

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

MERCK SERONO S.A.,
Patent Owner.

Case IPR2023-00480
U.S. Patent No. 7,713,947

DECLARATION OF AARON E. MILLER, M.D.

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I, Aaron E. Miller, M.D., hereby declare as follows.

I. Introduction

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained as an expert witness on behalf of Petitioner Hopewell Pharma Ventures, Inc. (“Hopewell”) for the above-captioned *inter partes* review (“IPR”). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$790/hr.

3. I understand that the petition for IPR involves U.S. Patent No. 7,713,947 (“the ’947 patent”), EX1001, which resulted from U.S. Application No. 11/722,018 (“the ’018 application”), which is the National Phase Entry of International Patent Application No. PCT/EP2005/056954, filed on December 20, 2005, which claims the benefit of the U.S. Provisional Application No. 60/638,669, filed on December 22, 2004, and the Foreign Patent Application No. EP04106909, filed on December 22, 2004. The ’947 patent issued on May 11, 2010, from the ’018 application. The ’947 patent names Giampiero De Luca, Arnaud Ythier, Alain Munafo, and Maria Lopez-Bresnahan as inventors. The face of the ’947 patent states that it is assigned to Merck Serono S.A. (“Merck”).

II. My Background and Qualifications

4. My Curriculum Vitae is submitted herewith as Exhibit 1003.

5. I received my M.D. in 1968 from the New York University School of Medicine. I previously received my B.A. in 1964 in psychology from Brandeis University. From 1968-1970, I was an intern and resident at the Bronx Municipal Hospital Center. I completed two neurology residencies between 1970-1971 and 1973-1975 at the Albert Einstein College of Medicine. In 1977, I completed a postdoctoral fellowship in neurovirology in the Department of Epidemiology, Division of Infectious Disease, at Johns Hopkins University School of Hygiene and Public Health. In 1978, I completed a postdoctoral fellowship in immunology at the Albert Einstein College of Medicine. I was also a recipient of a National Multiple Sclerosis Society Fellowship from 1976-1978. From July 1971-June 1973, I served as a lieutenant commander in the U.S. Naval Reserve.

6. I have received Certifications from the National Board of Medical Examiners (1969), the American Board of Internal Medicine (1972), and the American Board of Psychiatry and Neurology (1977). I have been licensed to practice medicine in the state of New York since 1969.

7. I am currently the medical director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at the Icahn School of Medicine at Mount Sinai, a position I have held since March 2004. I am also a professor of neurology

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at the Icahn School of Medicine at Mount Sinai, a position I have also held since March 2004. I was previously a clinical professor of neurology at the Mt. Sinai School of Medicine (2001-2004). Before that, I was an associate professor (1985-1992) and professor (1992-2003) of clinical neurology at the State University of New York Health Sciences Center at Brooklyn. I began my academic career at the Albert Einstein College of Medicine where I was an instructor in neurology from 1977-1978, an assistant professor of neurology (1978-1981), and a visiting professor of clinical neurology (1981-1999).

8. Prior to becoming the medical director at the Corinne Goldsmith Dickinson Center for Multiple Sclerosis, I was an attending neurologist at the Mt. Sinai Hospital, a position I have held since 1999. I am also an attending neurologist at the Metropolitan Jewish Geriatric Center, a position I have held since 1981. I am also the director of the division of neurology and an attending neurologist at the Maimonides Medical Center in Brooklyn, positions I have held since 1981. Previously, I was an attending neurologist at the Kings County Hospital Center (1981-2001), an attending neurologist at the Albert Einstein College Hospital (1978-1981), and an attending neurologist at the Bronx Municipal Hospital Center (1978-1999).

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9. I have held many professional appointments during my career. I am currently a member of the Scientific Advisory Committee at the National Multiple Sclerosis Society, an organization I have been actively involved with since 1988. I have had several other appointments at the National MS Society, including acting as Chairman of the National Medical Advisory Committee (2002-2010), the Professional Education Committee (1993-2002), and the National Medical Advisory Committee (2018-2020). I served on the Board of Directors for the National MS Society from 2003-2017 and I have served on several other committees.

10. I have also been involved with other MS organizations. For example, I was the co-chairman of the Professional Advisory Committee (1988-1991) and the chairman of the clinical advisory committee (1991-2004) for the New York Multiple Sclerosis Society. I have held various positions at the American Academy of Neurology, including as the chairman of the Annual Meeting Subcommittee (1997-2003), Co-Chairman of the Education Committee, (1997-2003), on the Board of Directors (2009-2013), and as the Chairman of the Editors-in-Chief Committee (2009-2011).

11. I have served on several committees to oversee data and safety monitoring, as well as end-point analysis, of various clinical trials. I have served as

an Editor of several industry publications, including *Continuum* published by the American Academy of Neurology and *Multiple Sclerosis and Related Disorders*. I have also authored or co-authored over 125 papers published in peer-reviewed journals, over half of which were related to multiple sclerosis. I have also authored or co-authored over 25 books or book chapters.

12. In my practice, I treat roughly 800-1000 unique patients a year with MS. As a neurologist, I have treated thousands of MS patients since the beginning of my career in 1977.

13. In view of my education, experience, and expertise described above, I am an expert in the field of neurology. Accordingly, I am an expert in the field of the subject matter described and claimed in the '947 patent.

III. Summary of Opinions

14. In this declaration, I consider the treatment methods of the '947 patent in relation to the general knowledge in the art before December 22, 2004. The prior art references that I considered included (but were not limited to) Bodor, Nicholas S. and Dandiker, Yogesh, "Oral Formulations of Cladribine," International Patent Application Publication No. WO2004/087101 A2 (filed March 26, 2004; published October 14, 2004) ("Bodor," EX1022), and Stelmasiak, Zbigniew, *et al.*, "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis," *Med. Sci. Monit.*, 1998, 4(1):4-8 ("Stelmasiak," EX1013). I also

considered the file history of the '947 patent (EX1004) and other exhibits cited herein. A summary of my opinions follows. The references I cite in this Declaration reflect the general knowledge in the art.

15. Multiple sclerosis (“MS”) is a “lifelong and [] often disabling” “progressive, degenerative disease of the central nervous system whose distinguishing feature is the development of scattered, focal lesions of the myelin sheath of the axons.” EX1043, 565; EX1009, 263. As I explain in detail below, most patients experience a relapsing-remitting form of MS, in which “neurological symptoms and signs develop over several days, plateau, and then usually improve over days to weeks.” EX1009, 263; EX1007, 131. Many of these patients will go on to develop secondary progressive disease, characterized by emerging “progressive neurological dysfunction” “as relapse frequency lessens over time.” *Id.* A smaller number of patients experience a primary progressive form of MS from onset, in which their disease gradually worsens over time without periods of remission. *Id.* Of the patients with progressive disease from onset, some may also experience relapses or exacerbations; this form was called progressive-relapsing MS (“PRMS”). EX1037, 909. A person of ordinary skill in the art (“POSA”) would have also recognized “early” secondary progressive MS (“ESPMS”) as a distinct disease subtype. EX1038, 60. Some SPMS and ESPMS patients will

continue to experience relapses. EX1037, 908; EX1009, 263. Therefore, a POSA would have known before December 2004 that, as a rule, an MS patient typically needs ongoing care to treat episodic relapses and disease progression. EX1013, 6; EX1009, 263.

16. Because of the role the immune system plays in the underlying pathophysiology of MS, immunosuppressive drugs was “the most common therapeutic approach” for treating MS before December 2004. EX1013, 4; EX1007, 131. Cladribine was developed in the early 1990’s to treat various leukemias and lymphomas. EX1015, Abstract. Because cladribine caused “prolonged, profound suppression of lymphocyte counts,” researchers began studying it in MS. EX1016, 420-21. In early studies, cladribine was shown to “modulat[e] autoimmune processes involving lymphocyte abnormalities such as MS” and “impressively decrease[]” relapse rates in patients with RRMS. EX1018, 1146; EX1013, 5, 7. During treatment, 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/ μ L, being characteristic of a treatment response. EX1018, 1146; EX1013, 5; EX1014, 1717.

17. As I explain in detail below, claims 36, 38, 39, and 41-46 of the ’947 patent would have been obvious in view of Bodor and Stelmasiak. Bodor discloses

administering an oral cladribine tablet to treat MS “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.” EX1022, 23:15-20. Thus, Bodor discloses a cladribine induction period in which 100 mg to 140 mg of cladribine was administered over 2 months followed by 10 months of no treatment. Stelmasiak discloses an oral cladribine dosing regimen for MS in which “[s]ix cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months,” with “[e]ach course consist[ing] of five doses of the drug taken once daily on consecutive days.” EX1013, 5. Thus, a POSA would have recognized that Stelmasiak administered cladribine in a cyclical manner. A POSA would have had a reason to add a “maintenance period” followed by a “cladribine-free period” to Bodor’s cladribine dosing regimen, as taught by Stelmasiak, to treat MS because MS is a chronic, progressive disease that typically requires periodic treatment. A POSA would have understood that cladribine is a “disease-modifying” therapy—i.e., cladribine does not cure MS, but can reduce the number of relapses by causing “prolonged, profound suppression of lymphocyte counts.” EX1016, 420; EX1013, 6. In fact, 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.” EX1046, 392. Thus, a POSA would have expected some patients to relapse after cladribine therapy, as evidenced in some cladribine clinical trials. For example, Stelmasiak reports that “a total of 6 relapses during the two-year study period (average relapse rate 0.43 per patient per year)” was reported in the “responders” group. EX1013, 6. Thus, a POSA would have understood from prior clinical studies that patients may relapse during or after cladribine therapy. As such, a POSA would have been motivated to retreat the relapsing patients with cladribine after “ten months of no treatment.” And because cladribine has been previously shown to have clinical efficacy in patients with MS, a POSA would have had a reasonable expectation of retreating a patient with cladribine.

18. Further, as I explain in more detail below, a POSA would have had a reason to lower the total dose of cladribine administered during the maintenance period, compared to the total dose administered during the induction period, and would have optimized the maintenance period dose. A POSA would have known, as explained below, that monitoring a patient’s lymphocyte counts was necessary because “cladribine causes prolonged, profound suppression of lymphocyte counts.” EX1016, 420; *see also* ¶ 34, *infra*. Based on the lymphocyte data in Figure 1 of Stelmasiak, a POSA would have understood that a lower dose of cladribine was sufficient to maintain the lymphocyte suppression effected during

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an induction period. Bodor instructs a POSA to optimize the cladribine dose: “one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning.” EX1022, 24:1-3. A POSA would have known how to adjust a patient’s cladribine dose depending on the patient’s lymphocyte counts because, as explained in more detail below, the dose of cladribine was a result-effective variable. Also, it would have been well within the expertise of a POSA to optimize the maintenance period dose because it is a common practice in the field to treat patients on an individual basis. In other words, different patients may require different dosages and/or lengths of treatment, and it would have been within the skill and expertise of a POSA to optimize the dose/length of the maintenance period for different patients.

IV. List of documents I considered in formulating my opinions

19. In formulating my opinions, I considered the following documents:

<i>Exhibit No.</i>	<i>Description</i>
1001	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)
1004	File History for U.S. Patent No. 7,713,947
1006	Noseworthy, J.H., et al., “Multiple Sclerosis,” <i>The New England Journal of Medicine</i> , 343(13):938-952 (2000)
1007	Neuhaus, O., et al., “Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection,” <i>TRENDS in Pharmaceutical Sciences</i> , 24(3):131-138 (2003)

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Exhibit No.	Description
1008	Weiner, H.L., et al., "Immunotherapy of Multiple Sclerosis," <i>Annals of Neurology</i> , 23(3):211-222 (1988)
1009	Wingerchuk, D.M., et al., "Biology of Disease, Multiple Sclerosis: Current Pathophysiological Concepts," <i>Laboratory Investigation</i> , 81(3):263-281 (2001)
1010	Kurtzke, J.F., "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)," <i>Neurology</i> , 33:1444-1452 (1983)
1012	Whitaker, J.N., "Rationale for Immunotherapy in Multiple Sclerosis," <i>Annals of Neurology</i> , 36:S103-S107 (1994)
1013	Stelmasiak, Z., et al., "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis," <i>Medical Science Monitor</i> , 4(1):4-8 (1998)
1014	Beutler, E., et al., "The treatment of chronic progressive multiple sclerosis with cladribine," <i>Proceedings of the National Academy of Sciences, USA</i> 93:1716-1720 (1996)
1015	Tortorella, C., et al., "Cladribine Ortho Biotech Inc," <i>Current Opinion in Investigational Drugs</i> , 2(12):1751-1756 (2001)
1016	Langtry, H.D., et al., "Cladribine, A Review of its Use in Multiple Sclerosis," <i>BioDrugs</i> , 9(5):419-433 (1998)
1017	Rudick, R.A., et al., "Management of Multiple Sclerosis," <i>The New England Journal of Medicine</i> , 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," <i>Neurology</i> , 54:1145-1155 (2000)
1019	Barkhof, R., et al., "Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis," <i>Neuroradiology</i> , 36:382-387 (1994)
1020	Pirko, I. and Rodriguez, M., "Pulsed Intravenous Methylprednisolone Therapy in Progressive Multiple Sclerosis: Need for a Controlled Trial," <i>Archives of Neurology</i> , 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," <i>Neurology</i> , 43:910-918 (1993)

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Exhibit No.	Description
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," <i>Archivum Immunologiae Experimentalis</i> , 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)
1025	File History for U.S. Patent No. 8,377,903
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	Romine, J. S., et al., "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis," <i>Proceedings of the Association of American Physicians</i> , 111(1):35-44 (1999)
1033	Bloom, P.M., "Treatment of Multiple Sclerosis With Lymphocyapheresis and Chemo-Immunosuppression," U.S. Patent No. 4,964,848 (filed June 27, 1988; issued October 23, 1990)
1036	Lassmann, H., et al., "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy," <i>TRENDS in Molecular Medicine</i> , 7(3):115-121 (March 2001)
1037	Lublin, F. D., et al., "Defining the clinical course of multiple sclerosis: Results of an international survey," <i>Neurology</i> , 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," <i>Multiple Sclerosis</i> , 8:59-63 (2002)
1042	Shurkovich, S., et al., "Randomized study of antibodies to INF- γ and TNF- α in secondary progressive multiple sclerosis," <i>Multiple Sclerosis</i> , 7:277-84 (2001)
1043	Khoury, S. J., "Multiple Sclerosis: What Have We Learned From Magnetic Resonance Imaging Studies?," <i>Archives of Internal Medicine</i> , 158:565-73 (1998)

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Exhibit No.	Description
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,” <i>Journal of Neurological Sciences</i> , 176:42-44 (2000)
1046	Romine, J. S., et al., “Cladribine: Use in Therapy of Multiple Sclerosis,” <i>Biodrugs</i> , 7(5):386-93 (1997)
1047	Selby, R., et al., “Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis,” <i>Canadian Journal of Neurological Sciences</i> , 25:295-99 (1998)
1048	Liliemark, J., “The Clinical Pharmacokinetics of Cladribine,” <i>Clinical Pharmacokinetics</i> , 32(2):120-31 (1997)
1049	Barkhof, F., et al., “Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis,” <i>Neuroradiology</i> , 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,” <i>Kidney International</i> , 56:244-252 (1999)

V. The Person of Ordinary Skill in the Art (“POSA”)

20. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. Because the '947 patent relates to methods of human therapeutic treatments, the level of skill of a POSA in this field is high. Given the high level of skill, a POSA would draw upon the knowledge and experience of related disciplines of a multi-disciplinary team that might lie outside the POSA's primary training. For example, a physician might rely upon the knowledge and

experience of a pharmacologist on a multi-disciplinary team to determine the appropriate dose for a particular patient. Thus, a POSA for the '947 patent would have had 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. The POSA typically would be a medical doctor with a specialty in neurology, specifically in treating autoimmune disorders of the nervous system, such as MS, 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.

21. A POSA would have also known how to research the scientific literature in the field relating to the treatment of autoimmune diseases, which would have included the underlying pathogenic mechanisms of MS, as well as various approaches to treating multiple sclerosis, and have knowledge of, and skills relating to, useful techniques for accomplishing the same.

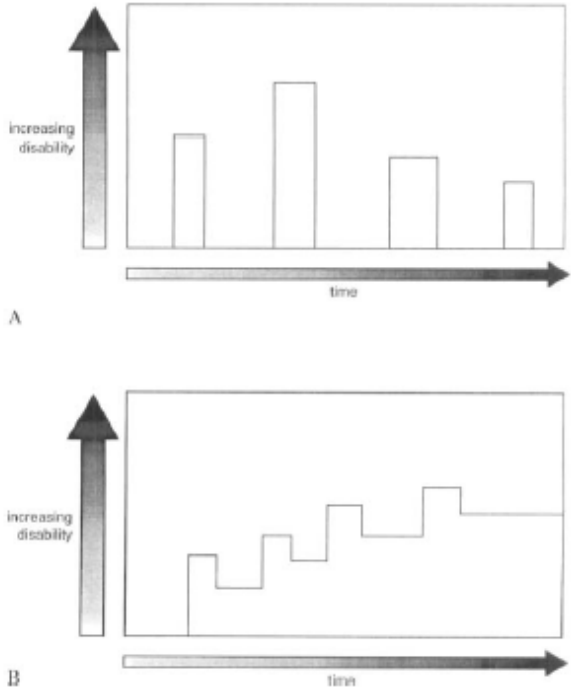
VI. State of the Art Prior to December 22, 2004

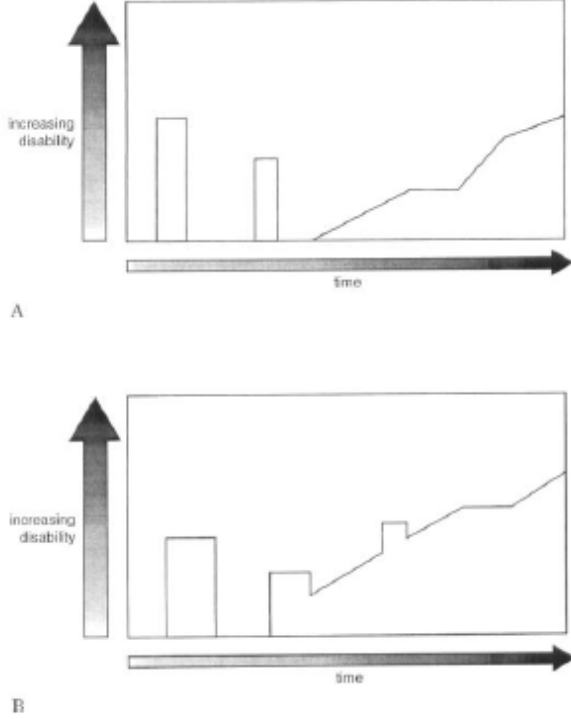
A. Multiple sclerosis is a chronic disease with no known cure

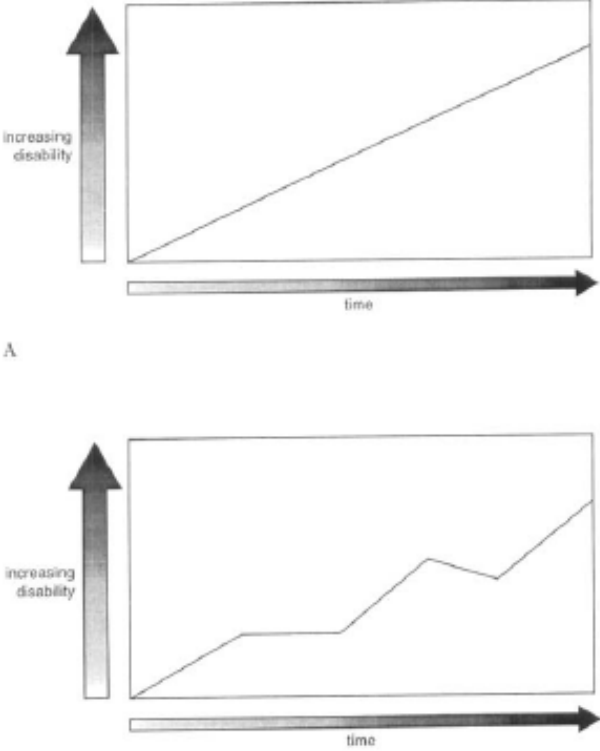
22. Multiple sclerosis ("MS") is "a chronic inflammatory disease of the nervous system in which a T-cell-mediated inflammatory process is associated with destruction of myelin sheaths." EX1036, Abstract. To date, there is no known

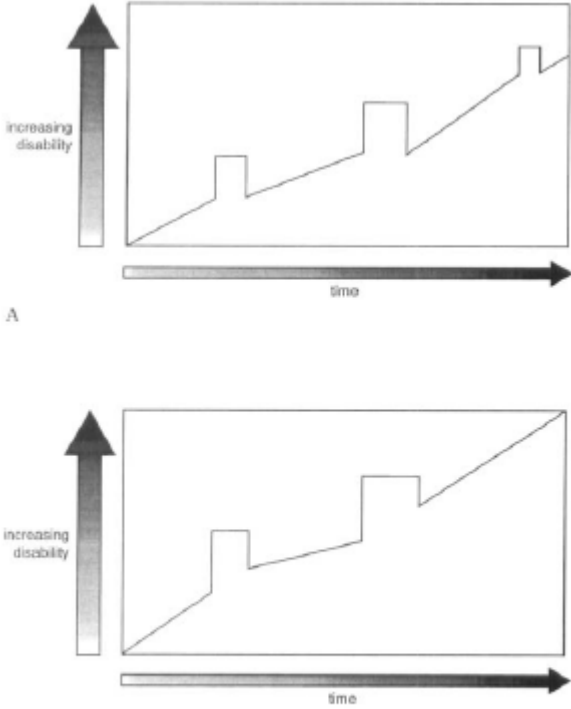
cure for MS. EX1024, 35. The clinical course of MS typically follows a “variable pattern over time but usually can be characterized by either episodic acute periods of worsening (relapses, exacerbations, bouts, attacks), gradual progressive deterioration of neurologic function, or combinations of both.” EX1037, 907. The heterogeneous nature of the disease prompted clinicians to adopt a standardized terminology “to describe the pattern and course of MS.” *Id.*, Abstract.

23. Thus, in 1996, the US National Multiple Sclerosis Society Advisory (NMSS) Committee on Clinical Trials in Multiple Sclerosis (“the Committee”) provided standardized definitions of the following MS clinical form: relapsing-remitting MS (“RRMS”), secondary progressive MS (“SPMS”), primary progressive MS (“PPMS”), and progressive-relapsing MS (“PRMS”). *Id.*, 908-909. I have provided the following table containing the 1996 Committee’s standardized definitions and illustrations for each form of MS as shown below:

MS Type and Definition	Illustration
Relapsing-Remitting (RRMS) “[C]learly defined disease relapses with full recovery or with sequelae and residual deficit... characterized by a lack of disease progression.”	 A B <i>Figure 1. Relapsing-remitting (RR) MS is characterized by clearly defined acute attacks with full recovery (A) or with sequelae and residual deficit upon recovery (B). Periods between disease relapses are characterized by lack of disease progression.</i>

MS Type and Definition	Illustration
Secondary Progressive (SPMS) “[I]nitial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus.”	 Figure 3. Secondary progressive (SP) MS begins with an initial RR course, followed by progression of variable rate (A) that may also include occasional relapses and minor remissions (B).

MS Type and Definition	Illustration
Primary Progressive (PPMS) “[D]isease progression from onset with occasional plateaus and temporary minor improvements allowed.”	 A <i>Figure 2. Primary progressive (PP) MS is characterized by disease showing progression of disability from onset, without plateaus or remissions (A) or with occasional plateaus and temporary minor improvements (B).</i>

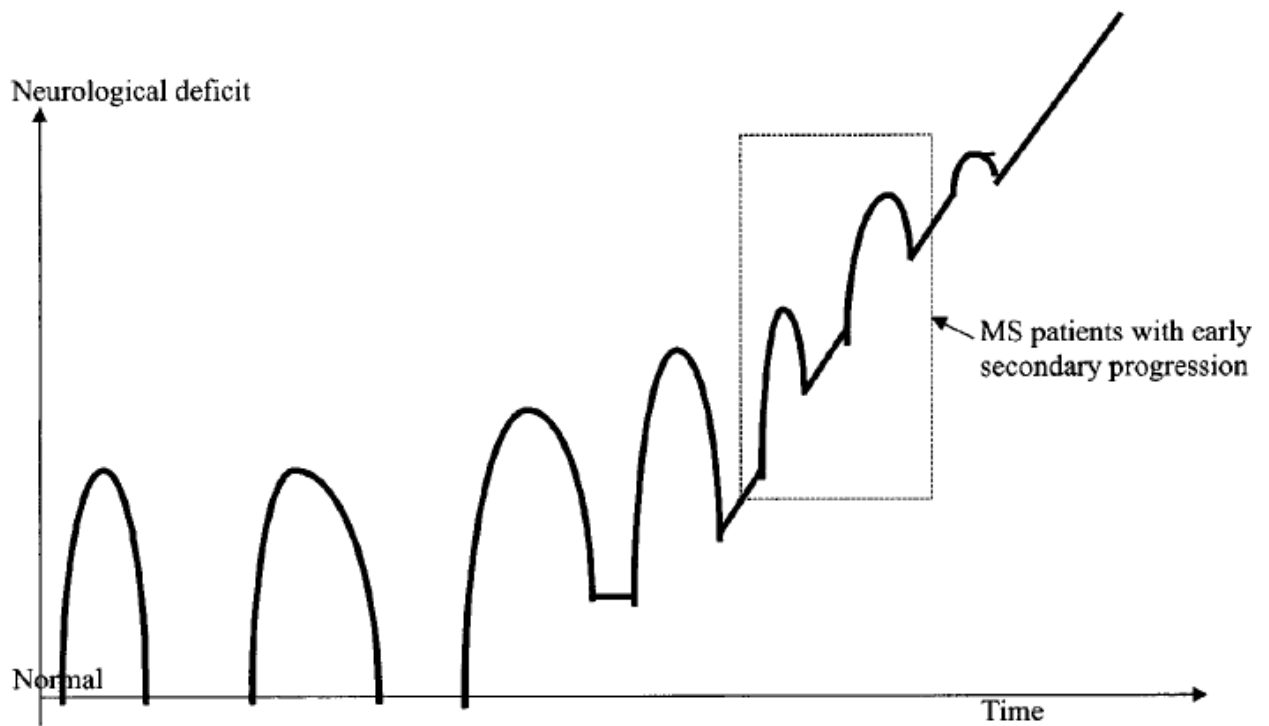
MS Type and Definition	Illustration
Progressive Relapsing (PRMS) “[P]rogressive disease from onset, with clear acute relapses... characterized by continuing progression.”	 Figure 4 consists of two line graphs, A and B, illustrating the progression of disability over time in Progressive Relapsing Multiple Sclerosis (PRMS). Both graphs have a vertical axis labeled 'increasing disability' with an upward-pointing arrow and a horizontal axis labeled 'time' with a rightward-pointing arrow. Graph A shows a line that starts at the origin and trends upwards with a series of small, frequent steps, representing continuous progression with minor relapses. Graph B shows a line that starts at the origin and trends upwards with a series of larger, more distinct steps, representing continuous progression with more significant acute relapses. In both graphs, the line never trends downwards, indicating that disability is not fully reversed after a relapse. <i>Figure 4. Progressive-relapsing (PR) MS shows progression from onset but with clear acute relapses with (A) or without (B) full recovery.</i>

Id., 908-909, FIGs. 1-4.

24. As shown above, the Committee recognized that the progressive courses of MS – SPMS and PPMS – may exhibit relapses and exacerbations like the RRMS course, in addition to disease progression. It was also known that despite the disease form, “[a]ll actively demyelinating lesions were associated with an inflammatory process, with the inflammatory infiltrates composed mainly of T cells and macrophages. EX1036, 118. As also shown above, the PPMS and PRMS forms show disease progression “from onset” without first exhibiting a relapsing-

remitting course, in contrast to the SPMS form, which shows an “initial RR course” before transitioning into a progressive course. Thus, while an SPMS patient initially had RRMS, PPMS and PRMS patients never had RRMS in the first place.

25. Prior to 2004, some in the also field began to recognize “early” SPMS or ESPMS as a distinct disease form, as well. For example, Casanova reports that “significant difference[s] on the AER [annual exacerbation rate]” was seen “among [relapsing-remitting multiple sclerosis] RRMS, early [secondary multiple sclerosis] SPMS and late SPMS.” EX1038, Abstract. During Casanova’s study, “13 patients (21.3%) changed from RRMS to SPMS, 6 patients at year 2 and 7 patients at year 3”—Casanova designated this group of patients as having “Early SPMS.” *Id.*, 60. Casanova proposes “to call ‘Early Secondary Progressive Multiple Sclerosis’ the interval of the ‘year of progression’ and the following year, because it is during this interval of time (and in the previous year) when there is more clinical inflammatory activity.” *Id.*, 63. Shurkovich provides a useful diagram to explain the ESPMS disease course:



EX1042, 278, FIG. 1.

26. In clinical practice, several signs and symptoms are monitored to assess a patient's disease progression and response to therapy. For example, "neurologic impairment of MS" is commonly assessed with the Expanded Disability Status Scale ("EDSS"). EX1010. The EDSS is "the most widely used outcome measure in clinical trials of multiple sclerosis." EX1017, 1605. The EDSS is an "ordinal rating scale ranging from 0 to 10, in increments of 0.5, with higher scores reflecting increasing severity." EX1017, 1605. In other words, "lower EDSS scores indicate better functioning." EX1016, 424. Thus, a POSA

would have understood that a decrease in a patient's EDSS score during treatment indicated an improvement in the patient's neurologic impairment.

27. Magnetic resonance imaging ("MRI") is also commonly used to assess a patient's disease state, as well. A POSA would have known that "areas of gadolinium enhancement on T1-weighted MRI [enhancing lesions] suggest recent inflammatory demyelination with disruption of the blood-brain barrier," which "indicates current sites of presumed inflammatory demyelination (active lesions)" and that "[m]onitoring by means of serial MRI studies with gadolinium enhancement helps to identify agents that may be active against this early inflammatory stage of multiple sclerosis." EX1006, 940, 946. Additionally, relapses are associated with "an acute episode of new disease activity, either a new lesion[s] or fresh activity in an old area of involvement" and clinical relapses are "dependent on involvement of an 'eloquent' area of the CNS." EX1037, 909-910. A POSA would have understood that a reduction in the number or size of these enhancing lesions were indicative of a treatment response. EX1014, 1718; EX1018, 1153; EX1031, 45.

B. Immunosuppression was a common therapeutic strategy to treat multiple sclerosis before December 2004

28. Before December 2004, much was understood about the pathology of MS. In the human immune system, monocytes and lymphocytes are different types

of immune cells that have different functions during an immune response.

Monocytes are part of the body's "innate" immune response, meaning they are not "intrinsically affected by prior contact with an infectious agent." EX1044, 1-3.

Monocytes act by engulfing and digesting microorganisms—a process referred to as "phagocytosis." EX1044, 2-7. Lymphocytes (including T cells), however, function in the body's "acquired" immune response. EX1044, 19-20.

29. Patients with MS "harbor T cells that react with CNS autoantigens." EX1007, 131. Although these T cells (a type of lymphocyte) may "remain dormant for decades, at some point they are activated in the periphery," which allows them to "migrate through the blood–brain barrier to the brain and spinal cord." EX1007, 131. Once these T cells are reactivated in the CNS, they "release pro-inflammatory Th1 cytokines and orchestrate the destruction of the myelin sheath by various types of immune cells." EX1007, 131.

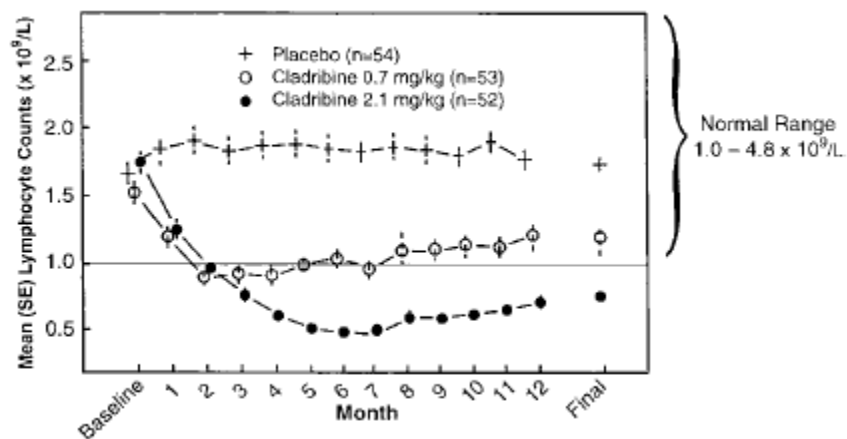
30. Because of the role autoantigen-specific T cells were known to play in MS, suppressing these lymphocytes was a target of MS therapies before December 2004. In fact, "the most common therapeutic approach" to MS before December 2004 was with immunosuppressive drugs. EX1013, 4; EX1007, 131. For example, Weiner states that the "a number of clinical trials designed to suppress the immune system or to restore immune balance in multiple sclerosis have been attempted."

EX1008, Abstract. Weiner explains that many MS immunotherapies are “designed to alter or suppress the immune response.” EX1008, 211. Whitaker also teaches that a first line of MS therapy “may be directed at limiting demyelination through systemic immunomodulation” with therapeutic agents that “attempt to alter the immune system,” such as immunosuppressants. EX1012, S104. Before December 2004, immunosuppressive agents, such as cladribine, mitoxantrone, azathioprine, and cyclophosphamide were used to treat MS. EX1016, 422-423; EX1007, 133. Thus, a POSA would have known that immunosuppression, and more specifically lymphocyte suppression, was a target of MS therapies before December 2004.

31. A POSA would have known that it was common to measure lymphocyte counts during clinical trials to assess a patient’s response to an immunosuppressive therapy, with a sustained decrease in count being characteristic of treatment response. EX1018, 1146. Weiner, for example, teaches that “treatment directed against lymphocyte traffic or activated T cells may be required for positive clinical effect,” especially in later stages of disease. EX1008, 216. For example, to measure cladribine-induced immunosuppression, Stelmasiak monitored patients’ lymphocyte counts every 3 months during a 24-month clinical trial. EX1013, 5. In Beutler’s cladribine study, a “[l]ymphocyte subset evaluation

was done monthly during the course of drug administration and less frequently thereafter.” EX1014, 1717.

32. During a phase III clinical study, Rice monitored patients’ “total lymphocyte count and lymphocyte subset counts (CD3⁺, CD4⁺, CD8⁺, CD19⁺, CD16⁺ plus CD56⁺, and CD4⁺/CD8⁺ ratio)” to assess cladribine in patients with progressive MS. Rice discloses in the figure below the average lymphocyte counts of patients taking placebo and those receiving cladribine:



EX1018, 1152, FIG. 4.

A POSA would have understood from Rice that the “normal range” of lymphocytes is between 1.0–4.8 x 10⁹/L, and that a decrease in the lymphocyte count to 1 x 10⁹/L (or 1000/ μ L) or below constitutes “suppression.” EX1018, 1152, Figure 4; see also EX1013, 5; EX1014, 1717.

C. Cladribine, a known immunosuppressant, was used to treat multiple sclerosis before December 2004

33. Cladribine, an adenosine deaminase inhibitor, was developed in the early 1990's to treat acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, cutaneous T-cell lymphoma, hairy-cell leukemia, and non-Hodgkin's lymphoma." EX1015, 1751. Cladribine was first launched in the US in February 1993. *Id.*

34. Cladribine's mechanism of action was well understood before December 2004. Cladribine was known to "selectively deplete[] lymphocytes" and "destroy the activated immunocytes that damage the central nervous system in multiple sclerosis." EX1046, Abstract. After administration, cladribine is phosphorylated within cells by the enzyme deoxycytidine kinase (dCK), and is then incorporated into DNA, "where it takes the place of adenosine triphosphate and effectively halts cell replication." EX1016, 421. The enzyme 5'-nucleotidase (5-NT) dephosphorylates (and therefore inactivates) cladribine. EX1016, 421. Lymphocytes "have a higher ratio of dCK to 5-NT than other cells" in the body, so they are "most subject to the effects of cladribine." EX1016, 421. Cladribine was known to have "activity against resting and dividing cells that express high deoxycytidine kinase activity." EX1016, 420. Accordingly, it was known in the art that "cladribine causes prolonged, profound suppression of lymphocyte counts."

EX1016, 420. In view of cladribine's "lymphocytotoxic activity," and the fact that it is not "harmful to normal bone marrow cells and other cell types," cladribine was considered a candidate for "modulating autoimmune processes involving lymphocyte abnormalities such as MS." EX1015, 1752; EX1018, 1146. Cladribine also became a focus of MS therapy because previous "[c]linical trials of general immunosuppressants in multiple sclerosis produced disappointing results" due to "systemic side-effects." EX1013, 6.

35. Beginning in the early 1990's, several clinical studies to evaluate cladribine in MS were carried out. These studies before December 2004 demonstrated a treatment response in patients with different forms of MS as measured by lymphocyte suppression, a decrease in EDSS scores, a reduction in relapse rate, and/or a decrease in enhancing lesions on MRI scans. In 1996, **Beutler** reported the results from a 2-year phase III clinical study designed to evaluate cladribine in patients with chronic progressive MS. EX1014, Abstract. During the first year, patients in the treatment arm were given "four monthly 7-day courses of 0.10 mg of cladribine per kg per day (0.7 mg/kg per course) for a total of four courses (total dose = 2.8 mg of cladribine per kg)." EX1014, 1716. During the second year of the study, patients who received placebo in the first year were

given cladribine, “but at one-half the total dose that had been administered during the first year” for a total dose of 1.4 mg/kg. EX1014, 1716.

36. Beutler reports that the “average EDSS and SNRS scores of patients receiving cladribine improved modestly during the first year of the study, whereas the scores of patients with placebo continued to deteriorate.” EX1014, 1717. Further, the lower dose of cladribine administered to patients in the second year of the study “also seemed to be effective in stabilizing their disease, albeit for a shorter time period, with peak improvement at ≈ 8 mo after treatment initiation.” EX1014, 1717. A POSA would have understood that a decrease in a patient’s EDSS score during treatment indicated an improvement in the patient’s neurologic impairment. *See* ¶ 26, *infra*.

37. Beutler also reports that a “highly significant difference was seen in the enhancing volumes, a measurement of current disease activity,” on MRI. EX1014, 1718. More patients in the high-dose cladribine group had no enhancing lesions (22) compared to the placebo group (11). EX1014, 1718. Beutler also reports that “there is clear evidence that the reduced dose of cladribine received by the initial placebo group during the second year on the study significantly reduced the occurrence of enhancing lesions on MRI scans.” EX1014, 1718. As explained above, a POSA would have understood that a reduction in the number or size of

these enhancing lesions were indicative of a treatment response. See ¶ 27, *infra*.

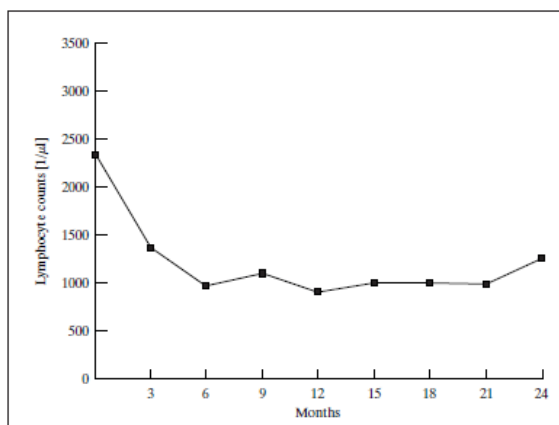
Thus, a POSA would have understood that some of the patients in Beutler's study exhibited a positive response to cladribine therapy because they had "enhancing lesions that disappeared." EX1014, 1718.

38. Beutler also notes a "marked depletion of CD4 cells [a type of lymphocyte] with both the high- and low-dose schedule." EX1014, 1719. Beutler concludes that "[b]ecause of its selective and prolonged effect on T cells, cladribine appeared to be a reasonable candidate drug for MS treatment." EX1014, 1719. As explained above, a POSA would have known that a sustained decrease in lymphocyte count was characteristic of a treatment response. EX1018, 1146; *see also* ¶ 32, *infra*. Beutler explains that "[o]ur studies clearly show that cladribine retards the progression of neurologic impairment of patients with chronic progressive MS." *Id.* at 1719-1720. Beutler's results are in line with disclosures in a previous Beutler patent. Beutler discloses a method of administering cladribine to treat MS that "reduce[s] the number of monocytes circulating in a treated mammal's blood stream," which "return[] to pretreatment levels about two weeks after the treatment stop[s]." EX1026, 11:19-24. On the other hand, "absolute lymphocyte counts [were] suppressed 0.5 to about 10 percent for more than one year," in MS patients treated with cladribine. EX1046, 13:32-36. In light of this

information, a POSA would have understood that while cladribine also suppresses monocyte counts, one would not have expected a patient's lymphocyte count to follow the same trend (i.e. length of suppression and time to recovery) as their monocyte count when receiving cladribine therapy, and I'm not aware that Merck provided any evidence to the contrary during prosecution.

39. In 1998, **Stelmasiak** reported the results of a small clinical study in which 10 patients with relapsing-remitting MS were treated with cladribine. EX1013, Abstract. Stelmasiak teaches that "[s]ix cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months," that "[e]ach course consisted of five doses of the drug taken once daily on consecutive days," and that cladribine was given "either subcutaneously (dose 5 mg per day, six patients) or orally (dose 10 mg per day, four patients)." EX1013, 5.

40. Stelmasiak reports that "[l]ymphocyte counts dropped from the initial count of 2336 ± 595 per μl (mean $\pm$ S.D.) to 968 ± 229 per μl at 6 months, and remained at approximately 1000 per μl for the next 15 months." EX1013, 5. Figure 1 of Stelmasiak shows the average lymphocyte count of the patients decreased substantially after 6 months of treatment and remained below baseline for the remainder of the study:



EX1013, 5, FIG. 1.

As explained above, a POSA would have understood that a decrease in the lymphocyte count to $1 \times 10^9/L$ (or $1000/\mu L$) or below constitutes “suppression” of the lymphocytes. EX1018, 1152, Figure 4; *see also* EX1013, 5; EX1014, 1717; ¶ 32, *infra*.

41. Stelmasiak notes that a “tendency toward normalization of lymphocyte counts became evident only at the end of the 2-year observation period,” but that the “magnitude of lymphocyte count reduction varied among the patients.” EX1013, 5-6. Stelmasiak also reports that “EDSS scores were significantly reduced during the treatment compared to the initial values,” and that “the decreases observed at the third to fifteenth month were significant by Wilcoxon matched pairs test.” EX1013, 6.

42. Stelmasiak concludes that “[i]n patients with relmitting-relapsing multiple sclerosis treatment with cladribine decreases lymphocyte counts in

peripheral blood, to 1/3 of the initial values on average,” “[t]he relapse rate in some (but not all) patients is impressively decreased,” and “[s]ide effects of the therapy are mild.” EX1013, 7. Stelmasiak further concludes that “[a]long with clinical evaluation in MS, the detailed pattern of cladribine-induced immunosuppression in clinical conditions deserves further study.” EX1013, 7. Stelmasiak further concludes that “[a]long with clinical evaluation in MS, the detailed pattern of cladribine-induced immunosuppression in clinical conditions deserves further study.” EX1013, 7.

43. In 1999, **Romine** also demonstrated a treatment effect of cladribine in patients with RRMS. Romine reports the results from an “18-month, placebo-controlled, double-blind study to evaluate cladribine in the treatment of 52 patients with relapsing-remitting multiple sclerosis.” EX1031, Abstract. Patients in the cladribine arm were given “0.07 mg/kg/day by subcutaneous injection for 5 consecutive days as six monthly courses for a total cumulative dose of 2.1 mg/kg.” EX1031, Abstract.

44. Romine’s data demonstrates a “statistically significant reduction in the frequency and severity of exacerbations in the cladribine group compared to the placebo group over months 7 through 12.” EX1031, 38. During months 7 to 12, the “relapse rate in the cladribine group was 0.77 per year [95% confidence interval

(“CI”), 0.37-1.41], compared to 1.67 per year in the placebo group (95% CI, 1.02-2.57).” EX1031, 38-39. Romine later determined that the “reduction in the distribution of frequency and severity of exacerbations in the cladribine group relative to the placebo group [was] sustained at 18 months.” EX1013, 39. A POSA would have understood the reduction in the frequency and severity of exacerbations (or relapses) was a “favorable effect of cladribine.” EX1013, Abstract.

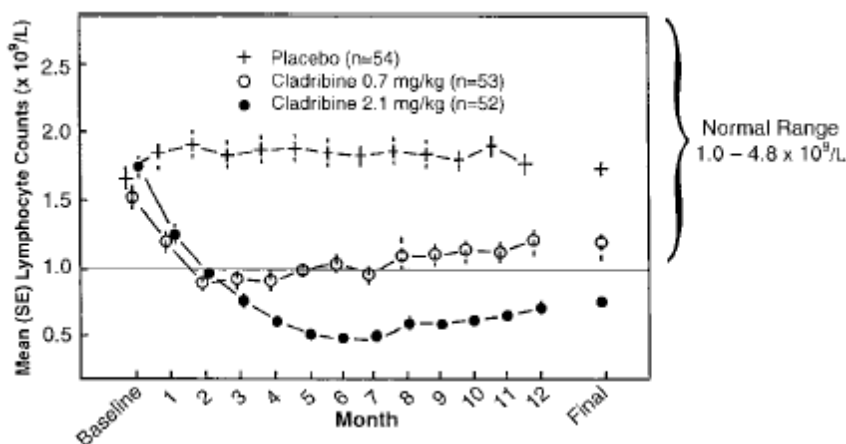
45. Romine also reported, “MRI results (Fig. 4, Table 3) revealed complete suppression of enhancing lesions after study month 6 in the cladribine group, whereas lesion enhancement persisted in the placebo group.” EX1031, 40. At 12 months, “there [was] a highly significant decrease in the occurrence of enhancing lesions ... relative to baseline in the cladribine group.” EX1031, 40. As explained above, a POSA would have understood that a reduction in the number or size of these enhancing lesions was indicative of a treatment response. See ¶ 27, *infra*.

46. As discussed above, a POSA would have understood enhancing lesions to “indicate[] current sites of presumed inflammatory demyelination (active lesions).” EX1006, 940. Thus, a POSA would have understood that the patients in Romine’s study exhibited a positive response to cladribine therapy because their

MRI-enhancing lesions were “completely suppressed” and there was a “statistically significant favorable effect of cladribine on the joint frequency and severity of relapses.” EX1031, Abstract.

47. In 2000, **Rice** reported the results from a clinical study to “evaluate the safety and efficacy of two doses of cladribine in patients with progressive MS.” EX1018, Abstract. Patients receiving cladribine were given “0.07 mg/kg/day for 5 consecutive days every 4 weeks for either two or six cycles (total dose, 0.7 mg/kg or 2.1 mg/kg, respectively).” EX1018, 1145. After the first 12 months of the study, “patients who fulfilled the hematologic dosing criteria were permitted to receive open-label cladribine treatment during the long-term extension phase of the study, provided at least 12 months had elapsed since the last dose of cladribine and there was evidence of disease progression.” EX1018, 1146.

48. Rice reports that the “largest observed effect was a suppression in lymphocyte count,” as demonstrated in the figure below.



EX1018, 1152, Figure 4.

As explained above, a POSA would have understood a suppression in lymphocyte counts to be indicative of a treatment response. EX1018, 1146; *see also* ¶ 32, *infra*.

49. Rice reports that “[g]adolinium-enhancing lesions were virtually eliminated by treatment with cladribine,” and that “[b]oth the 0.7 mg/kg and 2.1 mg/kg doses were significantly superior to placebo with respect to the proportion of patients having detectable enhanced T1 lesions as well as to the mean volume and number of such lesions at 6 months and final evaluation.” EX1018, 1153. As explained above, a POSA would have understood that the patients in Rice’s study exhibited a positive response to cladribine therapy because their enhancing lesions were eliminated. *Id.* And although Rice reported that “no significant treatment effects were found” using “EDSS scores as an outcome measure,” Rice explained that the severe disability of the majority of the patients enrolled in the study made it difficult to assess overall treatment difference by EDSS. EX1018, 1153.

50. Cladribine therapy was known to cause side effects associated with the drug’s toxicity, especially at higher doses. For example, Stelmasiak reports that in an earlier cladribine study, “dangerous marrow depression were reported in some multiple sclerosis patients.” EX1013, 7. In another earlier study, “all patients on average displayed marked signs of marrow toxicity: a progressive, although

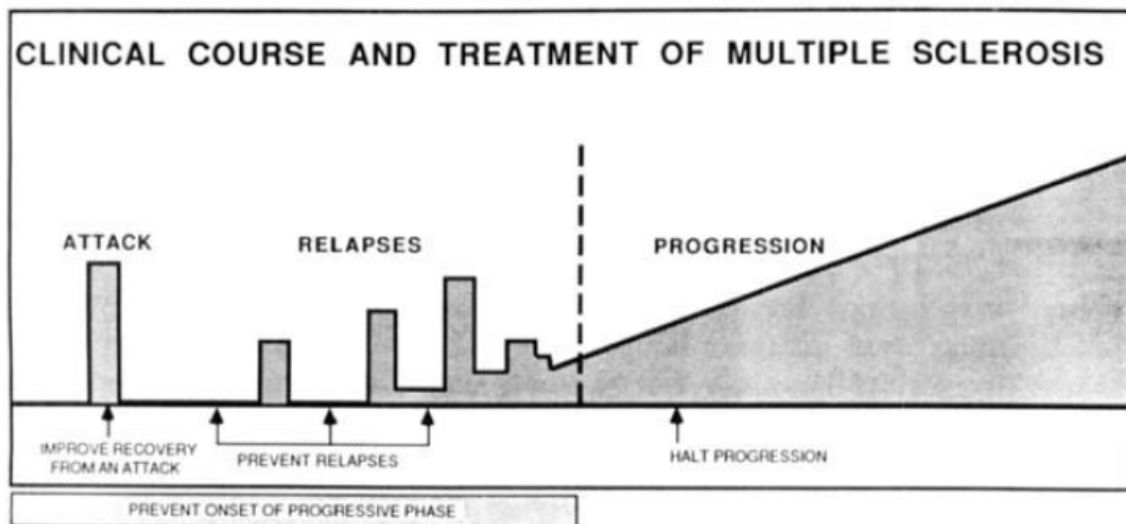
moderate and reversible fall in hemoglobin concentration, a distinct macrocytosis and a moderate thrombocytopenia (these changes were not reversing after the treatment was discontinued), and a modest, but noticeable drop in granulocyte counts.” EX1023, 326.

51. Further, a POSA would have known that suppressing a patient’s immune system would put them at an increased risk of infection. In fact, infections were a common side effect in cladribine clinical trials, due to its strong immunosuppressive action. Grieb, for example, reports that “many patients suffered from incidental upper respiratory tract infections,” during their study. EX1023, Abstract. And Langtry reports that “[i]nfections were reported in patients with MS receiving cladribine in clinical trials.” EX1016, 428.

52. In light of the potential side effects of immunosuppression, it was routine in the art to monitor a patient’s lymphocyte counts when treating a patient with certain immunosuppressants, such as cladribine. EX1008, 219. For example, it was recommended “to monitor disease activity in the peripheral blood by measuring such indexes as numbers of activated T cells or the presence of suppression.” *Id.* A POSA would have known that monitoring a patient’s lymphocyte counts was necessary because “cladribine causes prolonged, profound suppression of lymphocyte counts.” EX1016, 420.

D. MS often requires cyclical drug therapy to prevent relapses and limit progression of the disease

53. Because MS is a chronic disease, patients typically require ongoing care and repeated, or cyclical, treatments. As explained above, MS treatments are often “designed to alter or suppress the immune response.” EX1008, 211. Various treatment strategies exist for MS depending on the clinical course of the disease. Weiner teaches that “[d]ifferent immune mechanisms may be operating during various stages of the disease, and different strategies of immunotherapy have been attempted, depending on the clinical stage.” EX1008, 212. For example, as demonstrated in the figure below, different therapies are designed to treat acute attacks, prevent or decrease the number of relapses, and prevent onset of or halt the progressive phase. EX1008, 212-213.



EX1008, 212, FIG. 1.

54. Before December 2004, immunosuppressants, such as corticosteroids and cyclophosphamide, were commonly used to treat acute relapses and to prevent or decrease the number of relapses. EX1008, 212-213. Because of the cyclical nature of relapsing-remitting MS, patients are often treated in cycles—patients receive a drug for a period of time, stop taking the drug for a period of time, and then begin treatment again.

55. Barkhof teaches that “[t]reatment with methylprednisolone reduces the duration and severity of clinical relapses in multiple sclerosis (MS),” but also found that “the duration of effect of methylprednisolone treatment is temporary (on average 9.7 weeks).” EX1049, Abstract. Barkhof discloses “[p]atients entered the study at the time of an acute clinical relapse (development of new or worsening of old symptoms for at least 24 h, not related to a period of fever or concurrent disease), for which high-dose IV methylprednisolone treatment was given (1000 mg/day for 10 days).” EX1049, 382. After the initial treatment, “[w]hen new clinical relapses occurred, treatment was repeated.” EX1049, 382. Barkhof discloses that four patients received one additional course of methylprednisolone, two patients received two additional courses, two patients received three, and one patient received four additional courses of methylprednisolone. EX1049, 384.

56. Pirko reviews data from a small group of primary and secondary progressive MS patients who received “pulsed IVMP [intravenous methylprednisolone] at a dose of 1g/mo or 3 doses of 1 g/d every 3 months” for at least one year. EX1020, 1148. Pirko concludes the data “suggest that there may be a treatment effect of pulsed IVMP in a subset of patients with progressive MS.” EX1020, 1148. Pirko explains that the results from their review “suggests potential neuroprotective or extended immunomodulatory effects of IVMP.” EX1020, 1148.

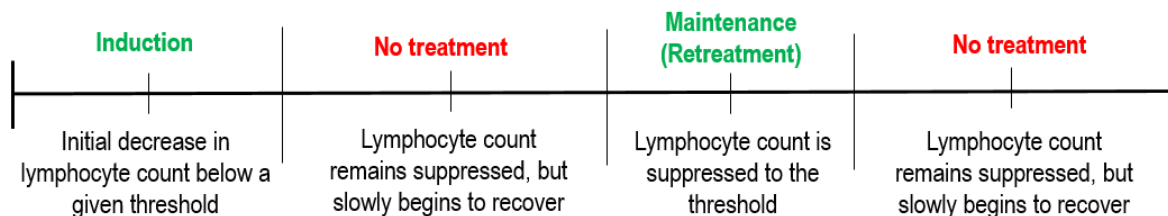
57. Pirko also discusses data from another study which demonstrated that “[p]ulsed IVMP therapy delayed the formation of T1 black holes, which are considered compatible with areas of axonal loss” and that the “treatment also slowed the progression of disability and had a protective effect on atrophy.” EX1020, 1148. A POSA would have known “T1 black holes” are “hypointense MS lesions on T₁-weighted scans” that correspond to areas of the brain with “severe tissue disruption,” which “correlate strongly with physical disability.” EX1045, 42.

58. Weiner 1993 discusses the results of a previous study that “demonstrated that a 2- to 3-week course of IV cyclophosphamide plus ACTH [adrenocorticotrophic hormone] could halt the progression of chronic progressive MS for a 1-year period in approximately 75% of the 20 patients.” EX1021, 911.

However, “there were patients whose reprogression began 6 to 9 months after treatment or as long as 3 years after treatment.” EX1021, 911. Weiner 1993 goes on to disclose results from a study in which four groups of patients with progressive MS were given induction doses of intravenous cyclophosphamide plus adrenocorticotrophic hormone (ACTH). After the induction period, two of the cohorts were given IV cyclophosphamide every 2 months for a 2-year period. EX1021, 911. Weiner 1993 reports that “[b]oosters had significant impact ($p = 0.03$) on delaying reprogression after 1 year; this is consistent with previous observations that the average time to reprogression following cyclophosphamide/ACTH induction is approximately 18 months.” EX1021, 913.

59. Thus, at the time the '947 patent was filed, 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. As such, a POSA would have understood that it was common for a patient to receive more than one course of drug therapy to treat active relapses, prevent relapses, and/or prevent or slow further progression of the disease. And, in fact, the general knowledge in the art also recognized that “the beneficial effect of a single course of cladribine” is “not permanent” and investigating “retreatment with cladribine will be especially important.” EX1046,

392. For example, “cycles (or courses) of cladribine may “be repeated at monthly intervals.” EX1026, 11:5-7. I have prepared the following figure to demonstrate how a POSA would have understood this dosing regimen concept:



E. Oral cladribine compositions for treating MS were known in the art before December 2004

60. Various oral cladribine compositions were known in the art before December 2004. Bodor teaches that “[o]ral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations.” EX1022, 2:9-11. Specifically, Bodor explains, “[p]atient compliance is enhanced insofar as oral dosage forms alleviate repeated health care provider visits, or the discomfort of injections or prolonged infusion times associated with some active drugs,” “reduced costs [are] associated with oral administration versus parenteral administration” because “[t]he cost of parenteral administration is much higher due to the requirement that a health care professional administer the cladribine in the health care provider setting, which also includes all attendant costs associated with such administration,” and “in

certain instances, therapeutic considerations such as the need for a slow release of cladribine over a prolonged period of time may be practically met only by oral or transmucosal delivery.” *Id.*, 2:11-21. Thus, by December 2004, a POSA would have understood that oral cladribine dosage forms were preferable to injectable dosage forms.

61. Prior to December 2004, a POSA would also have known how to prepare an oral dosage form of cladribine. For example, Schultz discloses “oral solid pharmaceutical dosage forms containing a mixture of cladribine (2-chloro-2'-deoxyadenosine; 2-CdA) and cyclodextrin.” EX1024, Schultz, Abstract. Such oral dosage forms “may be prepared in the form of tablets, caplets, gelcaps, capsules, chewable tablets, lozenges, fast dissolving wafers, and other known and effective delivery modes.” *Id.*, 5:37-40. Schultz explains, “solid mixtures of the cyclodextrins with the active ingredient are prepared via melt-extrusion, where the active ingredient is embedded in the cyclodextrin carrier.” *Id.*, 5:50-55.

62. According to Schultz, oral cladribine/cyclodextrin compositions “may also have application in the treatment of a variety of disease states and autoimmune disorders such as multiple sclerosis,” and “[f]or treatment of multiple sclerosis the dosage can range from about 0.04 to about 1.0 mg/kg of body weight

per day, preferably from about 0.05 to about 0.15 mg/kg/day, as described in U.S. Pat. No. 5,506,214.” *Id.*, 6:45-49, 6:53-57.

63. Bodor also discloses “compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine.” EX1022, Abstract. Bodor discloses a “pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form which maximizes the amount of cladribine in the inclusion and non-inclusion complexes.” *Id.*, 5:17-25. Bodor also “provides a process for the preparation of a complex cladribine-cyclodextrin complex [sic].” *Id.*, 6:3-9.

VII. The '947 Patent Specification and Claims

64. I have reviewed the '947 patent, which is generally directed to “the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.” EX1001, Abstract. The '947 patent purportedly provides “an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.” EX1001, 3:42-44. The dosing regimen generally includes orally administering cladribine following these sequential steps:

- (i) An induction period 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 wherein no Cladribine is administered;
- (iii) A maintenance period wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i); and
- (iv) A Cladribine-free period wherein no Cladribine is administered.

EX1001, 4:3-13.

65. I understand that the '947 patent has three independent claims.

Independent claim 36 is reproduced below:

36. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:

- (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.

EX1001, 19:13-30.

66. I understand that claims 36, 38, 39, and 41-46 of the '947 patent ultimately depend from claim 1 and add certain limitations, such as the length of the induction, cladribine-free, and maintenance periods, doses, etc.

VIII. Claim Construction

67. I understand that the terms of the claims are to be given their plain and ordinary meaning from the point of a POSA in question on December 22, 2004. I also understand that when a patent provides a definition of a particular claim term, I am to use that definition in determining the meaning of the term.

A. “Total Dose of Cladribine”

68. Each of claims 36, 38, 39, and 41-46 of the '947 patent recites administering a **“total dose of cladribine”** in each of steps (i) and (iii). The '947 patent defines “total dose” as “the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses.” EX1001, 4:18-22. Because the '947 patent specification provides an explicit definition for the term “total dose,” this is how a POSA would have construed this term. And I used this meaning of the term in my analysis.

B. “Induction Period”

69. Each of claims 36, 38, 39, and 41-46 of the '947 patent recites a method of treatment comprising an **“induction period.”** The '947 patent does not explicitly define “induction period.” However, the '947 patent states the following:

An “Induction Treatment” consists in the sequential succession of (i) an **induction period** wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and (ii) a Cladribine-free period.

EX1001, 4:51-55 (emphasis added). The '947 patent further specifies that “[a]n induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month,” and “lasts up to about 4 months or up to about 3 months or up to about 2 months.” EX1001, 4:60-64. An “induction period,” therefore, means a treatment period of a defined length that is followed by a treatment-free period. Further, as explained more below, the '947 patent requires that the dose of cladribine administered in the induction period be greater than the dose of cladribine administered in a maintenance period.

C. “Maintenance Period”

70. Each of claims 36, 38, 39, and 41-46 of the '947 patent also recite a method of treatment comprising a **“maintenance period.”** The '947 patent does

not explicitly define “maintenance period,” however, the ’947 patent states the following:

A “Maintenance Treatment” consists in the sequential succession of (i) a **maintenance period** wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a **lower dose** than the Cladribine dose orally administered during the induction treatment and (ii) a Cladribine-free period.

EX1001, 5:6-10 (emphasis added); *see also id.*, 3:59-63, 4:8-10, 8:35-39, 9:46-50, 10:7-12, 10:26-31, 10:54-58, 12:27-31, 12:47-52, 13:1-4, 15:65-16:3, 16:4-9. The ’947 patent further specifies that “[a] maintenance period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month,” and “lasts up to about 4 months or up to about 3 months or up to about 2 months.” *Id.* at 5:11-18. During prosecution of the ’947, Merck argued that none of the cited art taught “*lowering* treatment dosages with each successive use of the drug.” EX1004, 251. And during the prosecution of the ’903 patent, Merck argued that the maintenance period is characterized by administration of a *lower* total dose of cladribine compared to the induction period. EX1025, 151. Thus, a “maintenance period,” therefore, means a defined length of time in which cladribine is administered at a lower dose than the cladribine dose administered in an induction period.

71. Any term I have not expressly interpreted above, I apply its plain and ordinary meaning.

IX. Basis of my analysis with respect to obviousness

72. I understand that an obviousness analysis involves determining the scope and content of the prior art; comparing the differences between the claimed invention and the prior art; and resolving the level of ordinary skill in the pertinent art.

73. I understand that combining or modifying the teachings of the prior art to achieve the claimed invention is a way to establish obviousness. I understand that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not need to be explicit in any reference.

74. I also understand that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in so doing. I understand that this does not require absolute predictability of success.

75. I further understand that a claimed range may be obvious if a prior art reference discloses a range that overlaps with or is encompassed by the claimed range. I further understand that even if a prior art reference does not disclose a particular value or range of values, the prior art would still render a claim obvious if it would require only routine experimentation to arrive at the claimed value or range of values.¹ I understand that a particular parameter must first be recognized as a result-effective variable, which I understand is a variable that achieves a recognized result, before the determination of the optimum or workable ranges of the variable may be characterized as routine experimentation. I also understand that the patentee may present evidence of teaching away, unexpected results, or criticality, or other pertinent objective evidence indicating that the overlapping range would not have been obvious in light of that prior art.

76. I understand that when considering the obviousness of an invention, one should also consider whether there is any objective evidence that supports the non-obviousness of the invention. I understand that objective evidence of nonobviousness (also known as secondary considerations of non-obviousness) includes factors such as failure of others; unexpectedly superior results; skepticism

¹ I understand that experimentation can be 'routine' where a POSA would have a reasonable expectation of success in optimizing the value and would only need to use well-known problem-solving strategies to verify that expectation.

followed by praise in the industry; long-felt, but unmet, need; copying; and commercial success.

X. My analysis with respect to claim 36

77. Claim 36 is directed to a “method of treating multiple sclerosis” comprising the “oral administration of a formulation comprising cladribine” “following the sequential steps below:

- (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.

EX1001, 19:13-30. Claim 36 would have been obvious to a POSA over the combination of Bodor and Stelmasiak before December 22, 2004, as I explain in detail below. I have provided a chart in an Appendix below identifying where each limitation of claim 36 is taught in the art.

A. Bodor and Stelmasiak teach orally administering cladribine to treat multiple sclerosis

78. A POSA would have understood that Bodor and Stelmasiak both teach “method[s] for treating relapsing-remitting multiple sclerosis” “comprising the oral administration of a formulation comprising cladribine.” Bodor discloses cladribine has “been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions,” including “multiple sclerosis.” EX1022, 1:15-2:5. Bodor recognized that cladribine was being studied in both RRMS and progressive forms of MS. Specifically, Bodor states that “various dosage amounts and dosing regimens have been reported in the literature for use in the treatment of multiple sclerosis.” *Id.*, 22:27-28. Bodor cites to several references that disclose treating RRMS and progressive forms of MS with cladribine. Thus, Bodor recognized that cladribine was being used to treat RRMS and progressive forms of MS.

79. According to Bodor, “[o]ral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations.” *Id.*, 2:9-11. Bodor teaches, “the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration.” *Id.*, 23:7-9. To that end, Bodor discloses “compositions of cladribine and cyclodextrin which are especially suited

for the oral administration of cladribine.” *Id.*, Abstract. Specifically, Bodor teaches that “it is envisioned 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.” *Id.*, 23:15-20. According to Bodor, cladribine formulated into the described solid oral dosage forms is in “a high thermodynamic state,” which results in “improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.” *Id.*, 11:27-12:3, 23:9-20, Example 4, Table V, VI. Bodor also teaches a POSA how to prepare “oral tablets” containing cladribine. *Id.*, 23:15-20. Bodor further discloses administering its oral cladribine tablets to MS patients in two separate clinical studies. *Id.*, 33-39, Examples 4 and 5. As such, a POSA would have understood that Bodor teaches a POSA how to prepare and administer an oral cladribine composition to treat MS.

80. Stelmasiak reports the results of a clinical study in which “patients with the remitting-relapsing form of MS” were treated with cladribine. EX1013, Summary. According to Stelmasiak, “available immunosuppressants (such as cyclophosphamide, methotrexate, or cyclosporin A) evidenced at most a modest

and transient benefit to MS patients,” but “immunosuppressive activity of [cladribine] may be useful in the treatment of diseases of autoimmune etiology [e.g., MS].” *Id.*, 4. Specifically, patients were treated “with six courses of this drug (5 mg subcutaneously or 10 mg orally, once daily, repeated on five consecutive days) given once a month, followed by two additional courses at three month intervals.” *Id.* Stelmasiak discloses that the oral cladribine “was prepared as [a] sterile solution in isotonic saline, 1 mg/ml.” *Id.*, 5. Thus, a POSA would have understood that Stelmasiak discloses a “method for treating relapsing-remitting multiple sclerosis” “comprising the oral administration of a formulation comprising cladribine,” as recited in claim 36.

B. Bodor’s and Stelmasiak’s cladribine dosing regimens include an “induction period;” Bodor’s induction period is 2 months long

81. A POSA would have understood that Bodor and Stelmasiak both disclose cladribine dosing regimens that include an “induction period.” Bodor teaches that “for the treatment of multiple sclerosis, 10 mg of cladribine ... 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.” EX1022, 23:16-20. Bodor also teaches another dosing regimen of “10 mg of cladribine ... once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment.”

EX1022, 23:20-24. A POSA would have understood that Bodor's treatment scheme of administering 10 mg of cladribine for five to seven days in two consecutive months or six consecutive months constitutes an "induction period," as defined by the '947 patent. Further, a POSA would have understood Bodor's induction period to last for two months, as recited in claim 36.

82. Stelmasiak discloses that "[s]ix cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months," with "[e]ach course consist[ing] of five doses of the drug taken once daily on consecutive days." EX1013, 5. In other words, a POSA would have understood the patients received cladribine daily for five days once a month for six months and then stopped taking cladribine for three months. A POSA would have understood that the first six months of Stelmasiak's treatment scheme constitutes an "induction period," as defined by the '947 patent.

C. Bodor teaches the claimed total dose of cladribine administered in an induction period

83. Bodor teaches administering 1.4 mg/kg to 2 mg/kg of cladribine, which overlaps with the claimed range of "about 1.7 mg/kg to about 3.5 mg/kg." As explained above, a POSA would have understood that Bodor's treatment scheme of administering 10 mg of cladribine for five to seven days in two consecutive months constitutes an induction period. A POSA would have been

able to calculate the total amount of cladribine administered in each of the two months of Bodor's induction period as follows:

$$\begin{aligned} \text{Cladribine dose (in mg)} &= (10 \text{ mg} \times 5 \text{ days (or 7 days)}) \times 2 \text{ months} \\ &= 100 \text{ mg (or 140 mg)}. \end{aligned}$$

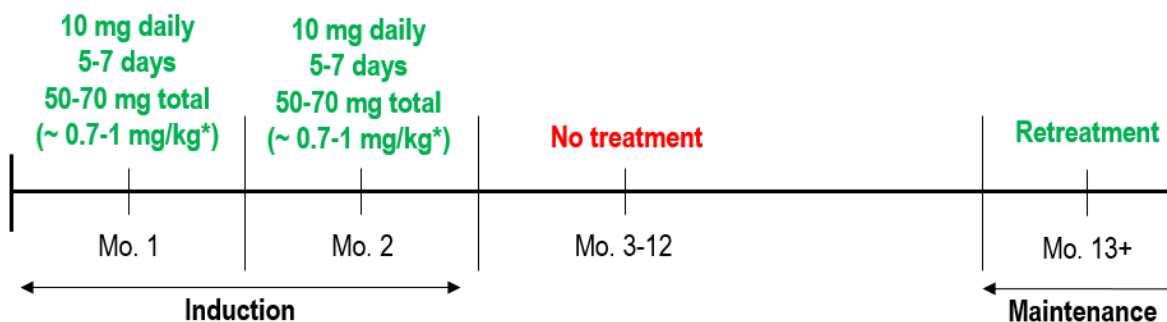
Thus, a POSA would have been able to determine that Bodor teaches administering a total of 100 to 140 mg of cladribine over a two-month induction period. A POSA would have further understood that, for an average adult weighing about 70 kg², Bodor's dose is equivalent to approximately 1.4 to 2 mg/kg (i.e., 100 mg ÷ 70 kg or 140 mg ÷ 70 kg), which overlaps with the claimed range of "about 1.7 mg/kg to about 3.5 mg/kg," which I understand renders the claimed range obvious. I am not aware of any evidence of teaching away, unexpected results, or criticality, or other pertinent objective evidence presented by Merck indicating that the overlapping range would not have been obvious in light of Bodor.

D. Bodor and Stelmasiak teach retreating with cladribine after a cladribine-free period

84. A POSA would have understood that Bodor teaches retreatment with cladribine after a cladribine-free period. Bodor teaches a cyclical regimen for treating MS by administering cladribine "once per day for a period of five to seven

² EX1050.

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.***” EX1022, 23:15-20 (emphasis added). I have prepared the following the following schematic to illustrate how a POSA would have understood Bodor’s dosing regimen:



* Based on an average body weight of 70 kg

85. Bodor also teaches another dosing regimen that administers cladribine ” once per day for a period of five to seven days per month for a total of six months, followed by ***eighteen months of no treatment.***” EX1022, 23:20-24 (emphasis added). As explained above, a POSA would have considered the first two months or six months of Bodor’s dosing regimens to be an induction period. Bodor explains that the induction period is then followed by “ten months of no treatment” or “eighteen months of no treatment.”

86. A POSA would have understood that Bodor teaches a cyclical cladribine regimen, in that cladribine is re-administered at the end of the specified cladribine-free period—otherwise, the specified length of time of the cladribine-

free period is meaningless. Bodor does not teach administering a different drug therapy after the cladribine-free period, so a POSA would have understood Bodor to re-administer cladribine at the end of the 10 month or 18 month cladribine-free period.

87. Further, as discussed above, it was well known that MS is a chronic disease that typically requires ongoing care and repeat treatment. *See* ¶ 53, *infra*. To date, there is no known cure for MS. MS patients typically receive more than one course of drug therapy to treat active relapses, prevent relapses, and/or prevent or slow further progression of the disease. *See* ¶¶ 53-59, *infra*. Because Bodor teaches a dosing regimen of cladribine that is effective for treating MS, a POSA would have thought to re-administer cladribine again after the specified cladribine-free period.

88. Stelmasiak also teaches a cladribine dosing regimen that includes an induction period, followed by a cladribine-free period, which is then followed by a “maintenance period,” as defined by the ’947 patent. As explained above, Stelmasiak discloses administering “[s]ix cladribine courses ... at monthly intervals” and “two additional courses ... at 9 and 12 or 15 months.” EX1013, 5. In other words, Stelmasiak discloses administering cladribine for six consecutive months (i.e., an induction period), and then re-administering cladribine at nine

months after a three month cladribine-free period. Stelmasiak then re-administers cladribine again at either 12 months after another three month cladribine-free period or at 15 months after another six month cladribine-free period. A POSA would have understood that re-administering cladribine at 9 months and 12 or 15 months constitutes a “maintenance period,” as defined by the ’947 patent. Accordingly, a POSA would have recognized that Stelmasiak administered cladribine in a cyclical manner.

E. Stelmasiak teaches administering a lower dose of cladribine in the retreatment period compared to the induction period; a POSA would have known how to optimize the maintenance period dose and length

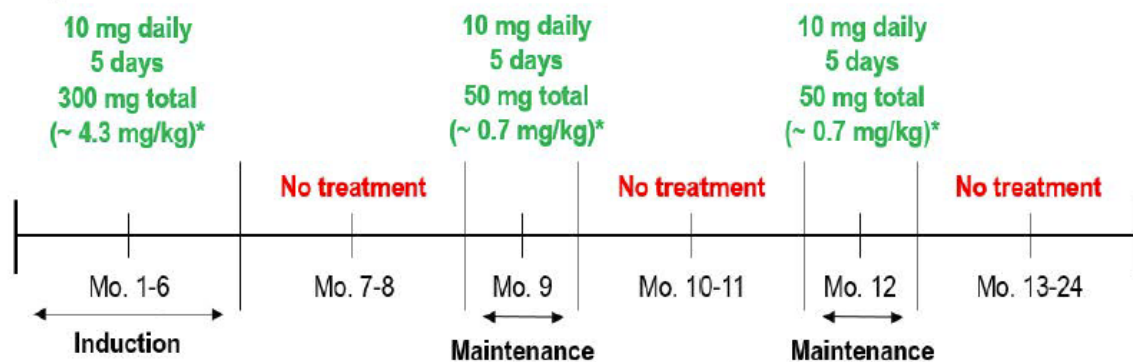
89. Stelmasiak expressly teaches administering a lower dose of cladribine in a maintenance period than is administering during an induction period.³ As explained above, Stelmasiak discloses the following dosing regimen:

Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months. Each course consisted of five doses of the drug taken once daily on consecutive days. Cladribine was given either subcutaneously (dose 5 mg per day, six patients) or orally (dose 10 mg per day, four patients).

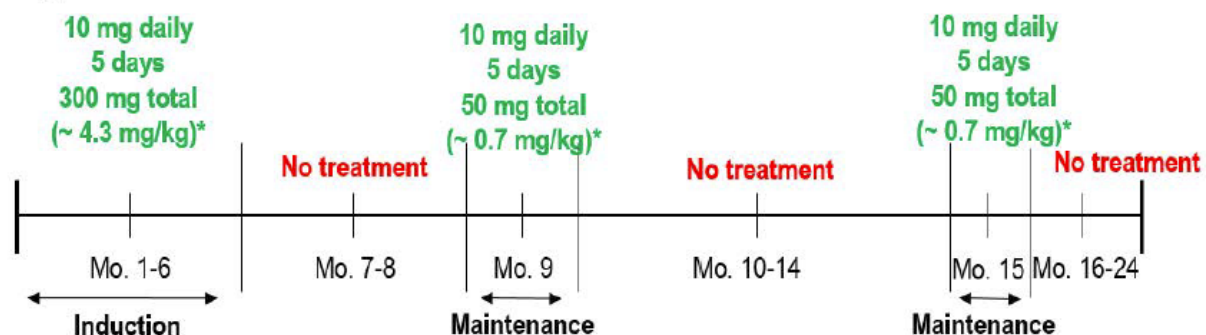
³ A POSA may also have considered administering cladribine in the maintenance period at the same total dose as in the induction period, however, as explained herein, a POSA would have also considered administering a lower dose of cladribine in the maintenance period. EX1022, 23:15-20.

EX1013, 5. Thus, a POSA would have known that after the six month induction period, patients received one additional course of cladribine at nine months and another additional course at 12 or 15 months. A POSA would have understood that patients who received oral cladribine were given a total dose of 300 mg during the induction period, 50 mg at nine months, and another 50 mg at 12 or 15 months. I have prepared the following figure to illustrate how a POSA would have understood Stelmasiak's dosing regimen:

Regimen 1



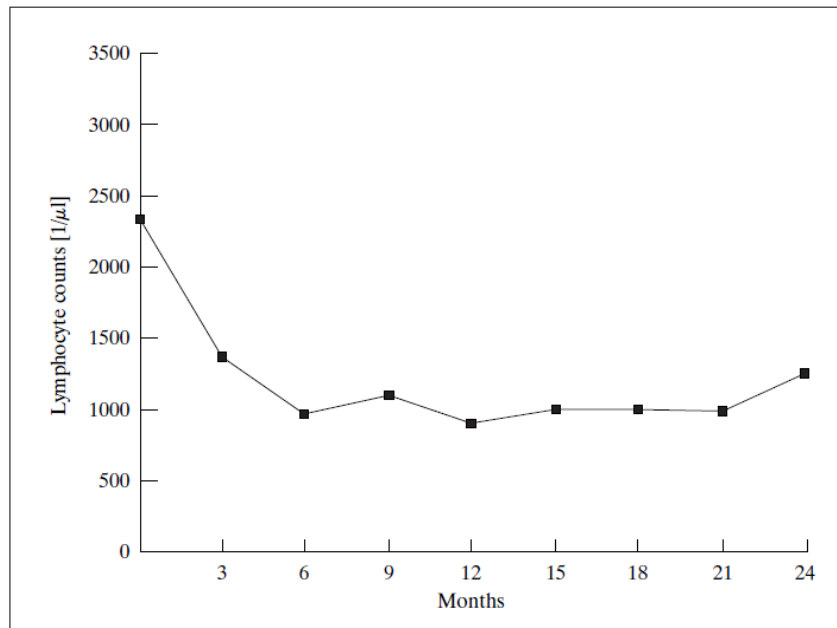
Regimen 2



* Based on an average body weight of 70 kg

90. Stelmasiak reports that this dosing regimen resulted in “[l]ymphocyte counts dropp[ing] from the initial count of 2336 ± 595 per μl (mean $\pm$ S.D.) to

968±229 per μl at 6 months, and remain[ing] at approximately 1000 per μl for the next 15 months.” EX1013, 5. Stelmasiak also plots average lymphocyte counts over time to illustrate the reduction in lymphocyte count:

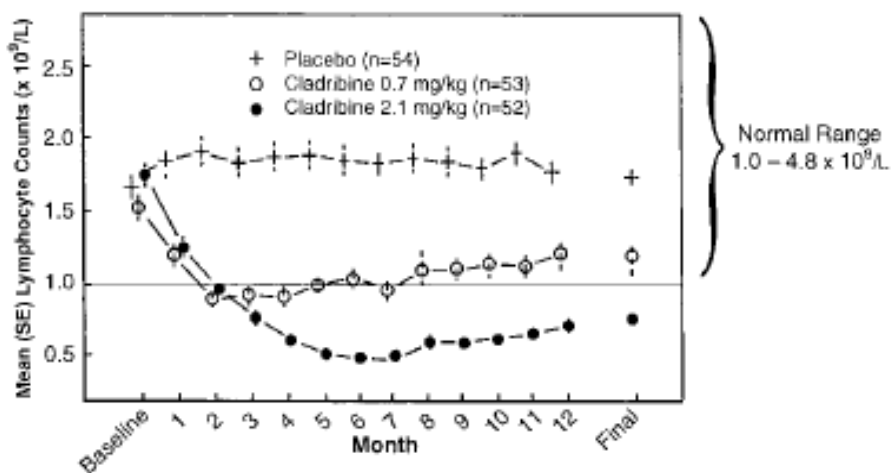


EX1013, 5, FIG. 1.

A POSA would have understood that the data shows that while 300 mg of cladribine suppressed the average lymphocyte count to less than 1000 per μl after six months, only 50 mg of cladribine was needed to maintain that level of lymphocyte suppression. A POSA would have understood that to $1 \times 10^9/\text{L}$ (or 1000/ μL or below constitutes “suppression.” See ¶ 32, *infra*. Stelmasiak also notes that this dosing regimen resulted in a “significant[.]” reduction in EDSS scores “compared to the initial values.” EX1013, 6. Thus, a POSA would have understood

that Stelmasiak teaches that a lower dose of cladribine in the maintenance period was effective in maintaining the lymphocyte suppression achieved during the induction period.

91. A POSA would have recognized the dose of cladribine and length of administration as result-effective variables because they achieve a recognizable result (e.g., lymphocyte suppression). As Stelmasiak and the general knowledge in the art teaches, it was routine in the art to monitor a patient's lymphocyte counts when treating a patient with a known immunosuppressant. *See* ¶¶ 31-32, *infra*. A POSA would have known that monitoring a patient's lymphocyte counts was necessary because cladribine causes prolonged, profound suppression of lymphocyte counts in both RRMS and progressive forms of MS. EX1031, 42-43; EX1018, 1152; EX1013, 5. It was also general knowledge in the art that a direct correlation exists between the dose and length of administration of cladribine and level of lymphocyte suppression. Rice, for example, reports "cladribine treatment to be associated with ***dose-dependent decreases*** in mean levels of CD4⁺, CD3⁺, CD8⁺, and to a lesser degree, CD19⁺ lymphocytes." EX1018, 1152 (emphasis added). In fact, as shown below, Rice demonstrates a higher dose of cladribine caused a more profound reduction of lymphocyte counts:



EX1018, FIG. 4. Rice also observes that cladribine-treated patients “had a small, **dose-dependent**, median percent decrease in T2 lesion volume.” *Id.*, 1151 (emphasis added). According to Rice, the “intensity of the dosing schedule” differed between Rice’s study and Beutler’s earlier study, “which may have contributed to the improved tolerability and lower incidence of infections in this study.” *Id.*, 1153. Because of cladribine’s toxicity, a POSA would have sought to administer the lowest effective dose. See ¶ 50-51.

92. Selby also reports dose-dependent decreases in lymphocyte counts. Selby, comparing their data to that of Beutler, states: “[o]ur series of patients received a lower total treatment dose (total of 2.1 vs 2.8 mg/kg, as well as a lower treatment dose per cycle (0.35 mg/kg vs. 0.7 mg/kg).” EX1047, 297. Selby reports that “[w]hen compared to the higher dose regimen [Beutler’s regimen], the rate of decline in the CD4 count using our regimen was less rapid.” *Id.* Selby also

observed “a partial but incomplete recovery in CD4 counts” one year post-therapy “while CD4 levels remained severely depressed in the higher-dose study.” *Id.*

Thus, a POSA would have recognized the dose of cladribine and length of administration to be result-effective variables.

93. A POSA would have known how to optimize the dose administered during the maintenance period by adjusting the amount of cladribine administered to a patient. And a POSA would have known to adjust a patient’s cladribine dose depending on the patient’s lymphocyte counts (e.g., by administering more or less cladribine) and/or the length of administration (e.g., administering cladribine for a shorter period of time to reduce the amount administered). In fact, Bodor instructs as much, stating:

Furthermore, one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning and/or by administering cladribine according to the invention with another active ingredient. The invention therefore provides a method to tailor the administration/treatment to the particular exigencies specific to a given mammal. Therapeutically effective amounts may be easily determined, for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.

EX1022, 24:1-9. Bodor is consistent with the general knowledge in the art, e.g., as reflected in Beutler, which teaches that “one can tailor the dosage and duration for which [cladribine] is administered to the stage of the disease and the condition of the patient being treated.” EX1046, 5:20-22. Adjusting the amount of cladribine administered or the length of time the cladribine is administered would have been routine. Thus, Bodor recognizes a POSA’s ability to optimize the cladribine dose and length of dosing time and provides suggestions of how to do so. In sum, because a POSA recognized the dose of cladribine and length of administration to be result-effective variables, a POSA would have known to optimize the dose based on a patient’s lymphocyte count, and nothing more than routine experimentation would have been needed. By doing so, a POSA would have arrived at the claimed maintenance period dose and length by routine optimization.

F. Stelmasiak teaches a cladribine-free period after the maintenance period; a POSA would have known how to optimize the length of the second cladribine-free period

94. Stelmasiak teaches a cladribine-free period following a maintenance period. As described, Stelmasiak teaches a regimen that included monthly administration of cladribine for six months (an induction period), followed by two additional courses at nine months and 12 or 15 months. EX1013, Abstract, 5. Patients did not receive cladribine between maintenance periods. And after the last maintenance period, patients were “observed” for an additional 9 to 12 months,

during which time they did not receive cladribine. EX1013, Abstract. Thus, a POSA would have understood Stelmasiak's dosing regimen to include a cladribine-free period after a maintenance period.

95. A POSA would have known the length of the cladribine-free period is a result-effective variable because it achieves a recognizable result—e.g., the amount of time a patient does not receive cladribine will affect the patient's lymphocyte suppression induced by the cladribine. For example, the general knowledge in the art that the effects of a single dose of cladribine were not permanent and lymphocyte counts eventually rebounded after a cladribine-free period. EX1046, 392; EX1047, 296, 297. A POSA would also have followed the maintenance period with another drug-free period, similar to Stelmasiak's dosing regimen, because cladribine toxicity was a concern. For example, Stelmasiak reports that in an earlier cladribine study, "dangerous marrow depression were reported in some multiple sclerosis patients." EX1013, 7. In another earlier study, "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." EX1023, 326. A POSA would have had the skill to monitor a

patient's lymphocyte count and side effects associated with lymphocyte and myelosuppression, and optimize the length of time of the second cladribine-free period to mitigate side effects while maximizing lymphocyte suppression.

G. A POSA would have had a reason to combine Bodor and Stelmasiak to arrive at the claimed method

1. A POSA would have been motivated to formulate an oral cladribine composition per Bodor, with a reasonable expectation of success

96. Prior to 2004, oral cladribine therapies were under development because oral delivery, as opposed to parenteral delivery, improved patient compliance by alleviating “repeated health care provider visits” and the “discomfort of injections or prolonged infusion times associated with some active drugs.” EX1022, 2:11-13. It was also known that the “cost of parenteral administration [compared to oral delivery] is much higher due to the requirement that a health care professional administer the cladribine in the health care provider setting, which also includes all attendant costs associated with such administration.” EX1022, 2:15-19.

97. Before December of 2004, Bodor developed an oral cladribine dosage form with “improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.” EX1022, 12:1-3. To that end, Bodor discloses “a method for increasing or enhancing the oral bioavailability of cladribine

comprising orally administering to a subject in need thereof, a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form which maximizes the amount of cladribine in the inclusion and non-inclusion complexes.” EX1022, 5:17-25.

98. Also, as discussed above, Bodor discloses that cladribine has “been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions,” including multiple sclerosis. EX1022, 1:15-2:5. Bodor discloses administering its oral cladribine in a dosing regimen specifically designed to treat MS. *Id.*, 23:15-20. As such, a POSA would have been motivated to treat MS with Bodor’s oral cladribine composition.

2. A POSA would have been motivated to treat MS by administering Bodor’s oral cladribine composition according to Stelmasiak’s induction period/cladribine-free period/maintenance period/cladribine-free period framework

99. A POSA would have been motivated to treat MS by administering an oral cladribine composition according to the claimed dosing regimen, as taught in the art. As discussed above, it was well known that MS is a chronic disease that typically requires ongoing care and repeat treatment. *See* ¶ 53, *infra*. Bodor

discloses a cladribine dosing regimen to treat MS that includes a 2-month induction period followed by a 10 month cladribine-free period. As discussed above, a POSA would have been motivated to administer an oral cladribine composition to treat MS, with a reasonable expectation of success. Both Bodor and Stelmasiak teach a POSA to administer cladribine during an induction period. Bodor specifically instructs administering an oral cladribine composition, which has demonstrates “enhance[d]” oral bioavailability, for a 2-month induction period. EX1022, 5:17-25. After a 2-month induction period, Bodor teaches a 10-month cladribine-free period. Thus, a POSA would have believed Bodor’s dosing regimen to have a sufficient immunosuppressive effect to treat MS.

100. A POSA would have expected at least some patients to exhibit a relapse in clinical signs or symptoms after Bodor’s treatment cycle, which would require further treatment. EX1013, 7. Many MS patients experience a relapsing-remitting form of MS, in which periods of remission occur between relapses or exacerbations. EX1009, 263; EX1007, 131. Such clinical signs or symptoms of a relapse may include, for example, “acute worsening of neurologic function” and “current sites of presumed inflammatory demyelination” on an MRI scan. EX1037, 908; EX1006, 940. A POSA would have understood that cladribine is a “disease-modifying” therapy—i.e., cladribine does not cure MS, but can reduce the number

of relapses by causing “prolonged, profound suppression of lymphocyte counts.” EX1016, 420; EX1013, 6. Thus, a POSA would expect some patients to relapse after cladribine therapy, as evidenced in some cladribine clinical trials. For example, Stelmasiak reports that “a total of 6 relapses during the two-year study period (average relapse rate 0.43 per patient per year)” was reported in the “responders” group. EX1013, 6. The general knowledge in the art also reports that in patients with RRMS who were treated with 2.1 mg/kg of cladribine, “the relapse rate in the cladribine group was 0.77 per year.” EX1031, 38-39. The general knowledge in the art also recognized that “the beneficial effect of a single course of cladribine” is “not permanent” and investigating “retreatment with cladribine will be especially important.” EX1046, 392. Thus, a POSA would have understood from such clinical studies that patients may relapse during or after cladribine therapy and would have been motivated to retreat the relapsing patients with cladribine after “ten months of no treatment.”

101. A POSA would have thought to re-administer cladribine to decrease the relapse rate, as taught by Stelmasiak. Stelmasiak reports “a very marked (almost five-fold on average)” reduction in the relapse rate and “more pronounced improvement in [patients’] neurological status as measured by EDSS scores” after the retreatment (i.e., the maintenance period) with cladribine. EX1013, 5-7. And,

according to Stelmasiak, regarding side effects, “cladribine favourably compare[d] with other immunosuppressants.” EX1013, 7. Stelmasiak explains that cladribine “pharmacokinetics and pharmacodynamics” may be responsible for its “beneficial activity in MS,” as well as its ability to “cross the blood-brain barrier.” EX1013, 7. Thus, a POSA would have had a reason to continue treating the patients with cladribine after the induction/cladribine-free cycle of Bodor.

102. A POSA would have thought to re-administer cladribine for two months during the retreatment (or maintenance) period 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. EX1022, 23:15-20. Thus, it would have been logical for a POSA to have used Bodor’s 2-month treatment period as a starting point, knowing that it could be routinely optimized. As discussed above, because the length of cladribine administration was recognized as a result-effective variable, 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). A POSA would have been motivated to optimize a patient’s lymphocyte count because, while lymphocyte

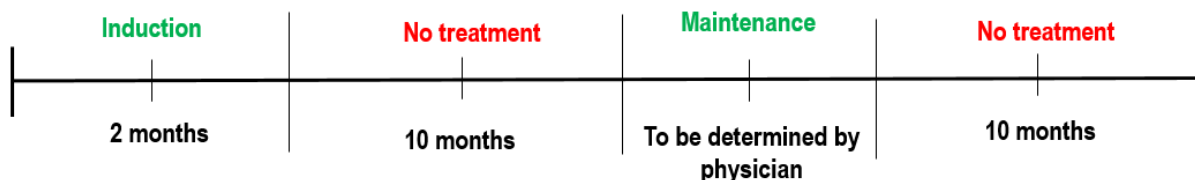
suppression was a goal of cladribine therapy, toxicity was also a concern. EX1013, 7; EX1023, 326.

103. A POSA would also have followed the maintenance period with another drug-free period, similar to Stelmasiak's dosing regimen, because cladribine toxicity was a concern. For example, Stelmasiak reports that in an earlier cladribine study, "dangerous marrow depression were reported in some multiple sclerosis patients." EX1013, 7. In another earlier study, "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." EX1023, 326. Further, a POSA would have known that suppressing a patient's immune system would put them at an increased risk of infection. In fact, infections were a common side effect in cladribine clinical trials, due to its strong immunosuppressive action. Grieb, for example, reports that "many patients suffered from incidental upper respiratory tract infections," during their study. EX1023, Abstract. And Langtry reports that "[i]nfections were reported in patients with MS receiving cladribine in clinical trials." EX1016, 428. As such, a POSA

would have been motivated to incorporate cladribine-free periods into an MS treatment regimen to mitigate side effects associated with cladribine toxicity.

104. A POSA would have known the length of the cladribine-free period is a result-effective variable because the amount of time a patient does not receive cladribine will affect the patient's lymphocyte count and limit toxicity. The general knowledge in the art demonstrated lymphocyte counts eventually rebounded after a cladribine-free period. EX1046, 392; EX1047, 296, 297. A POSA would have had the skill to monitor a patient's lymphocyte count and side effects associated with lymphocyte and myelosuppression and optimize the length of time of the second cladribine-free period to mitigate side effects while maximizing lymphocyte suppression. Thus, it would have been logical for a POSA to have used Bodor's 10-month treatment period as a starting point, knowing that it could be routinely optimized.

105. I have prepared a figure to illustrate 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:



As shown above, a POSA would have been motivated to administer Bodor's oral cladribine composition for two months, followed by 10 months of no cladribine therapy. After the 10 month cladribine-free period, a POSA would have been motivated to retreat with cladribine, followed by another break in cladribine therapy. A POSA would have reasonably expected this dosing regimen to treat MS because cladribine was known in the art to treat MS and the dosing regimen is similar to that of Stelmasiak.

106. And because MS is a chronic condition with no known cure, a POSA would have further continued to administer cladribine in a treatment period/drug-free period cycle based on the patient's response to therapy (e.g., lymphocyte counts) and disease progression (e.g., when relapsing). As discussed above, it was routine in the art to monitor a patient's lymphocyte counts when treating a patient with a known immunosuppressant. And a POSA would have known that monitoring a patient's lymphocyte counts was necessary because "cladribine causes prolonged, profound suppression of lymphocyte counts." EX1016, 421. A POSA would also have known from the prior art (*see, e.g.*, EX1008, 212-213) that administering treatments cyclically to prevent or treat relapsed was common in the art.

3. A POSA would have been motivated to administer “about 1.7 mg/kg to about 3.5 mg/kg” in an induction period

107. As explained above, a POSA would have been able to determine that the total claimed dose of cladribine administered during the induction period of “about 1.7 mg/kg to about 3.5 mg/kg” overlaps with Bodor’s range of about 1.4 mg/kg to about 2 mg/kg. See ¶ 83, *infra*. I understand that if prior art disclosure overlaps with a claimed range, the prior art renders the claimed range obvious. I am not aware of any evidence of teaching away, unexpected results, or criticality, or other pertinent objective evidence presented by Merck indicating that the overlapping range would not have been obvious in light of Bodor.

4. 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

108. As discussed above, Stelmasiak expressly teaches administering a lower dose of cladribine in a maintenance period than is administering during an induction period. Stelmasiak reports that the induction treatment with oral cladribine was characterized by a drop in lymphocyte counts “from the initial count of 2336 ± 595 per μl (mean $\pm$ S.D.) to 968 ± 229 per μl .” EX1013, 6. I have annotated Figure 1 from Stelmasiak to illustrate how a POSA would have understood the reported lymphocyte suppression with respect to Stelmasiak’s dosing regimen:

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

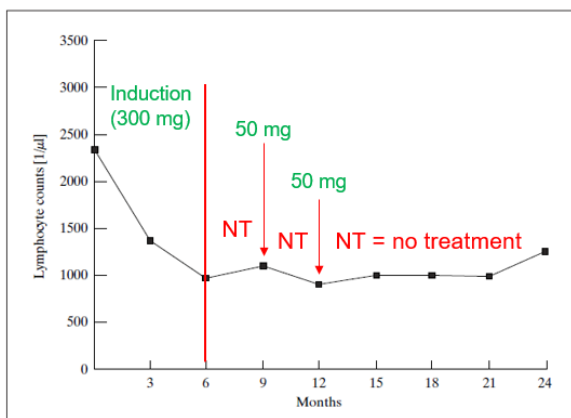
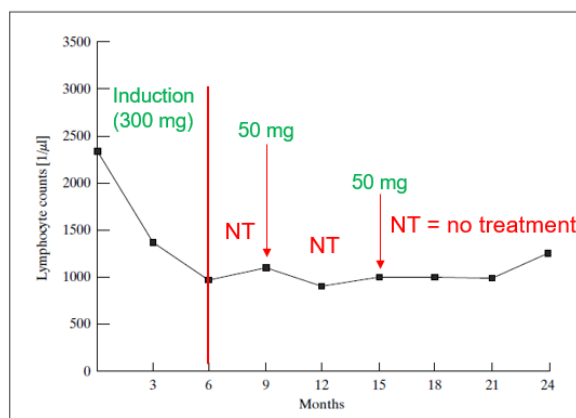


Figure 1. Average lymphocyte counts during and after treatment with cladribine.



EX1013, 5, FIG. 1 (annotated).

As shown above, patients receiving oral cladribine were given a total dose of 300 mg during the induction period (from months 1-6), 50 mg at nine months, and another 50 mg at 12 or 15 months. A POSA would have understood from the lymphocyte data in Figure 1 that 300 mg of cladribine administered over 6 months reduced the patients' average lymphocyte count from about 2300/ μ L to about 970/ μ L, but a dose of 50 mg at months 9 and 12 or 15 maintained the reduction in lymphocytes for another 6-9 months. In other words, a POSA would have understood that a lower dose of cladribine was sufficient to maintain the lymphocyte suppression effected during the induction period. Thus, a POSA would have had a reason to lower the total dose of cladribine administered during the maintenance period, compared to the total dose administered during the induction period.

5. A POSA would have been motivated to optimize the prior art to arrive at the claimed total cladribine dose and length of the maintenance period

109. The claimed total dose of cladribine reached at the end of the maintenance period (“about 1.7 mg/kg”) would have been obvious to a POSA in light of Bodor and Stelmasiak. As explained above, a POSA would have known that the cladribine dose and length of administration are result-effective variables, meaning they achieve a recognizable result. For example, Rice and Selby both report dose-dependent decrease in lymphocyte counts. EX1018, 1152; EX1047, 297; *see also* ¶¶ 91-92, *infra*.

110. According to Bodor, “the oral delivery of cladribine has been plagued by low bioavailability (see, *e.g.*, J. Liliemark *et al.*, *J. Clin. Oncol.*, 10(10): 1514-1518, 1992).” EX1022, 2:22-25. The general knowledge in the art demonstrated the “oral bioavailability of cladribine “varies from 37 to 51 % when the saline solution for intravenous administration is given to patients to drink.” EX1048, 122. Stelmasiak discloses administering oral cladribine “prepared as [a] sterile solution in isotonic saline,” which a POSA would have understood was the same dosage form disclosed by Liliemark. EX1013, 5; EX1048, 22; *see also* EX1023, 324. Bodor teaches that its oral cladribine tablet formulation “increase[es] or enhance[es] the oral bioavailability of cladribine.” EX1022, 5:17-25. Thus, a POSA would have understood Bodor’s oral cladribine tablet to have an increased

or enhanced bioavailability compared to earlier oral solutions known in the art, such as Stelmasiak, Liliemark, and Grieb. EX1013, 5; EX1023,324; EX1013, 5. As such, a POSA would have understood the need to administer a lower dose of Bodor's oral cladribine tablets to achieve the same effect as compared to Stelmasiak's (and Grieb's) oral solution. 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." EX1013, 5, FIG. 1; EX1023, 324, FIG. 1.

H. A POSA would have had a reasonable expectation of success

111. Bodor states that "various dosage amounts and dosing regimens have been reported in the literature for use in the treatment of multiple sclerosis." EX1022, 22:27-28. Bodor cites to several references that disclose treating RRMS and progressive forms of MS with cladribine. Thus, a POSA would have understood that Bodor recognized that the general knowledge in the art taught cladribine for treating various forms of MS.

112. Bodor provides a detailed formulations and a manufacturing process for making its oral cladribine tablets. EX1022, 31-33, Example 3. Bodor further provides bioavailability and pharmacokinetic data for oral cladribine compared to subcutaneous cladribine. EX1022, 33-39, Examples 4-5. A POSA would have had the skill to follow Bodor's instructions to prepare an oral cladribine composition,

with a reasonable expectation of success. Bodor also teaches a POSA how to administer its oral cladribine to treat MS: “it is envisioned 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.” EX1022, 23:15-20. As such, a POSA would have reasonably expected to treat MS with an oral cladribine composition, as taught by Bodor.

113. A POSA would have reasonably expected to treat MS by administering Bodor’s oral cladribine composition according to Stelmasiak’s induction period/cladribine-free period/maintenance period/cladribine-free period framework. Bodor discloses cladribine has “been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions,” including multiple sclerosis. EX1022, 1:15-2:4. Bodor also explains that “[o]ral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations.” EX1022, 2:9-11. To that end, Bodor discloses “compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine.” EX1022, Abstract. And Bodor teaches a POSA to administer its oral cladribine composition

for 2 months, followed by a 10-month period in which no cladribine is administered. *Id.*, 23:15-20.

114. A POSA would have reasonably expected to incorporate a maintenance and additional cladribine-free period into Bodor's regimen, as disclosed in Stelmasiak, because cladribine was known to be a "disease-modifying" therapy—i.e., cladribine does not cure MS, but can reduce the number of relapses by causing "prolonged, profound suppression of lymphocyte counts." EX1016, 421; EX1013, 6. A POSA would expect some patients to relapse after cladribine therapy, as evidenced in some cladribine clinical trials, and would have reasonably expected to readminister cladribine for 2 months followed by 10 months of no treatment, as taught by Bodor. A POSA would have had the skill to optimize cladribine's total dose and length of administration in the maintenance period because patient-specific dose optimization is a common practice in the clinic. EX1022, 24:1-9.

115. A POSA would have also had reasonably expected the claimed cladribine regimen to successfully treat patients with MS, given the teachings of Bodor and Stelmasiak, and the high skill in the art. As explained above, before December 2004, cladribine was known to cause "prolonged, profound suppression of lymphocyte counts." EX1016, 420. Further, before 2004, researchers published

several clinical studies reporting the efficacy of cladribine in MS patients. EX1014, 1719-20; EX1013, 7; EX1023, Abstract. According to the general knowledge in the art, cladribine “impressively” decreases the relapse rate in some patients. EX1014, 1719-1720; EX1013, 7. Thus, because oral cladribine has been previously shown to have clinical efficacy in patients with MS using cyclical treatment/no treatment regimens (EX1013, 7; EX1022, 23:15-20), a POSA would have had a reasonable expectation of successfully treating MS by orally administering Bodor’s “improved” oral dosage form of cladribine following the claimed steps of an induction period, cladribine-free period, a maintenance period, and a cladribine-free period.

116. A POSA would have reasonably expected Bodor’s induction dose to have efficacy in treating MS because Bodor expressly instructs that the dose is suitable “for the treatment of multiple sclerosis.” EX1022, 23:15-16. Bodor reports its oral composition had “enhance[d]” oral bioavailability, as compared to parenteral formulations. EX1022, 5:17-18. Thus, a POSA would have reasonably expected the claimed total dose of cladribine reached at the end of the induction period to treat MS.

117. A POSA would have reasonably expected to optimize the cladribine dose and length of the maintenance period. As explained above, a POSA would

have known that the cladribine dose is a result-effective variable because it achieves a recognizable result (e.g., lymphocyte suppression). A POSA would have understood from Stelmasiak that a lower dose of cladribine was sufficient to maintain the lymphocyte suppression effected during the induction period. Bodor instructs a POSA to optimize the cladribine dose: “one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning.” EX1022, 24:1-3. Bodor defines “therapeutically effective amount” as “treatments at dosages ***effective to achieve the therapeutic result sought.***” EX1022, 22:1-26 (emphasis added). Bodor is consistent with the general knowledge in the art, e.g., as reflected in Beutler, which teaches that “one can tailor the dosage and duration for which [cladribine] is administered to the stage of the disease and the condition of the patient being treated.” EX1026, 5:20-22. Bodor even provides a general strategy for doing so: “[t]herapeutically effective amounts may be easily determined [] empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.” EX1022, 24:6-9. And a POSA would have easily done so by adjusting the daily dose administered. Further, it would have been well within the skill of a POSA to optimize the maintenance period dose because

patient-specific dose optimization is a common practice in the clinic. EX1022, 24:1-9.

118. A POSA would have reasonably expected to optimize the second cladribine-free period after the maintenance period. As explained above, a POSA would have known the length of the cladribine-free period is a result-effective variable because it achieves a recognizable result—e.g., the amount of time a patient does not receive cladribine will affect the patient’s lymphocyte suppression induced by the cladribine. *See* ¶ 95. A POSA would have followed the maintenance period with another drug-free period, as taught by Stelmasiak, because cladribine toxicity was a concern. And a POSA would have known that it was routine in the art to monitor a patient’s lymphocyte counts when treating a patient with certain immunosuppressants, such as cladribine. EX1008, 219. It would have been well within the skill of a POSA to optimize the length of time of the second cladribine-free period to mitigate side effects while maximizing lymphocyte suppression.

119. In sum, Bodor and Stelmasiak would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XVII, below, there is no objective evidence that weighs against the strong obviousness showing here.

XI. My analysis with respect to claim 38

120. I understand that claim 38 depends from claim 36 and thus, contains each and every limitation of claim 36. Claim 38 further recites “wherein the induction period lasts about 2 months.”

121. As explained above, Bodor discloses an induction period of 2 months. Also as discussed above, MS is a progressive, incurable disease and patients with certain forms of MS experience relapsing-remitting cycles. As such, a POSA would have been motivated to administer Bodor’s oral cladribine dosage form to an MS patient for two months, followed by a ten-month- cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23:15-20; EX1013, Abstract. And a POSA would have had the necessary skill to administer cladribine for two months in the induction period, given the teachings of Bodor and the high level of skill in the art. EX1022, 23.

122. Accordingly, a POSA would have been motivated to arrive at the method of claim 38 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

XII. My analysis with respect to claim 39

123. I understand that claim 38 depends from claim 36 and thus, contains each and every limitation of claim 36. Claim 39 further recites “wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.”

124. As discussed above in ¶ 83, Bodor teaches administering a total of 100 to 140 mg of cladribine in an induction period. Thus, a POSA would have understood that, for an average adult weighing about 70 kg⁴, Bodor’s dose is equivalent to approximately 1.4 to 2 mg/kg, which encompasses the dose of “about 1.7 mg/kg.” I understand that if prior art disclosure encompasses a claimed value, the prior art renders the claimed value obvious. I am not aware of any arguments made by Merck to establish the criticality of the claimed induction dose in light of the prior art.

125. Accordingly, a POSA would have been motivated to arrive at the method of claim 39 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

XIII. My analysis with respect to claims 41 and 42

126. I understand that claims 41 and 42 depend from claim 36 and thus, contain each and every limitation of claim 36. Claim 41 further recites “wherein

⁴ EX1050, 244-252.

the cladribine-free period (ii) lasts about 10 months” and claim 42 further recites “wherein the cladribine-free period (iv) lasts about 10 months.”

127. As explained above, Bodor discloses a 10 month cladribine-free period following the induction period. Also as explained above, a POSA would have had the skill and experience to follow Bodor's instructions to orally administer cladribine for two months in an induction period, followed by a 10 month cladribine-free period, with a reasonable expectation of success.

128. Also as explained above, a POSA would have had a reason to incorporate maintenance and cladribine-free periods into Bodor’s dosing regimen, with a reasonable expectation of success. As such, a POSA would have been motivated to administer Bodor’s oral cladribine dosage form to an MS patient for two months, followed by a ten-month- cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23:15-20; EX1013, Abstract. A POSA would have also had reasonably expected the claimed cladribine regimen to successfully treat patients with MS, given the teachings of Bodor and Stelmasiak, and the high skill in the art. Thus, a POSA would have arrived at the dosing regimens of claims 41 and 42.

129. Accordingly, a POSA would have been motivated to arrive at the method of claims 41 and 42 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

XIV. My analysis with respect to claim 43

130. I understand that claim 43 depends from claim 36 and thus, contain each and every limitation of claim 36. Claim 43 further recites “wherein the maintenance period lasts about 2 months.”

131. As explained above in ¶¶ 100 and 114, a POSA would have understood that cladribine is a “disease-modifying” therapy—i.e., cladribine does not cure MS, but can reduce the number of relapses. EX1016, 420; EX1013, 6. Thus, a POSA would expect some patients to relapse after cladribine therapy, as evidenced in some cladribine clinical trials. As such, a POSA would have re-treated the patient with cladribine in a maintenance period. Also as explained above, a POSA would have had a reason to incorporate maintenance and cladribine-free periods into Bodor’s dosing regimen, with a reasonable expectation of success. As such, a POSA would have been motivated to administer Bodor’s oral cladribine dosage form to an MS patient for two months, followed by a ten-month- cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23:15-20; EX1013, Abstract. A POSA would have also had

reasonably expected the claimed cladribine regimen to successfully treat patients with MS, given the teachings of Bodor and Stelmasiak, and the high skill in the art.

132. A POSA would have thought to re-administer cladribine for two months during the retreatment (or maintenance) period 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. EX1022, 23:15-20. Thus, it would have been logical for a POSA to have used Bodor's 2-month treatment period as a starting point, knowing that it could be routinely optimized.

133. Accordingly, a POSA would have been motivated to arrive at the method of claim 43 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

XV. My analysis with respect to claim 44 and 45

134. I understand that claims 44 and 45 depend from claim 36 and thus, contain each and every limitation of claim 36. Claims 44 and 45 further recite "wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine," and "wherein the formulation is orally administered at a daily dose of 10 mg cladribine," respectively.

135. As explained above, Bodor teaches administering "***10 mg of cladribine*** in the instant complex cladribine-cyclodextrin complex in the instant

solid dosage form ... ***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.” EX1022, 23:15-20 (emphasis added). Bodor’s cladribine-cyclodextrin complex is formulated as a “solid oral dosage form,” which “improves oral bioavailability and/or achieves lower interpatient and/or inpatient variation of the drug.” EX1022, 5:1-7. Thus, a POSA would have understood that Bodor’s cladribine composition is administered orally. Thus, Bodor explicitly instructs orally administering a “daily dose of 10 mg cladribine.” This amount is encompassed by the broader “daily dose of 3 to 30 mg cladribine” range.

136. Accordingly, a POSA would have been motivated to arrive at the method of claims 44 and 45 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

XVI. My analysis with respect to claim 46

137. I understand that claim 46 depends from claim 36 and thus, contains each and every limitation of claim 36. Claim 46 further recites “wherein the formulation is orally administered 1 to 7 days per month during the induction period.”

138. As explained above, Bodor teaches administering “10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant

solid dosage form ... *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.” EX1022, 23:15-20 (emphasis added). Thus, Bodor teaches administering its oral cladribine composition for 5 to 7 days in each month of the induction period. Bodor’s range of 5 to 7 days per month overlaps with the claimed range of “1 to 7 days per month,” rendering the range obvious. I am not aware of any evidence of teaching away, unexpected results, criticality, or other pertinent objective evidence presented by Merck indicating that the overlapping range would not have been obvious in light the prior art.

139. Accordingly, a POSA would have been motivated to arrive at the method of claim 46 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

XVII. No objective indicia of non-obviousness exist.

140. I understand that when considering the obviousness of an invention, one should also consider whether there is any objective evidence that supports the non-obviousness of the invention. I understand that Merck did not present any objective evidence of non-obviousness, such as failure of others; unexpectedly superior results; skepticism followed by praise in the industry; long-felt, but unmet, need; copying; and commercial success, during prosecution of the ’947 patent, and I am unaware of any such evidence.

XVIII. Conclusion

141. In view of the facts discussed above, and my understanding with respect to obviousness, claims 36, 38, 39, and 41-46 of the '947 patent would have been obvious over Bodor and Stelmasiak, in light of the general knowledge in the art.

Appendix

Claim 36	Bodor (EX1022) and Stelmasiak (EX1013)
36. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:	“At the present time, it is envisioned 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.” EX1022, 23:15-20. “Lymphocytotoxic nucleoside analog cladribine (2-chlorodeoxyadenosine) has recently been reported to favourably alter the clinical course of chronic progressive multiple sclerosis (MS). In the present study 10 patients with the remitting-relapsing form of MS were treated with six courses of this drug (5 mg subcutaneously or 10 mg orally, once daily, repeated on five consecutive days) given once a month, followed by two additional courses at three month intervals.” EX1013, Abstract.
(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and	“At the present time, it is envisioned 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.” EX1022, 23:15-20. “Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months. Each course consisted of five doses of the drug taken once daily on consecutive

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Claim 36	Bodor (EX1022) and Stelmasiak (EX1013)
	days.” EX1013, 5.
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;	“At the present time, it is envisioned 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.” EX1022, 23:15-20.
(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;	“At the present time, it is envisioned 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. ” EX1022, 23:15-20.
(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and	“At the present time, it is envisioned 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.” EX1022, 23:15-20. “Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months. Each course consisted of five doses of the drug taken once daily on consecutive days.” EX1013, 5.
wherein the total dose of cladribine reached at the end	“Furthermore, one of skill will appreciate that the therapeutically effective amount of cladribine

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Claim 36	Bodor (EX1022) and Stelmasiak (EX1013)
of the maintenance period is about 1.7 mg/kg;	administered herein may be lowered or increased by fine tuning and/or by administering cladribine according to the invention with another active ingredient.” EX1022, 24:1-9.
(iv) a cladribine-free period wherein no cladribine is administered.	“In the present study 10 patients with the remitting-relapsing form of MS were treated with six courses of this drug (5 mg subcutaneously or 10 mg orally, once daily, repeated on five consecutive days) given once a month, followed by two additional courses at three month intervals. The patients were observed for two years after the initiation of the therapy. ” EX1013, Abstract.

Inter Partes Review of U.S. Patent No. 7,713,947
Declaration of Aaron E. Miller, M.D.
(EX1002)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further 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 § 1001 of title 18 of the United States Code.

Dated: 23 / JAN / 2023

Aaron Miller, M.D.

Dr. Aaron E. Miller, M.D.