff, B. Meningeal Carcinomatosis Complicating Gynecologic Malignancies: A Literature Review and Report of a Case. Obstetrical and Gynecological Survey 37:10-16, 1982.

9. Lublin, F.D., Tippett, D.L., and Maurer, P.H. Central Nervous System and Blood Lymphocytes in Experimental Allergic Encephalomyelitis. Journal of Clinical and Laboratory Immunology 10:139-142, 1983.

10. Lublin, F.D. Role of Myelin Antigens in Murine Relapsing Experimental Allergic Encephalomyelitis. Journal of Clinical and Laboratory Immunology 13:179-182, 1984.

11. Stoll, D.B., Lublin, F.D., Brodovsky, H., Laucius, J.F., Patchefsky, A., and Cooper, H. Association of Subacute Motor Neuronopathy with Thymoma. Cancer 54:770-772, 1984.

12. Lublin, F.D. Immunomodulation of Relapsing Experimental Allergic Encephalomyelitis. Neurology 34:1615-1617, 1984.

13. Lublin, F.D. Adoptive Transfer of Murine Relapsing Experimental Allergic Encephalomyelitis. Annals of Neurology 17:188-190, 1985.

14. Lublin, F.D. Relapsing Experimental Allergic Encephalomyelitis: An Autoimmune Model of Multiple Sclerosis. Springer Seminars in Immunopathology 8:197-208, 1985.

15. Kim, S., Tuck, L.-L. Ho., Capagnoni, A., Barbarese, E., Knobler, R., Lublin, F.D., Chanderkar, L., and Paik, W. Myelin basic protein-specific methylase 1 activity in shiverer mutant mouse brain. Journal of Neuroscience Research 16:357-365, 1986.

16. Jabourian, Z., Lublin, F.D., Adler, A., Gonzales, C., Northrup, B., and Zwillenberg, D. Hydrocephalus in Kartagener's Syndrome. Ear, Nose, and Throat Journal 65:468-472, 1986.

17. Korngold, R., Feldman, A., Rorke, L., Lublin, F.D., and Doherty, P.C. Acute Experimental Allergic Encephalomyelitis in Radiation Bone Marrow Chimeras Between High and Low Susceptible Strains of Mice. Immunogenetics 24:309-315, 1986.

18. Lublin, F.D., Knobler, R.L., Doherty, P.C., and Korngold, R. Relapsing Experimental Allergic Encephalomyelitis in Radiation Bone Marrow Chimeras Between High and Low Susceptible Strains of Mice. Clinical and Experimental Immunology 66:491-496, 1986.

19. Goldowitz, D., Lublin, F.D., and Knobler, R.L. Brain Transplantation in the Study of Host Regulation of Susceptibility to Experimental Allergic Encephalomyelitis. Annals of the New York Academy of Sciences 495:707-710, 1987.

20. Brainard, G.C., Knobler, R.L., Podolin, P.L., Lavasa, M., and Lublin, F.D. Modulation of the Hamster Immune System by Photoperiod. Life Sciences 40:1319-1326, 1987.

21. Chanderkar, L.P., Shanker, G., Knobler, R.L., Lublin, F.D., Paik, W.K. and Kim, S. Reduced S-Adenosylmethionine: Protein-Lysine N-Methyltransferase Activity (Protein Methylase III) in Shiverer Mutant Mouse Brain. Neurochemical Research 12:445-449, 1987.

22. Goldowitz, D., Knobler, R.L., and Lublin, F.D. Heterotopic Brain Transplants in the Study of Experimental Allergic Encephalomyelitis. Experimental Neurology 97:653-661, 1987.

23. Lublin, F.D., Lavasa, M., Viti C. and Knobler R.L. Suppression of Acute and Relapsing Experimental Allergic Encephalomyelitis with Mitoxantrone. Clinical Immunology and Immunopathology 45:122-128, 1987.

24. Barolat, G., Knobler, R.L., and Lublin, F.D. Trigeminal Neuralgia in a Patient with Multiple Sclerosis Treated with High Cervical Spinal Cord Stimulation - Case Report. Applied Neurophysiology 51:333-337, 1988.

25. Lublin, F.D., Knobler, R.L., Marini, J., and Goldowitz, D. Brain Transplantation in Genetic Analysis of Experimental Allergic Encephalomyelitis. Annals New York Academy of Sciences 540:252-254, 1988.

26. Joseph, J., D'Imperio, C., Knobler, R.L., and Lublin, F.D. Down Regulation of IFN-Gamma Induced Class II Expression on Human Glioma Cells by Recombinant Beta Interferon. Annals New York Academy of Sciences 540:475-476, 1988.

27. Brainard, G.C., Watson-Whitmeyer, M., Knobler, R.L., and Lublin, F.D. Neuroendocrine Regulation of Immune Parameters: Photoperiod Control of the Spleen in Syrian Hamsters. Annals New York Academy of Sciences 540:704-706, 1988.

28. Knobler, R.L., Lublin, F.D., Streletz, L.J., Northrup, B., Barolat, G., and Marcus, S.G. Intracerebral Beta Interferon in Brain Tumor Therapy: Monitoring Cerebral Function with Compressed Spectral Analysis. Annals New York Academy of Sciences 540:573-575, 1988.

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