

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.
Petitioner,

v.

ARES TRADING S.A.
Patent Owner

Case IPR2023-00482
U.S. Patent No. 10,849,919

DECLARATION OF AARON E. MILLER, M.D.

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I, Aaron E. Miller, 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. 10,849,919 (“the ’919 patent”), EX1001, which resulted from U.S. Application No. 16/199,119 (“the ’119 application”), which claims the benefit of the U.S. Provisional Application No. 62/590,442, filed on November 24, 2017. The ’919 patent issued on December 1, 2020, from the ’119 application. The ’919 patent names Fernando Dangond and Mattias Dotzauer as inventors. I understand that the USPTO’s Assignment database states that the ’919 patent is assigned to Ares Trading S.A. (“Ares”), which I understand is a wholly owned subsidiary of Merck KGaA (collectively, “Merck”).

II. My Background and Qualifications

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

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2. 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.

3. 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.

4. 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 at the Icahn School of Medicine at Mount Sinai, a position I have also held since

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March 2004. I was previously a clinical professor of neurology at the Mount 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).

5. Prior to becoming the medical director at the Corinne Goldsmith Dickinson Center for Multiple Sclerosis, I was an attending neurologist at the Mount Sinai Hospital, a position I have held since 1999. I was also the director of the division of neurology and an attending neurologist at the Maimonides Medical Center in Brooklyn from 1981 to 2004. 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).

6. 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

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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.

7. 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), Secretary of the Board of Directors (2013-2017), and as the Chairman of the Editors-in-Chief Committee (2009-2011).

8. 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

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journals, over half of which were related to multiple sclerosis. I have also authored or co-authored over 25 books or book chapters.

9. 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.

10. 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 '919 patent.

III. Summary of Opinions

11. In this declaration, I consider the treatment methods of the '919 patent in relation to the state of the art before November 24, 2017. The prior art references that I considered when comparing the claims of the '919 patent to the state of the art included the Clinicaltrials.gov webpage for NCT00436826, "A Phase 2 Study of Cladribine Add-on to Interferon-beta (IFN-beta) Therapy in Multiple Sclerosis (MS) Subjects with Active Disease" ("Clinicaltrials.gov," EX1005), Montalban, X. *et al.*, "Efficacy of Cladribine Tablets as Add-On to IFN-beta Therapy in Patients with Active Relapsing MS: Final Results from the Phase II ONWARD Study (P3.029), *Neurol.* 2016, 86(16 Suppl.) ("Montalban," EX1006), Schreiber, K and Sorensen, P, "Cladribine in the treatment of multiple

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sclerosis,” *Clin. Invest.* 2011, 1(2):317-326 (“Schreiber,” EX1008), Alvarez-Gonzalez, C. *et al.*, “Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis,” *Ann. Clin. Trans. Neurol.* 2017, 4(7):506-511 (“Alvarez-Gonzalez,” EX1009), and Giovannoni, M.B. *et al.*, “A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis,” *N. Engl. J. Med.* 2010, 362(5):416-426 (“Giovannoni,” EX1007). I also considered the file history of the ’919 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.

12. As I explain in detail below, claims 1-6, 8, 9, 12, 14-16, 18-20, 24-27, and 34 of the ’919 patent would also have been obvious in view of Alvarez-Gonzalez and Giovannoni.

13. As I also explain in detail below, claims 11, 23, and 33 of the ’919 patent would have been obvious in view of Alvarez-Gonzalez, Giovannoni, and Montalban.

14. As I further explain in detail below, claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, and 34 of the ’919 patent would have been obvious in view of Clinicaltrials.gov, Schreiber, and Montalban.

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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” with no known cure. EX1022, 565; EX1061, 263; EX1033, 35. Before 2017, the clinical course of MS typically follows a “variable pattern over time [which] 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.” EX1014, 907. The heterogeneous nature of the disease prompted clinicians to adopt the standardized terminology “to describe the pattern and course of MS”: relapsing-remitting MS (“RRMS”), secondary progressive MS (“SPMS”), primary progressive MS (“PPMS”), and progressive-relapsing MS (“PRMS”). *Id.*, 908-909. 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. EX1014, 909. Because there was, and is, “no clear” criteria to determine when a patient transitioned from RRMS to SPMS, some in the field began to recognize the transition period between RRMS and SPMS as a distinct disease state, dubbed “early” SPMS or ESPMS. EX1013, 280; EX1016, 63; EX1017, 278, FIG. 1.

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16. By November 2017, it was understood in the art that all five of the MS forms (RRMS, ESPMS, SPMS, RRMS, and PRMS) involved immune cells called T- and B-lymphocytes that attack the nerves in the central nervous system (“CNS”) and causing inflammation. EX1020, 1593-1594, 1597. It was also well understood that in all forms of MS, these inflammatory processes created areas of damage to the nerves, called lesions. EX1020, 1593. New, active lesions could cause relapses, i.e. acute exacerbations of symptoms (also known as disease activity), whereas the accumulation of damage and the slow expansion of existing lesions could cause the insidious progression of clinical symptoms (known as disease progression). EX1013, 280; EX1020, 1593-1595. While disease activity was generally associated with RRMS (and to an extent ESPMS), and disease progression was generally associated with progressive forms of MS, like SPMS and PPMS, it was also well known that “patterns of inflammation” associated with T and B cells, “are similar between relapsing and progressive MS.” EX1013, 280; EX1016, 63; EX1020, 1593-1594, 1597. Patients with PPMS or SPMS with disease activity were labeled as having “PP-active” or “SPMS-active.” EX1013, 280, 282.

17. Several prior art references taught that cladribine, including oral cladribine, was effective in treating the inflammation and related disease activity

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that could be present in each of the forms of MS. For example, **Giovannoni** and **Schreiber** (EX1007 and EX1008) taught that 10-mg cladribine tablets were effective in treating disease activity in RRMS during a phase III clinical trial called CLARITY. Giovannoni and Schreiber further taught that this oral cladribine dosage form was “convenient” and addressed issues stemming from prior parenteral cladribine dosage forms, such as treatment adherence. EX1007, 417; EX1008, 317, 324. **Clinicaltrials.gov** (EX1005, 9-13), which discloses the methodology of a phase IIb trial, and the inventor-authored **Montalban** (EX1006) paper taught the effective treatment of disease activity in patients with RRMS and SPMS, using the same oral cladribine dosing regimen used in CLARITY, as I explain below. Finally, **Alvarez-Gonzalez** (EX1009) reported the successful treatment of a PP-active patient using subcutaneous cladribine in a dosing regimen that “resemble[d] bioequivalence” with the oral dosing regimen used in the CLARITY. EX1009, 509.

18. In light of the general knowledge in the art, a POSA seeking to treat PP-active and SPMS-active patients, including those patients who did not have ESPMS, would have chosen cladribine because of its demonstrated efficacy against disease activity. A POSA would have further used oral cladribine because, as I discuss in detail below, a POSA would have known that an oral dosage form

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was preferred in the art to parenteral forms. Specifically, a POSA would have been motivated to substitute Alvarez-Gonzalez's subcutaneous cladribine with oral cladribine. And a POSA would have specifically selected Giovannoni's oral dose and dosing regimen because Alvarez-Gonzalez reported that their successful subcutaneous regimen "resemble[d]" bioequivalence to Giovannoni's oral dosing regimen. EX1009, 509. Finally, a POSA would have a reasonable expectation that this oral cladribine regimen would effectively treat a PP-active patient because Alvarez-Gonzalez discloses that its subcutaneous regimen, which resembled bioequivalence to Giovannoni's oral dosing regimen, did, in fact, treat disease activity in a PPMS patient (who, by definition, did not have ESPMS). EX1009, 509; EX1007, 416.

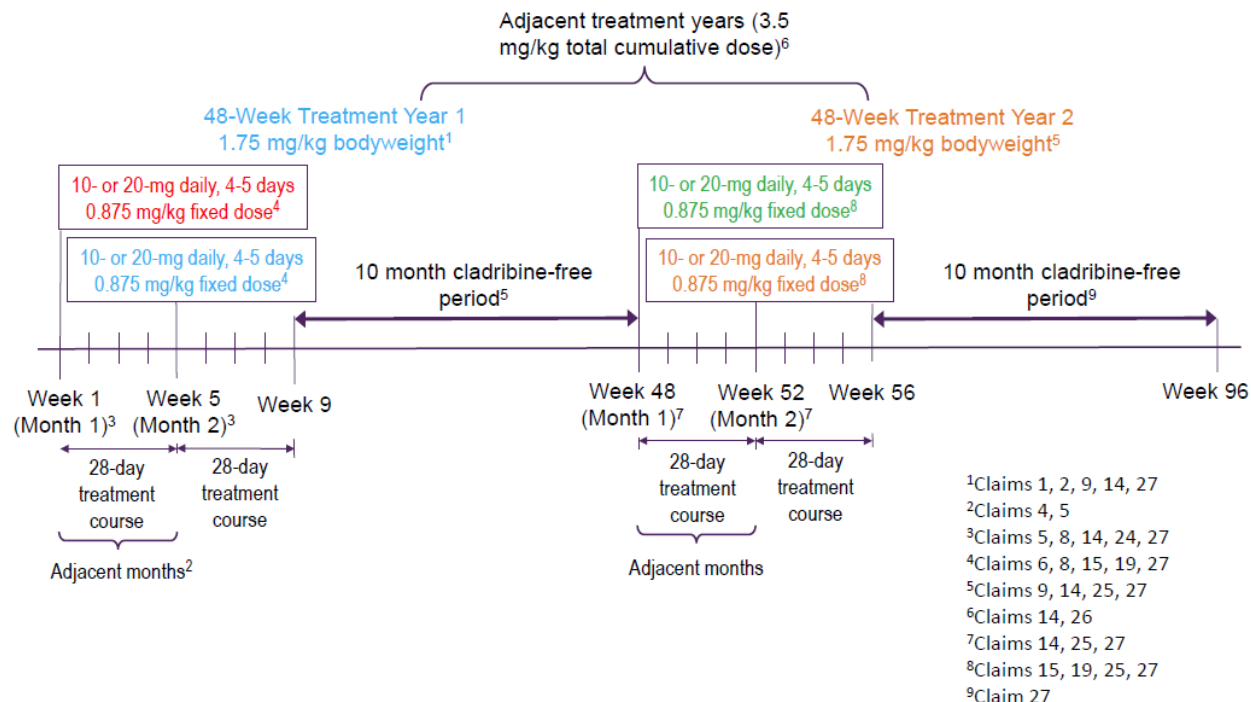
19. A POSA would have also been motivated to use oral cladribine to treat SPMS-active patients because Clinicaltrials.gov and Montalban explicitly instruct doing so. EX1005, 9-13. A POSA would have been further motivated to use Clinicaltrials.gov's specific cladribine dosing regimen to treat a SPMS-active patient because Montalban, which discloses the actual results of Clinicaltrials.gov's study, demonstrated this regimen was indeed effective in treating patients who had fully transitioned from RRMS to SPMS (i.e., SPMS-active patients), and thus, by definition, did not have ESPMS. EX1006, 1. And,

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because Clinicaltrials.gov was silent regarding the specific strength of oral cladribine tablet to use in its regimen (which a POSA would need to determine in order to implement the dosing regimen), a POSA would have been motivated to use the 10-mg cladribine tablets disclosed in Schreiber. Schreiber teaches administering 10-mg cladribine tablets in a dosing regimen that is the same as the one disclosed in Clinicaltrials.gov. EX1008, 320. Schreiber discloses that the “formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324. Finally, a POSA would have a reasonable expectation that this oral cladribine regimen would effectively treat SPMS-active patients, exactly as claimed, because Montalban disclosed the regimen did in fact treat such patients. EX1006, 1.

20. The challenged claims of the '919 patent claim nothing beyond the specific elements of the CLARITY dosing regimen, disclosed in at least Giovannoni, Clinicaltrials.gov, and Schreiber. EX1005, 11; EX1007, 417-418, Supplementary FIG. 1; EX1008, 320, 326. Based on the references discussed in the declaration, I have prepared the following graphic to illustrate how the claimed methods correspond to the dosing regimen disclosed in the prior art:

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Schematic 1.

21. And, for the reasons described below in Section XIII, I conclude that none of the evidence that I reviewed supports the patentability of any of the challenged claims. 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, and 34 of the '919 patent. Accordingly, it is my opinion that claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, and 34 of the '919 patent would have been obvious to a POSA, as I explain in detail below.

IV. List of documents I considered in formulating my opinions

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

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Exhibit No.	Description
1001	U.S. Patent No. 10,849,919 B2 to Dangond et al., “Cladribine Regimen for Treating Progressive Forms of Multiple Sclerosis,” (filed November 23, 2018; issued December 1, 2020).
1003	<i>Curriculum Vitae</i> for Aaron Miller, M.D.
1004	Prosecution History of U.S. Patent No. 10,849,919
1005	Archived Clinicaltrials.gov Pages for “A Phase 2 Study of Cladribine Add-on Interferon-beta (INF-beta) Therapy in Multiple Sclerosis (MS) Subjects With Active Disease (ONWARD),” ClinicalTrials.gov, captured by Wayback Machine on Jul. 3, 2013 (pp. 10-13); and “A Phase 2 Study of Cladribine Add-on Interferon-beta (INF-beta) Therapy in Multiple Sclerosis (MS) Subjects With Active Disease (ONWARD),” ClinicalTrials.gov, captured by Wayback Machine on Nov. 2, 2014 (pages 5-8), with Affidavit of Nathaniel E. Frank-White (pp. 1-2, 14)
1006	Montalban, X., et al., “Efficacy of Cladribine Tablets as Add-On to IFN-beta Therapy in Patients with Active Relapsing MS: Final Results from the Phase II ONWARD Study P3.029,” published Apr. 4, 2016. (“Montalban”)
1007	Giovannoni, G., et al., “A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis,” <i>The New England Journal of Medicine</i> , 362 (5), (Feb. 4, 2010), with attached supplementary appendix. (“Giovannoni”)
1008	Schreiber, K., et al., “Cladribine in the Treatment of Multiple Sclerosis,” <i>Clinical Investigation</i> , 1 (2), (2011). (“Schreiber”)

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Exhibit No.	Description
1009	Alvarez-Gonzalez, C., et al., “Cladribine to Treat Disease Exacerbation after Fingolimod Discontinuation in Progressive Multiple Sclerosis,” <i>Annals of Clinical and Translational Neurology</i> , 4 (7), (March 17, 2017). (“Alvarez-Gonzalez”)
1010	U.S. Patent No. 8,377,903 to De Luca et al., “Cladribine Regimen for Treating Multiple Sclerosis,” (filed Apr. 23, 2010; issued Feb. 19, 2013).
1011	Lassman, H., et al., “Heterogeneity of Multiple Sclerosis Pathogenesis: Implications for Diagnosis and Therapy,” <i>TRENDS in Molecular Medicine</i> , 7 (3), (March 2001).
1013	Lublin, F.D., et al., “Defining the Clinical Course of Multiple Sclerosis: The 2013 Revisions,” <i>Neurology</i> , 83 (2014).
1014	Lublin, F.D., et al., “Defining the Clinical Course of Multiple Sclerosis: Results of an International Survey,” <i>Neurology</i> , 46 (1996).
1015	Simsek, D., et al., “Understanding the characteristics of secondary progressive multiple sclerosis to facilitate early identification,” <i>Multiple Sclerosis Journal</i> , 21(11):77 (2015)
1016	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 (2002).
1017	Skurkovich, S., et al., “Randomized study of antibodies to IFN- γ and TNF- α in secondary progressive multiple sclerosis,” <i>Multiple Sclerosis</i> , 7 (2001).
1018	Sand, I.K., et al., “Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis,” <i>Multiple Sclerosis Journal</i> , 20(12), (2014).

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Exhibit No.	Description
1019	Willis, M.A., et al., “Progressive Multiple Sclerosis,” <i>Continuum</i> , 22(3), (2016).
1020	Lassmann, H., “Targets of therapy in progressive MS,” <i>Multiple Sclerosis Journal</i> , 23(12), (2017).
1021	Clinicaltrials.gov for NCT00313976 “Study to Compare Double-Dose Betaferon to the Approved Dose, for Patients with Early Secondary Progressive Multiple Sclerosis”
1022	Khoury, S. J., “Multiple Sclerosis: What Have We Learned From Magnetic Resonance Imaging Studies?,” <i>Archives of Internal Medicine</i> , 158:565-73 (1998)
1023	Mavenclad European Public Assessment Report (EPAR), European Medicines Agency
1024	Langtry, H.D., et al., “Cladribine, A Review of its Use in Multiple Sclerosis,” <i>BioDrugs</i> 9(5):419-433 (1998)
1025	Sipe, J.C., et al., “Cladribine in treatment of chronic progressive multiple sclerosis,” <i>The Lancet</i> , 344(8914):9-13 (1994).
1026	International Publication No. WO 2004/087101 A2 to Bodor, N., et al., filed March 26, 2004; published October 14, 2004
1027	Leist, T.P., et al., “Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial,” <i>Lancet Neurology</i> , 13:257-67 (Feb 2014)
1029	Rudick, R.A., et al., “Management of Multiple Sclerosis,” <i>The New England Journal of Medicine</i> , 337(22):1604-1611 (1997)

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Exhibit No.	Description
1030	Noseworthy, J.H., et al., “Multiple Sclerosis,” <i>The New England Journal of Medicine</i> , 343(13):938-952 (2000)
1031	Tortorella, C., et al., “Cladribine Ortho Biotech Inc,” <i>Current Opinion in Investigational Drugs</i> , 2(12):1751-1756 (2001)
1032	Romine, J. S., et al., “Cladribine: Use in Therapy of Multiple Sclerosis,” <i>Biodrugs</i> , 7(5):386-93 (1997)
1033	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)
1035	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)
1036	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)
1038	Schultz, T.W., <i>et al.</i> , “Cyclodextrine Cladribine Formulations,” U.S. Patent No. 6,194,395 B1 (filed February 25, 1999; issued February 27, 2001)
1039	Andrade, C., “Bioequivalence of Generic Drugs: A Simple Explanation for a US Food and Drug Administration Requirement,” <i>J Clin Psychiatry</i> 76(6):742-744 (2015)
1040	Polman, C.H., et al., “Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the ‘McDonald Criteria,’” <i>Annals of Neurology</i> , 58:840-46 (2005)
1058	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)

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Exhibit No.	Description
1059	Kurtzke, J.F., “Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS),” <i>Neurology</i> , 33:1444-1452 (1983)
1061	Wingerchuk, D.M., et al., “Biology of Disease, Multiple Sclerosis: Current Pathophysiological Concepts,” <i>Laboratory Investigation</i> , 81(3):263-281 (2001)
1062	Neuhaus, O., et al., “Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection,” <i>TRENDS in Pharmaceutical Sciences</i> , 24(3):131-138 (2003)
1066	Archived Clinicaltrials.gov Pages for NCT00213135 “CLARITY - Safety and Efficacy of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (MS),” ClinicalTrials.gov, captured by Wayback Machine on Jul. 3, 2013 (pp. 6-8), with Affidavit of Nathaniel E. Frank-White (pp. 1-3, 9)
1067	Hernandez, A., et al., “The Definition of Placebo in the Informed Consent Forms of Clinical Trials,” <i>PLoS ONE</i> 9(11):e113654 (2014)
1068	Weiten, W., <i>Psychology: Themes and Variations</i> , Third Ed., “Chapter 3: The Biological Bases of Behavior,” Brooks/Cole Publishing Company, 1995
1069	Mavenclad FDA Approval Letter, March 29, 2019

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

23. 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 ’919 patent relates to methods of human therapeutic treatments, the level of skill of a POSA in this field is high. Given the

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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 '919 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.

24. 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 November 24, 2017

A. Multiple sclerosis is a chronic disease with a number of different forms that can each exhibit disease activity

25. 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,” i.e. lesions. EX1011, Abstract; EX1020, 1593. In the nervous system, cells called neurons “receive, integrate, and transmit information.” EX1068, 74. Axons are “long, thin fiber[s] that transmit[] signals away from soma [the nucleus of a neuron] to other neurons or to muscles or glands.” *Id.*, 75. Axons are encased by an “insulating material” composed of a “white, fatty substance called myelin.” *Id.* Destruction of the myelin sheath leads to a host of symptoms, including optic neuritis, diplopia, muscle weakness, spasticity and eventual loss of ambulatory function. EX1024, 420. To date, there is no known cure for MS. EX1033, 35.

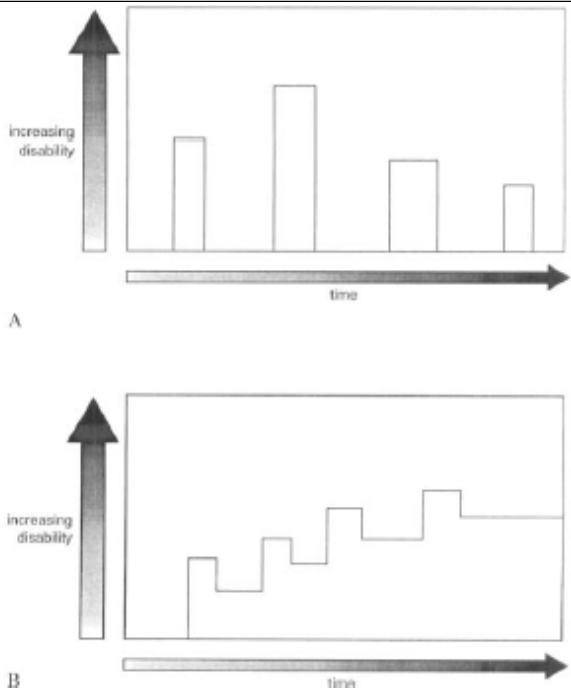
26. MS is often diagnosed using what was known as the McDonald criteria, “balancing early diagnosis with the need to avoid false-positive diagnosis.” EX1040, 840. The McDonald 2005 criteria consist of “core features”: “emphasis on objective clinical findings, dependence on evidence of dissemination of lesions in time and space [e.g., as evidenced on MRI scan], use of supportive and confirmatory paraclinical examination to speed the process and to help

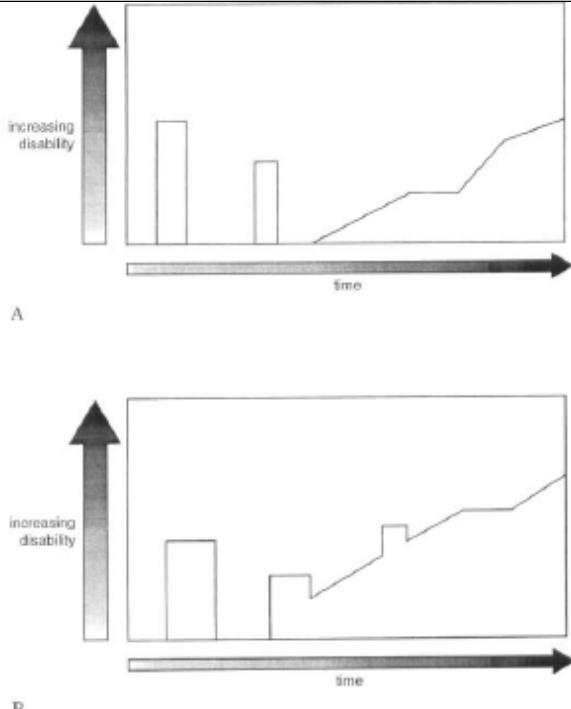
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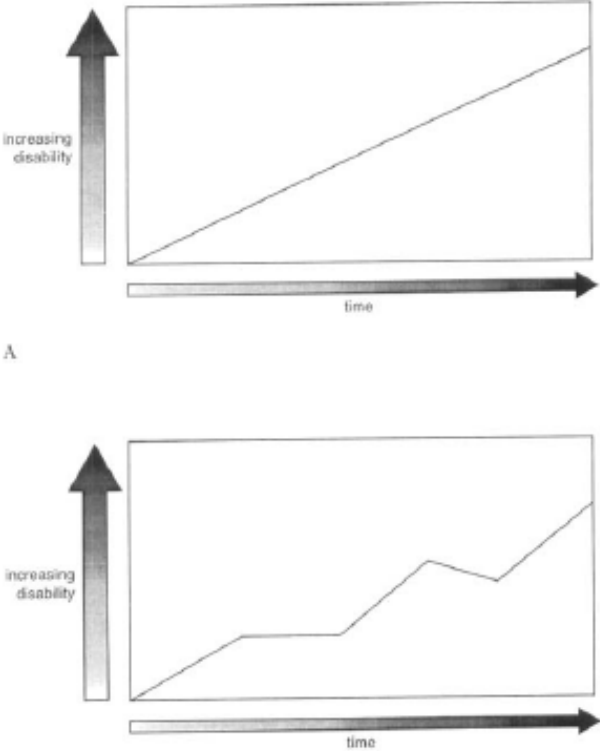
eliminate false-negative and -positive diagnoses, focus on specificity rather than sensitivity, and need to eliminate better explanations for the diagnosis.” *Id.*, 841, 844. Examples of clinical findings or symptoms include muscle weakness, numbness, or pain or tingling in parts of the body. EX1013, 279.

27. The clinical course of MS typically follows a “variable pattern over time [which] 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.” EX1014, 907. The heterogeneous nature of the disease prompted clinicians to adopt a standardized terminology “to describe the pattern and course of MS.” *Id.*, Abstract.

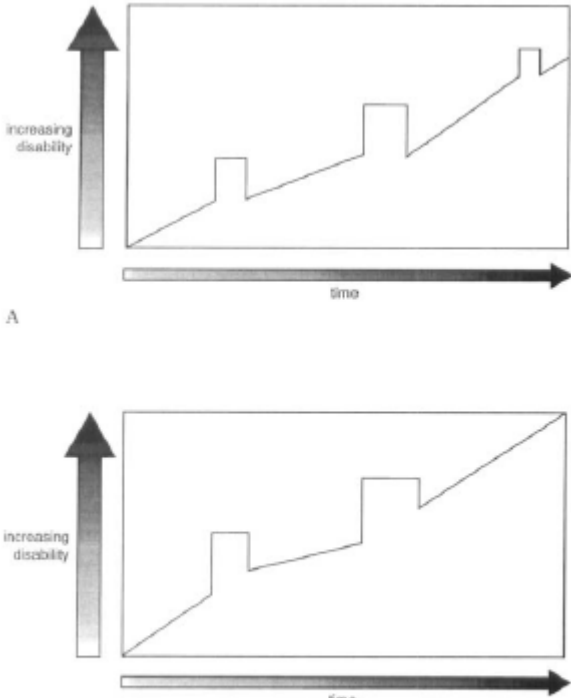
28. Thus, in 1996, the US National Multiple Sclerosis Society (NMSS) Advisory Committee on Clinical Trials in Multiple Sclerosis (“the Committee”) provided standardized definitions of the following MS clinical subtypes: relapsing-remitting MS (“RRMS”), secondary progressive MS (“SPMS”), primary progressive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

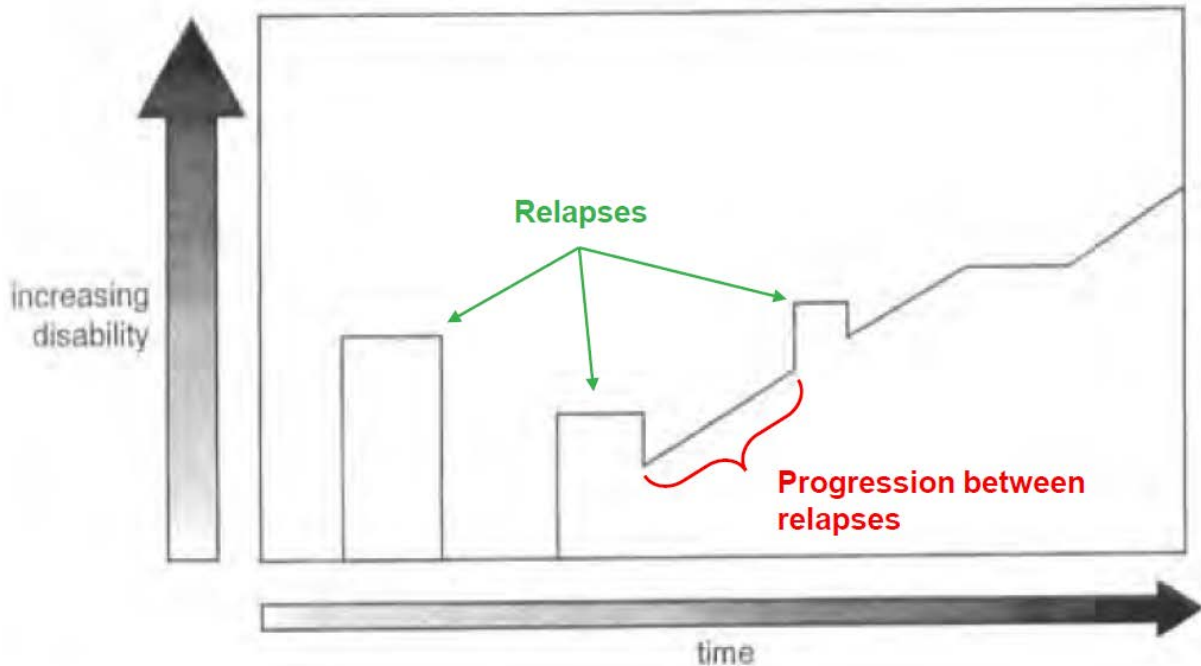
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MS Type and Definition	Illustration
Progressive Relapsing (PRMS) “[P]rogressive disease from onset, with clear acute relapses ... characterized by continuing progression.”	 Figure 4 consists of two line graphs, A and B, illustrating the progression 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 rises with a series of steps, representing acute relapses, where each step is followed by a period of stability or partial recovery, but the overall trend is a continuous upward slope. Graph B shows a similar pattern of steps, but the downward slopes between the steps are steeper, indicating a more significant recovery following each relapse, though the overall progression still shows a net increase in disability over time. A B <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. The Committee specified that they did “not include[] “MRI parameters in these definitions.” *Id.*, 910. As such, a POSA would have understood that the “relapses” mentioned in the definitions were clinical relapses, and did not include MRI lesions.

29. As shown above, the Committee recognized, and a POSA would have understood, that the progressive courses of MS—SPMS and PRMS—may exhibit relapses and exacerbations like the RRMS course, in addition to disease progression. To better illustrate this, I have annotated the Committee’s figure for

the SPMS course with “occasional relapses and minor remissions” to highlight a POSA’s understanding of relapses versus disease progression:



Id. (annotated).

30. 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. EX1014, 909. Thus, while an SPMS patient initially had RRMS, PPMS and PRMS patients never had RRMS in the first place.

31. The Committee’s 1996 definitions “were rapidly incorporated into clinical practice and utilized in the eligibility criteria of almost all subsequent MS clinical trials,” and in 2012, the Committee re-examined these definitions in view

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of “clinical, imaging, and biomarker advances” that had occurred since 1996. EX1013, 278, 279. The Committee published the results of its re-examination in 2014. The Committee ultimately decided to “retain[] the basics of the 1996 phenotype descriptions,” because they “had become part of standard MS practice and clinical research.” *Id.*, 279, 283. However, the Committee did refine the descriptions of the MS clinical subtypes to include “descriptors that include consideration of disease activity (based on clinical relapse rate and imaging findings) and disease progression.” EX1013, Abstract.

32. The Committee first recommended the “[i]nclusion of activity as a modifier of a basic clinical course phenotype” for both RRMS and progressive forms of MS, which “allow[ed] elimination of the PRMS category.”¹ *Id.*, 280. The Committee defined activity as the “clinical assessment of relapse occurrence or lesion activity detected by CNS imaging.” *Id.*, 283. It was recommended that a “patient with PPMS who has an acute attack (thus fulfilling prior criteria for PRMS) would be considered to be PP-active,” while “a patient with PPMS with no

¹ Accordingly, in 2017, a POSA would have understood that “PRMS” was an outdated term that POSAs were no longer relying on.

acute attacks and no MRI activity would be considered to be PP–not active.” *Id.*, 280.

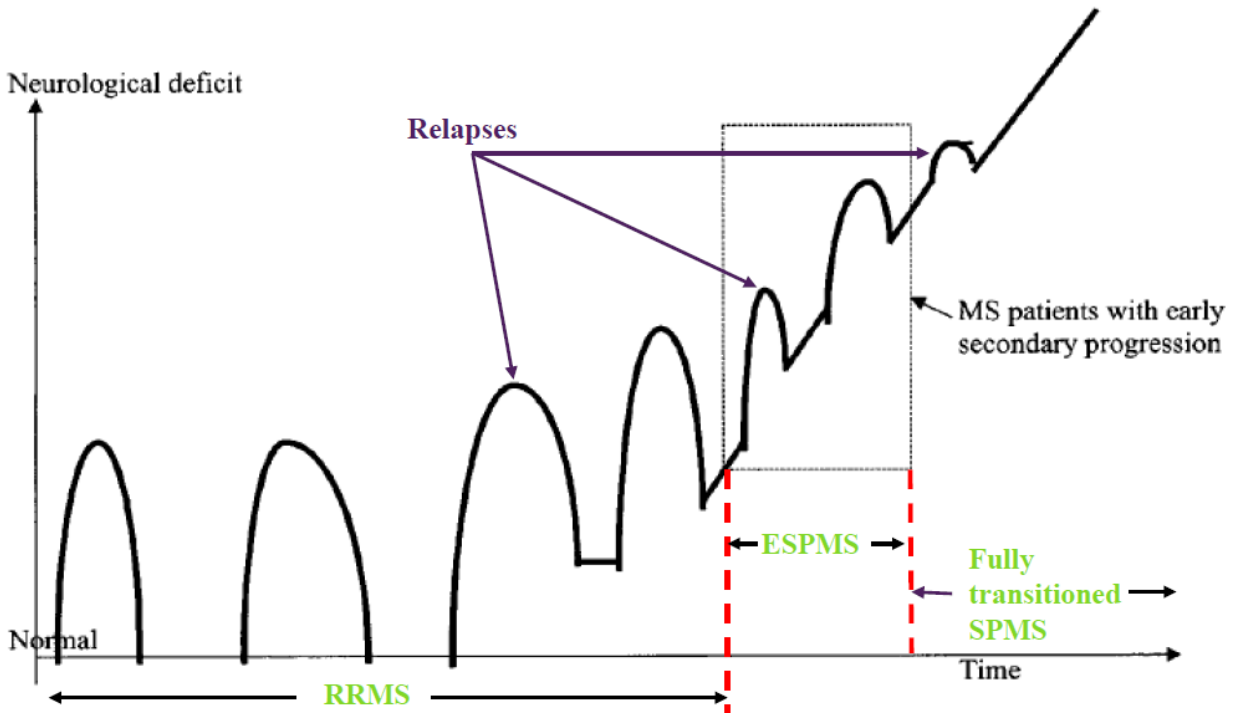
33. The Committee also recommended an “additional modifier of disease course is whether or not there is clinical evidence of disease progression, independent of relapses, over a given period of time in patients who have a progressive disease course (PPMS or SPMS).” *Id.* For example, a “patient with SPMS who has gradually worsened and has gadolinium-enhancing lesions on MRI² would be classified as SPMS-active and progressing.” *Id.* (footnote added). Thus, a POSA would have understood that before November 2017, patients with PPMS or SPMS with disease activity were referred to be “PP-active” or “SPMS-active.” EX1013, 280, 282.

34. The Committee also noted that “[t]o date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS; the transition is usually gradual.” *Id.*, 280. However, while the Committee did not explicitly label this transition period, others

² As discussed below in paragraph 36 below, “gadolinium-enhancing lesions” are a type of lesion that may be detected on an MRI scan to identify disease activity in a patient.

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recognized the transition period between RRMS and SPMS as a distinct form of MS, dubbed “early” SPMS or ESPMS. In fact, the art recognized that “early SPMS may represent a window of opportunity for intervention,” and “better tools are required to identify early SPMS.” EX1018, 1655. 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.” EX1016, 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. In 2001, Skurkovich provided the following illustration, which I have annotated to demonstrate a POSA’s understanding of ESPMS and that each of RRMS, ESPMS, and SPMS could exhibit disease activity (here, acute exacerbations of “neurological deficit,” which a POSA would have understood are clinical relapses, associated with active inflammation):



EX1017, 278, FIG. 1 (annotated). Thus, a POSA would have recognized that different forms of MS have been identified—RRMS, ESPMS, SPMS, PPMS, and PRMS—and that each of these forms could exhibit disease activity.

Simsek also reports results from a study to “assess the difference between early RRMS and early SPMS patients on sociodemographics, daily activities and clinical characteristics including symptoms and MRI parameters and quantify the likelihood of late stage RRMS patients being classified as early SPMS.” EX1015, 77. Simsek’s results suggest that 58% of the RRMS population should be classified as having early SPMS. *Id.* Other clinical trials recognized and sought to treat ESPMS, as well. EX1021, *generally*; EX1017, 278. Accordingly, a POSA would

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have understood that ESPMS was a distinctly recognized disease course, along with RRMS, SPMS, and PPMS. Further, before 2017, a POSA would have understood that an MS patient with PPMS, including PP-active, could not, by definition, have ESPMS because ESPMS is the transition state between RRMS and SPMS, and a patient with PPMS never exhibited RRMS. EX1014, 908-910, FIG.

2. Similarly, an MS patient with SPMS, including SPMS-active, who has fully transitioned from RRMS to SPMS cannot, by definition, have the distinct transitional ESPMS form. EX1017, 278.

35. In clinical practice, several signs and symptoms are monitored to assess a patient's disease progression and response to therapy. For example, in clinical practice, "neurologic impairment of MS" is commonly assessed with the Expanded Disability Status Scale ("EDSS"). EX1059, *generally*. The EDSS is "the most widely used outcome measure in clinical trials of multiple sclerosis." EX1029, 1605. The EDSS is an "is an ordinal rating scale ranging from 0 to 10, in increments of 0.5, with higher scores reflecting increasing severity." *Id.* In other words, "lower EDSS scores indicate better functioning." EX1024, 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.

36. Magnetic resonance imaging (“MRI”) is also commonly used to assess a patient’s disease state and response to treatment, 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.” EX1030, 940, 946. A POSA would have understood that a reduction in the number or size of these enhancing lesions were indicative of a treatment response. EX1058, 1718; EX1036, 1153; EX1033, 42.

B. Anti-inflammatory therapy, by way of immunosuppression, was a common therapeutic strategy to treat relapsing and progressive forms of MS before November 2017

37. Before November 24, 2017, much was understood about the pathology of MS. As explained above, MS is a chronic inflammatory disease, mediated by T cells, which causes destruction of the myelin sheath, an insulating substance surrounding axons in the nervous system. See ¶ 25, *infra*. Patients with MS “harbor T cells that react with CNS autoantigens.” EX1062, 131. Although these T cells (a type of lymphocyte) may “remain dormant for decades, at some point they are

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activated in the periphery,” which allows them to “migrate through the blood–brain barrier to the brain and spinal cord.” *Id.* 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.” *Id.*

38. By December 2017, it was understood that in RRMS, “inflammation driven by the systemic immune reaction gives rise to new focal [or active] lesions.” EX1020, 1595. A POSA would have known that these lesions were associated with clinical relapses depending on where such new lesion activity occurred. EX1013, 280; EX1014, 910. As such, a POSA would have understood that RRMS was generally characterized by disease activity, such as clinical relapses and active lesions associated with this acute inflammation. EX1020, 1593, 1595. In contrast, patients with progressive forms of MS (e.g., SPMS or PPMS) had less acute, systemic inflammation and fewer “active lesions” as compared to RRMS patients. *Id.*, 1593-1596. Instead, these progressive forms of MS are characterized by “slowly expanding lesions” “where active tissue injury is mainly associated with proinflammatory microglia activation, macrophage recruitment is sparse, and expression of anti-inflammatory markers is minimal to absent.” *Id.*, 1594.

39. However, the art recognized “exceptions” to these general characterizations because “these categories [i.e., forms] do not provide temporal

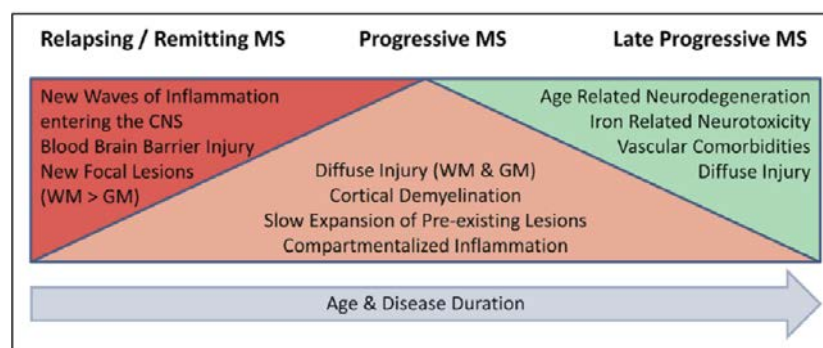
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information about the ongoing disease process.” EX1020, 1595; EX1013, 280; EX1009, 507. To that end, in 2014, the Committee modified its characterization of MS forms, specifically recommending adding the “disease activity” modifier – reflecting “ongoing inflammatory [] processes” – to *both* relapsing and progressive forms of MS because “disease activity detected by clinical relapses or imaging” can be a “meaningful additional descriptor[] in either relapsing or progressive disease.” EX1013, 280.

40. Lassmann 2017 confirmed that, while the “patterns of inflammation” associated with T and B cells, “are similar between relapsing and progressive MS,” there are certain generalized differences between relapsing and progressive forms of MS, including the facts that “the global extent of lymphocytic inflammation is higher in acute or relapsing MS in comparison to progressive MS,” and “the relative incidence of different lesion features changes with time of disease evolution.” EX1020, 1593-1594. More specifically, “in the early relapsing/remitting stage” and extending into the “early stages of (primary and secondary) progressive MS,” “inflammation driven by the systemic immune reaction gives rise to new focal lesions dominantly located in the white matter.” *Id.*, 1595. “In contrast, in the progressive stage, [these] new active lesions become rare, but many of the focal lesions display a rim of activated microglia at the

border and some macrophages with recent myelin degradation products [which] suggests slow expansion of pre-existing lesions.” *Id.*, 1593-94 (footnote added). Additionally, in progressive MS, a “dominant feature” is “the presence of compartmentalized inflammatory response, where T cells, B cells, and plasma cells are trapped within the brain and spinal cord behind a closed or repaired blood-brain barrier.” *Id.*, 1596. Finally, “in the last stage of MS, progressive neurodegeneration occurs even in the absence of an overt inflammatory response.” *Id.*

41. However, Lassmann 2017 also explained that “it has to be acknowledged that there is no strict separation of these disease stages,” namely, between relapsing and progressive forms of MS. EX1020, 1595. Instead, Lassmann 2017 states that “the respective pathogenetic mechanisms in part act in parallel,” and provides the following illustration:



Id., 1595, FIG. 1. And Lassmann 2017 cautions that “it is important to consider that the mechanisms, which dominate in a given disease stage are also involved in the other stages.” *Id.*, 1597. Thus, before November 24, 2017, the general

knowledge in the art understood that overlapping pathophysiological mechanisms were involved in relapsing and progressive forms of MS.

42. Accordingly, it was recognized before November 24, 2017, that, while treatment targets for MS were generally different for different forms of the disease, the overlap in inflammatory mechanisms underlying both relapsing and progressive MS had “implications for the clinical management of patients with progressive MS as well as for clinical trial design” for those patients; namely, that patients with progressive MS could benefit from anti-inflammatory therapy, by way of immunosuppression. EX1019, Abstract; EX1020, 1597.

43. For example, Lassmann 2017 notes that “it may be useful in clinical trials to define the effect of anti-inflammatory versus neuroprotective treatments in those disease stages, where the respective mechanisms dominate, but when a positive treatment effect is proven, it is likely that they are also in part effective during other disease stages.” EX1020, 1597. Thus, where a drug has a proven anti-inflammatory effect in relapsing MS, a POSA would also expect that this anti-inflammatory effect would likely be effective, at least in part, against the inflammation in progressive stages of MS. Indeed, Lassmann 2017 further recommends that “therapeutic strategy in [the progressive stage] of the disease should be the blockade of the inflammatory response within the CNS,” and

recommends employing “anti-inflammatory drugs” that “reach the inflammatory response behind a closed blood-brain barrier.” *Id.*, 1596.

44. Others provided similar recommendations, such as Willis, who explains that “the revised diagnostic classification” provided by the Committee in 2014, “may help identify” progressive MS patients “likely to benefit from” immune-modulating therapies, as well as Alvarez-Gonzalez, who explains that “it makes evident sense to include clinical semiology as well as MRI appearance” for patients with progressive MS “when deciding about the likelihood of response to DMT [disease-modifying treatment].” EX1019, 796; EX1009, 507 (footnote added).

45. And, as explained in more detail below, a POSA would have known that cladribine was one such immune-modulating, anti-inflammatory drug that POSAs recognized would be effective against the underlying inflammatory mechanisms present in both relapsing and progressive MS.

C. Cladribine, a known immunosuppressant, was used to treat multiple sclerosis before November 2017

46. 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,

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and non-Hodgkin's lymphoma." EX1031, Abstract. Cladribine was first launched in the US in February 1993. *Id.*

47. Cladribine's mechanism of action was well understood before November 2017. Cladribine was known to "selectively deplete[] lymphocytes" and "destroy the activated immunocytes that damage the central nervous system in multiple sclerosis." EX1032, 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." EX1024, 421. The enzyme 5'-nucleotidase (5-NT) dephosphorylates (and therefore inactivates) cladribine. *Id.* 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." *Id.* Cladribine was known to have "activity against resting and dividing cells that express high deoxycytidine kinase activity." *Id.*, 420. Accordingly, it was known in the art that "cladribine causes prolonged, profound suppression of lymphocyte counts," which "suggests that a cladribine-induced reduction in the number of lymphocytes may help to slow progression of the disease [MS]." *Id.*, 420-21.

48. It was also known in the art that "cladribine crosses the blood-brain barrier and might, therefore, be effective in progressive forms of MS." EX1008,

324. As such, a POSA would have recognized cladribine's potential for treating "inflammation driven by the systemic immune reaction," typically seen during active disease, and the "inflammatory response behind a closed blood-brain barrier," typically seen in more advanced progressive disease. EX1020, 1595-96.

1. Clinical studies assessing parenteral cladribine in MS patients began in the early 1990's

49. Accordingly, beginning in the early 1990's, several clinical studies to evaluate parenteral cladribine in both relapsing and progressive MS were carried out. EX1008, 319; EX1058, Abstract; EX1035, Abstract; EX1033, Abstract; EX1036, Abstract. These studies demonstrated that cladribine: (a) "significantly reduced" "the frequency and severity of relapses" in RRMS; (b) "markedly reduced" gadolinium-enhancing lesions (a type of active lesion) detected on MRI in progressive MS; and (c) provided "evidence of efficacy" in patients with progressive MS. EX1008, 319; EX1009, 509; *see also* EX1033; EX1036; EX1025; EX1058. Thus, a POSA would have understood that cladribine was effective against disease activity in both relapsing and progressive forms of MS.

2. By the mid-2000's, oral cladribine compositions and dosing regimens for treating MS were known in the art

50. Prior to November 2017, 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'-

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deoxyadenosine; 2-CdA) and cyclodextrin.” EX1038, 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.*, 5:52-55.

51. 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, 6:53-56.

52. Bodor also discloses “compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine.” EX1026, Abstract. Bodor teaches, “[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 further discloses 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

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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. Bodor teaches that its oral cladribine tablets “achieve[] lower interpatient and/or inpatient variation of the drug.” *Id.*, 5:4-7.

53. By November 2017, oral cladribine administration was preferred to parenteral cladribine administration. 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.” *Id.*, 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. Giovannoni

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also teaches that the “need for parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.”

EX1007, 417; *see also* EX1008, 317. Thus, by November 2017, a POSA would have understood that oral cladribine dosage forms were preferable to injectable dosage forms.

54. Before November 24, 2017, several clinical studies had been performed in MS patients using 10-mg cladribine tablets. In 2004, Merck filed a patent application (that issued in 2013 as the '903 patent (EX1010)) describing the results of a sixty-patient clinical trial evaluating short-course administration of a 10-mg oral cladribine tablet prepared “as described” in Bodor. De Luca reports that patients who received oral cladribine saw a “decrease in brain lesions.” *Id.*, 16:45. As a result, De Luca claimed a “method of treating [ESPMS] and [RRMS]” with a similar dosing regimen as used in the trial. EX1010, 14:6-16:50, 18:7-25.

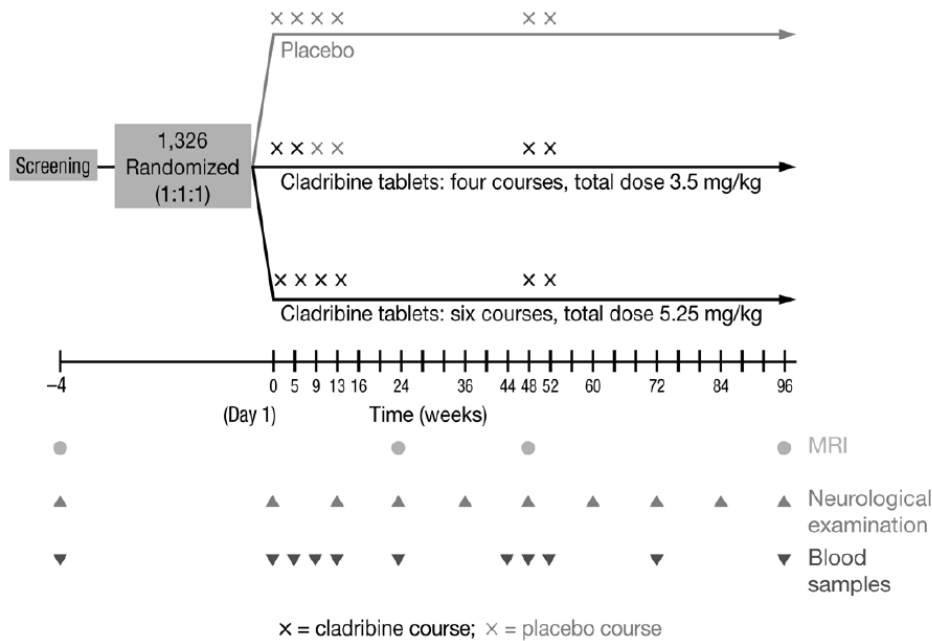
55. In 2010, Giovannoni reported the results of a phase III, placebo-controlled clinical trial studying oral cladribine therapy in patients with RRMS. EX1007, Abstract. Giovannoni discloses that “[e]ligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo.” *Id.*, 417. Patients were administered cladribine “orally as short courses,

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each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” *Id.* Patients in the 3.5 mg/kg cladribine arm received two courses of cladribine therapy during the first 48-week period of the study and another two courses in the second 48-week period of the study. *Id.*, 418. Giovannoni reports that “treatment with cladribine resulted in reductions in the rates of clinical relapse and in the risk of disability progression and in the suppression of active inflammatory lesions, as visualized on MRI.” *Id.*, 425-426. Giovannoni also states that “[b]oth the regimens of 3.5 mg and 5.25 mg per kilogram appeared to be equally efficacious.” EX1007, 425. A POSA would have understood that Giovannoni’s reported reductions in the number or size of enhancing lesions and in the number of relapses was indicative of a positive response to treatment. See ¶¶ 36, 49, *infra.* were indicative of a treatment response. And a POSA would have thus understood that the 3.5 mg/kg dosing regimen disclosed in Giovannoni was found to achieve the same efficacy against disease activity – namely, rate of relapse, disability progression, and MRI measures of disease activity – as the higher 5.25 mg/kg dosing regimen.

56. Giovannoni provides the following schematic of the CLARITY dosing regimen within a supplementary appendix:

Supplemental Figure 1. Study design and timing of assessments



EX1007, Supplementary Appendix Page 1. The published CLARITY trial protocol specifies that patients in the “low dose” arm were given “0.875 mg/kg/course” for a “[t]otal dose [of] 3.5 mg/kg over 96 weeks.” EX1066, 7. Following CLARITY, Merck enrolled certain patients in an extension study (CLARITY Extension), where it was reported that the benefits of oral cladribine treatment “were maintained” in these patients “for 4 years or more without further active treatment.” EX1006, 1.

57. In 2014, Leist reported the results of a phase 3 study, ORACLE, that “investigated the effect of oral cladribine on conversion to clinically definite MS in patients with a first clinical demyelinating event, when given at the same doses

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shown to be effective in relapsing-remitting MS.” EX1027, Abstract. Leist also administered oral cladribine with the same dosing regimen used in the Giovannoni study. Leist discloses that patients “assigned cladribine 3.5 mg/kg (total cumulative dose) received cladribine 0.875 mg/kg per course for two courses, plus placebo for two courses during the first 48 weeks, then two courses of cladribine 0.875 mg/kg during the second 48 weeks.” *Id.*, 258. Leist concludes that “in this population of patients with a first clinical demyelinating event suggestive of MS, treatment with cladribine ... 3.5 mg/kg over 2 years significantly delayed conversion to both clinically definite MS ..., and also significantly reduced MRI lesion counts compared with placebo.” *Id.*, 266. Leist also noted that treatment adherence for each group was “nearly 100%.” *Id.*, 262.

58. In 2016, Montalban reported the results of the ONWARD trial, a phase III, placebo-controlled clinical trial which administered 3.5 mg/kg of cladribine tablets to patients with “active relapsing [MS].” EX1006, 1. And, as set forth below, the study details for the ONWARD trial—including the purpose, primary and secondary outcome measures, study dates, treatment arms and interventions, and eligibility criteria—were posted publicly no later than July 3, 2013 on Clinicaltrials.gov, as captured by the Wayback Machine (the “Clinicaltrials.gov”). EX1005, 9-13. As also set forth below, a POSA would also

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have been able to readily locate Clinicaltrials.gov using standard and routine search techniques.

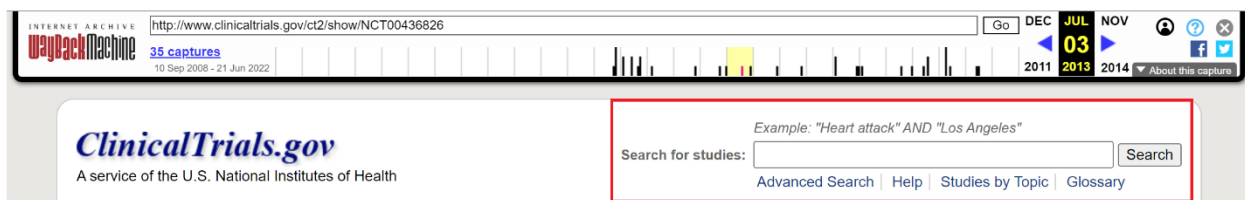
59. As an initial matter, I am familiar with Clinicaltrials.gov, which is a database of clinical trial information maintained by the National Institutes of Health and that is accessible and searchable by the public. Over the course of my career, I have accessed Clinicaltrials.gov numerous times, including before November 24, 2017, in order to obtain information relating to MS-related clinical trials. I have done this by navigating to Clinicaltrials.gov and then using its search feature to locate such clinical trials by name, subject matter, disease state, treatment, or other relevant key words.

60. I have also reviewed the Affidavit of Nathaniel E. Frank-White and its attachments, which include a copy of Clinicaltrials.gov. See EX1005. I understand from Mr. Frank-White's affidavit that Clinicaltrials.gov was archived by the Wayback Machine on July 3, 2013, and thus reflects how Clinicaltrials.gov appeared on Clinicaltrials.gov as of that date. EX1005, 9-13.

61. It is my opinion that a POSA would also have been able to readily locate Clinicaltrials.gov using standard and routine search techniques. Specifically, a POSA would have been aware of Clinicaltrials.gov as a convenient and searchable U.S. government repository for details relating to clinical trials,

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including for MS. Before Nov 2017, the clinicaltrials.gov website was key-word searchable. And given the fact that the oral cladribine for the treatment of MS was reported in various publications no later than July 23, 2013 (such as in the Giovannoni and Schreiber, EX1008), a POSA would have found it routine to look for and obtain its study details by simply navigating to Clinicaltrials.gov, typing in obvious search terms, such as “cladribine multiple sclerosis” or “ONWARD cladribine,” and arriving at the Clinicaltrials.gov page for the ONWARD trial. Indeed, the Wayback Machine archives of Clinicaltrials.gov depicts this exact search feature (that I have annotated below):



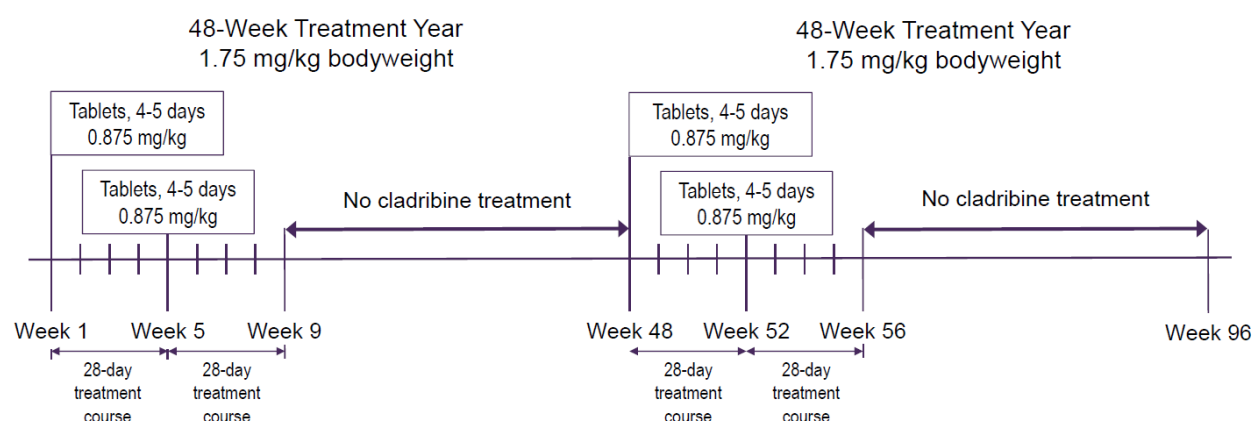
EX1005, 10.

62. The clinical trial protocol for Clinicaltrials.gov, discussed above, provides various study details from the ONWARD clinical trial, which was designed to “evaluate the safety, tolerability, and effectiveness of oral cladribine when taken in combination with Interferon-beta (IFN-beta) therapy for the treatment of multiple sclerosis (MS).” EX1005, 10. Clinicaltrials.gov discloses that patients, including RRMS patients and SPMS patients with “superimposed relapses” received “cladribine tablets orally as cumulative dose of 0.875 milligram

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per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

63. I have prepared the following the following schematic to illustrate how a POSA would have understood the 3.5 mg/kg Clinicaltrials.gov’s dosing regimen as disclosed:



Schematic 3.

64. A POSA would have understood that the oral cladribine dosing regimen disclosed in Clinicaltrials.gov was the same regimen used by Giovannoni and Leist. Montalban reports that this dosing regimen “demonstrated significant efficacy benefits.” EX1006, 1. Specifically, Montalban reports that the “mean number of qualifying relapses on study was lower (0.23) in patients treated with cladribine 3.5mg/kg plus IFN- β (N=124) vs. patients who received placebo plus IFN- β (0.56; N=48),” and the “mean numbers of new T1-Gd+, active T2 and CUA

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lesions/patient/scan were reduced in the combined treatment arm vs. placebo plus IFN- β .” *Id.* Montalban concludes that oral cladribine “demonstrated significant efficacy benefits,” including in patients with “SPMS with ongoing relapses” (i.e., with disease activity). *Id.* Thus, a POSA would have understood from Giovannoni, Leist, Clinicaltrials.gov, and Montalban that the same oral cladribine dosing regimen has repeatedly been shown to be efficacious against RRMS and SPMS in patients with active disease.

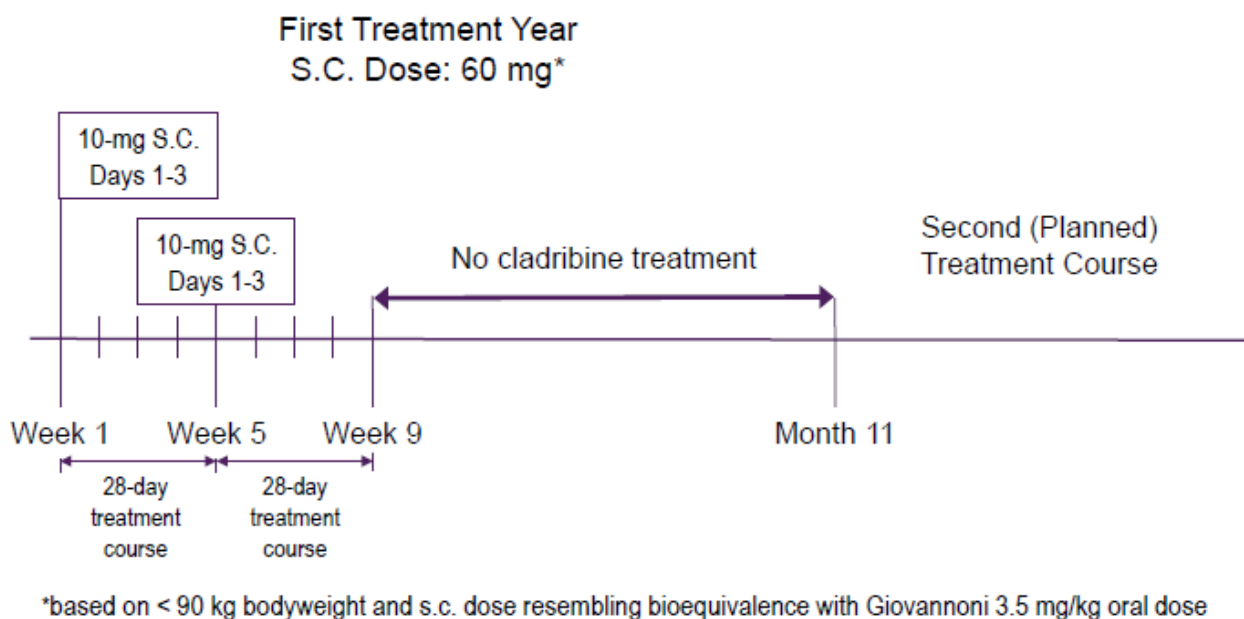
65. Finally, before November 24, 2017, other clinicians and researchers took note of these prior cladribine trials and further undertook additional study of similar cladribine dosing regimens. For example, in 2011, Schreiber provided an “evaluat[ion of] whether cladribine possesses properties” that may provide an “oral treatment[] with a favorable benefit-to-risk profile for the treatment of MS.” EX1008, 317. Schreiber recognizes the preference in the art for oral dosage forms: “parenteral administration may present relative or absolute barriers to acceptance of the therapy.” *Id.* Schreiber summarized the results of the early parenteral cladribine trials and the CLARITY trial, as well as the methodologies for the then-ongoing ORACLE and ONWARD trials. EX1008, 319-322. Schreiber concluded that “the oral dosing regimen [of cladribine used in CLARITY] is convenient,” “efficacy is high,” and cladribine “might [also] be effective in progressive forms of

MS.” *Id.*, 324. Schreiber also taught that the “formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” *Id.*

66. As another example, in May 2017, Alvarez-Gonzalez published a case study regarding a PPMS patient who developed “rebound disease,” with 45 active lesions detected on MRI, and “who was successfully treated” using “a short course of subcutaneous cladribine.” EX1009, Abstract, 506. Specifically, the patient had been previously diagnosed with PPMS, was later “enrolled in the phase III trial of fingolimod 0.5 mg/day in PPMS,” and then developed “45 Gadolinium-enhancing lesions [] within 6 months” after fingolimod was stopped. *Id.*, Abstract, 506, 507. “Given the significant clinical and MRI-detected disease” in the patient, and in further view of cladribine’s efficacy against disease activity including as demonstrated in the CLARITY and ORACLE trials, Alvarez-Gonzalez “offered treatment using cladribine 60 mg s.c. over 5 weeks.” *Id.*, 506, 507, 509. This was “based on 100% bioavailability of [c]ladribine s.c. (versus 42% [f]or the oral prodrug),” and so “60 mg [c]ladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” *Id.*, 509.

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67. In particular, Alvarez-Gonzalez administered “[c]ladribine 10-mg s.c. ... on days 1, 2, and 3 in week one,” and “administered further doses [of] [c]ladribine 10-mg s.c. on days 1, 2 and 3 in week 5,” with “a second treatment cycle [] planned 11 months after the first.” *Id.* (footnote removed). I have prepared the following schematic to illustrate how a POSA would have understood Alvarez-Gonzalez’s dosing regimen:

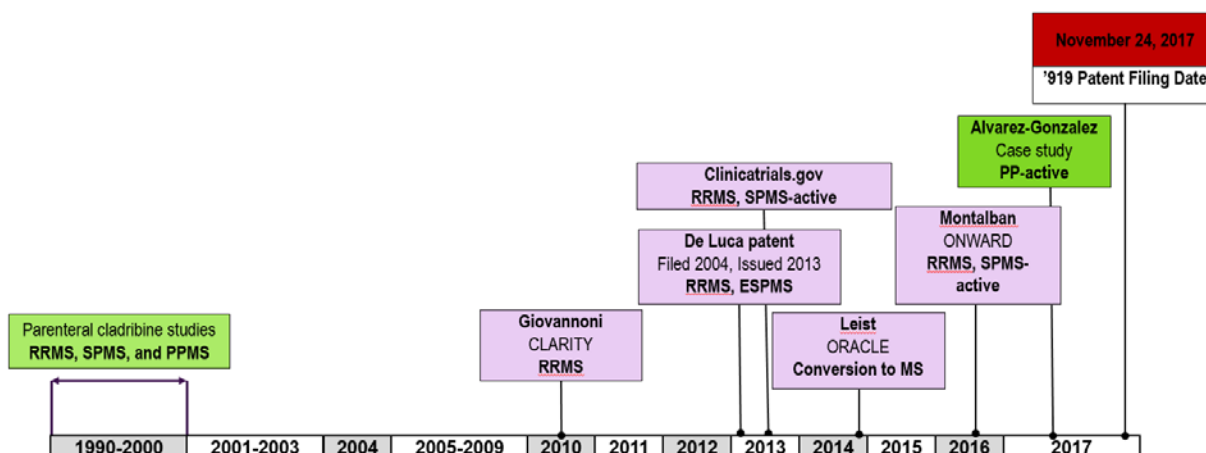


Schematic 2.

68. In sum, and in the timeline I prepared below to demonstrate a POSA’s understanding of the general knowledge in the art, before November 24, 2017, a POSA would have been aware of a multitude of prior art showing that cladribine therapy—including the administration of 10-mg oral tablets in short courses over

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two treatment years in a cumulative dose of 3.5 mg/kg—is effective in treating disease activity in each of RRMS, ESPMS, SPMS, and PPMS.



VII. The '919 Patent Specification, Claims, and Prosecution History

A. The '919 patent specification

69. I have reviewed the '919 patent; a POSA would have understood that it is generally directed to “[s]pecific oral dosings, specific oral dosage forms, and/or specific oral dose regimens including Cladribine can be effective for the treatment of progressive forms of Multiple Sclerosis, especially Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.” EX1001, Abstract.

According to the '919 patent, “[f]our courses of the disease are generally differentiated: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.” *Id.*, 1:47-50.

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The '919 patent states that “[i]t is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification.” *Id.*, 1:67-2:4. The '919 patent further states that “Early Secondary Progressive Multiple Sclerosis (ESPMS) is some form of Multiple Sclerosis that marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS.” *Id.*, 2:63-67.

70. The '919 patent reports data from the ONWARD clinical study designed to “to confirm the effect of Cladribine tablets 3.5 mg/kg in patients with SPMS or RRMS.” *Id.*, 55:24-26. According to the '919 patent, “Cladribine-treated SPMS patients were 89% less likely to have a qualifying relapse than those treated with placebo,” while “Cladribine-treated RRMS patients were only 50% less likely to have a qualifying relapse than those treated with placebo.” *Id.*, 56:16-18. However, the '919 patent also states with respect to the ONWARD study that: (a) “there was no difference in annualized relapse rate between patients with relapsing-remitting MS and patients with secondary progressive MS with relapses,” and (b) “[n]o treatment effect was observed for the SPMS or RRMS subgroups on either time to 3-month or 6-month confirmed EDSS progression.” *Id.*, 47:66-48:1, 56:20-22.

B. The '919 patent claims

71. I understand that the '919 patent has four independent claims.

Independent claims 1, 14, 24, and 27 are reproduced below:

1. A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS), and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).

14. A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising:

orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year,

wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis

(SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS), and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).

24. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a treatment year comprising the following regimen:

(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;

(ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;

wherein patients having a bodyweight

in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine)

in the 1st treatment week of said treatment course,

2) 4 tablets or capsules (40 mg of Cladribine)

in the 2nd treatment week of said treatment course;

in the range of 50 to less than 60 kg are administered

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1) 5 tablets or capsules (50 mg of Cladribine)
in the 1st treatment week of said treatment
course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine)
in the 2nd treatment week of said treatment
course;

in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine)
in the 1st treatment week of said treatment
course,

2) 6 tablets or capsules (60 mg of Cladribine)
in the 2nd treatment week of said treatment
course;

in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine)
in the 1st treatment week of said treatment
course,

2) 7 tablets or capsules (70 mg of Cladribine)
in the 2nd treatment week of said treatment
course;

in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine)
in the 1st treatment week of said treatment
course,

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2) 7 tablets or capsules (70 mg of Cladribine)
in the 2nd treatment week of said treatment
course;

in the range of 90 to less than 100 kg are
administered

1) 9 tablets or capsules (90 mg of Cladribine)
in the 1st treatment week of said treatment
course,

2) 8 tablets or capsules (80 mg of Cladribine)
in the 2nd treatment week of said treatment
course;

in the range of 100 to less than 110 kg are
administered

1) 10 tablets or capsules (100 mg of
Cladribine) in the 1st treatment week of said
treatment course,

2) 9 tablets or capsules (90 mg of Cladribine)
in the 2nd treatment week of said treatment
course; or

in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of
Cladribine) in the 1st treatment week of said
treatment course,

2) 10 tablets or capsules (100 mg of
Cladribine) in the 2nd treatment week of said
treatment course.

27. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS), and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS), said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during two treatment years comprising the following regimen:

(i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;

(ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;

(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and

(iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and

wherein patients having a bodyweight

in the range of 40 to less than 50 kg are administered

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1) 4 tablets or capsules (40 mg of Cladribine)
in the 1st treatment week of both the 1st and
the 2nd treatment course, respectively,

2) 4 tablets or capsules (40 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively:

in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine)
in the 1st treatment week of both the 1st and
the 2nd treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively:

in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine)
in the 1st treatment week of both the 1st and
the 2nd treatment course, respectively,

2) 6 tablets or capsules (60 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively;

in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine)
in the 1st treatment week of both the 1st and
the 2nd treatment course, respectively,

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2) 7 tablets or capsules (70 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively;

in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine)
in the 1st treatment week of both the 1st and
the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively;

in the range of 90 to less than 100 kg are
administered

1) 9 tablets or capsules (90 mg of Cladribine)
in the 1st treatment week of both the 1st and
the 2nd treatment course, respectively,

2) 8 tablets or capsules (80 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively;

in the range of 100 to less than 110 kg are
administered

1) 10 tablets or capsules (100 mg of
Cladribine) in the 1st treatment week of both
the 1st and the 2nd treatment course,
respectively,

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2) 9 tablets or capsules (90 mg of Cladribine)
in the 2nd treatment week of both the 1st and
the 2nd treatment course, respectively; or
in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of
Cladribine) in the 1st treatment week of both
the 1st and the 2nd treatment course,
respectively,

2) 10 tablets or capsules (100 mg of
Cladribine) in the 2nd treatment week of both
the 1st and the 2nd treatment course,
respectively.

Id., 64:45-56, 65:59-66:11, 66:51-67:39, 67:48-68:64.

72. Claims 2-6, 8, 9, 11, and 12 ultimately depend from claim 1, claims 15, 16, 18-20, and 23 ultimately depend from claim 14, claims 25 and 26 ultimately depend from claim 24, and claims 30 and 33-34 ultimately depend from claim 27. Claims 2-6, 8, 9, 11, 12, 15, 16, 18-20, 23, 25, 26, 30, 33, and 34 add certain limitations, such as doses, dosing regimens, cladribine-free period, and specific patient populations, etc.

C. The '919 patent prosecution history

73. I have reviewed the prosecution history of the '919 patent and the art cited in Merck's Information Disclosure Statement ("IDS") and reviewed by the

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Examiner. EX1004. None of these references are substantially the same as the art relied on in the Grounds of this Declaration. In fact, four of the references cited herein were not disclosed by Merck in the IDS or cited in the prosecution history at all—Alvarez-Gonzalez, Schreiber, Clinicaltrials.gov, and Montalban. Nor are any of the references or arguments disclosed or cited during prosecution cumulative of the disclosures within these references or cumulative of my obviousness analysis below. For example, the Examiner was never presented with any prior art or arguments expressly stating that disease activity may be present in SPMS and PPMS in addition to ESPMS and RRMS. Nor was the Examiner presented with any prior art or arguments stating that a treatment like cladribine, that was previously shown to be effective against disease activity in RRMS and ESPMS, may also be expected to have efficacy against disease activity in SPMS and PPMS. Finally, the Examiner was never presented with any prior art or arguments disclosing that oral cladribine dosing regimens like the ones recited in the '919 patent would be in fact effective in treating PP-active and SPMS-active. Yet as I discuss in more detail below, the prior art references I have specifically relied on for my obviousness analysis as the state of the art that I specifically discuss herein would have taught a POSA that the dosing regimens recited in the '919 patent claims would, in fact, be effective in treating PP-active and SPMS-active.

VIII. Claim Construction

74. I understand that the terms of the claims are to be given their plain and ordinary meaning from the point of a person of ordinary skill in the art in question at the time of the invention. 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. “A progressive form of multiple sclerosis”

75. Independent claims 1, 14, 24, and 27 recite a method of treating “a progressive form of multiple sclerosis,” including PPMS and SPMS. EX1001, 64:45-56; 65:59–66:11; 66:51–6:39; 67:48–68:64. The claims broadly recite “a progressive form” of MS without specifying whether the form exhibits activity, progression, or both. As explained above in ¶¶ 29, 32-33, *infra*, a POSA would have understood that patients with a progressive form of MS could experience disease activity in addition to progression. As such, the plain language of the claims encompasses “a progressive form” of MS that exhibits disease activity—specifically, SPMS-active and PP-active.

76. Construing “a progressive form of [MS]” to encompass SPMS-active and PP-active is consistent with the ’919 patent and prosecution history because the ’919 patent contemplates using the claimed methods to treat SPMS-active and PP-active. First, the ’919 patent states that a “PPMS population with greater MRI

activity” (i.e., PP-active patients) “may be more suitable to treatment” with the claimed method. EX1001, 60:54-57. Second, it states that the claimed method reduced the risk of “qualifying relapse” in SPMS (i.e., treated disease activity in SPMS-active). EX1001, 3:25-67. Thus, the term “a progressive form of [MS]” should be construed as encompassing SPMS-active and PP-active.

B. “Early Secondary Progressive Multiple Sclerosis (ESPMS)”

77. Independent claims 1, 14, and 27 recite a method of treating specific progressive forms of MS, “wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS),” and wherein the progressive form of does not include “Early Secondary Progressive Multiple Sclerosis (ESPMS).” I understand that different words in a claim are presumed not to have the same meaning.

78. The ’919 patent provides the following explanation of ESPMS:

[T]his so-called Early Secondary Progressive Multiple Sclerosis (ESPMS) is some form of Multiple Sclerosis that marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS.

EX1001, 2:63-67. Thus, the ’919 patent supports a construction of the term “Early

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Secondary Progressive Multiple Sclerosis (ESPMS)” that differentiates ESPMS from SPMS as a distinct form of MS, and that “marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS.” *Id.*

79. Merck’s arguments during prosecution were consistent with the above construction. In particular, to overcome the Examiner’s rejection of the claims in view of the De Luca prior art that disclosed treating ESPMS with orally administered cladribine, Merck stated that SPMS “*does not include*” ESPMS (emphasis added). EX1004, 317-318. Thus, Merck itself confirmed that ESPMS is distinct from SPMS in order to obtain allowance of the claims.

80. The proposed construction is also consistent with how a POSA would have understood the term ESPMS. As I explain above, a POSA would have recognized ESPMS was a distinct form of MS. See ¶ 34, *infra*. Thus, the term “Early Secondary Progressive MS,” should therefore be construed as a distinct form of MS that is not SPMS, and that marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS. And I used this meaning of the term in my analysis.

C. “Week/month/year”

81. The ’919 patent explains that in a medical context, “a week” is “a period of time of about 5, about 6 or about 7 days, more preferably about 7 days,”

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“a month” is “about 28, about 29, about 30 or about 31 days,” and “a year” is “12 months, or about 48 or about 52 weeks.” EX1001, 53:45-67. I have used these definitions in my analysis.

82. For any term I have not expressly interpreted above, I apply its plain and ordinary meaning.

IX. Basis of my analysis with respect to obviousness

83. 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.

84. 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.

85. I further 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.

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86. 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.

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

X. Claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 24-27, 33, and 34 would have been obvious over Alvarez-Gonzalez and Giovannoni

A. Claim 1

88. Claim 1 is directed to a “method of treating a progressive form of Multiple Sclerosis” comprising the “orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg.” Claim 1 specifies that “the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary

Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis” and that “the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” EX1001, 64:45-56.

89. As shown in Appendix A and as I explain in detail below, Alvarez-Gonzalez and Giovannoni together disclose every limitation of claim 1, and a POSA would have been motivated to combine their teachings with a reasonable expectation of success to arrive at the method recited in claim 1. Thus, claim 1 would have been obvious to a POSA over the combination of Alvarez-Gonzalez and Giovannoni before November 24, 2017.

1. Alvarez-Gonzalez teaches treating a progressive form of multiple sclerosis with cladribine

90. A POSA would have understood that Alvarez-Gonzalez discloses treating a PP-active patient using cladribine. Alvarez-Gonzalez reports a PP-active patient was “successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, 506. Alvarez-Gonzalez explains that a PPMS patient previously treated with fingolimod experienced a “significant exacerbation” of symptoms six months after ending a fingolimod clinical study. *Id.*, 507. The patient “was unable to walk,” had developed “a new sensory level for touch and pain from T₆ downwards bilaterally,” and had an EDSS of 8. *Id.* The patient’s MRI “showed 48 new T₂ lesions, of which 45 were Gd⁺ on T₁.” *Id.* All these are signs or symptoms of

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ongoing disease activity, as described by the 2014 Committee recommendations and as widely used in the field before November 24, 2017, and thus, a POSA would have recognized – consistent with the standardized terminology at the time – that the patient had PP-active. See ¶¶ 32-33, *infra*. As explained above “a progressive form of MS,” encompasses treating PP-active. See ¶¶ 75-76, *infra*.

91. Alvarez-Gonzalez further explains that based on the general knowledge in the art regarding cladribine, such as the drug’s “class I evidence of efficacy” “in people with relapsing MS,” its “selective lymphocyte mechanism of action,” and its “known relative safety in people with advanced MS,” and “evidence for Cladribine being effective in pwMS from previous phase III trials (citing CLARITY and ORACLE trials),” the authors hypothesized that cladribine “would have a reasonable likelihood of success” in treating a PP-active patient. EX1009, 509. Alvarez-Gonzalez reports that three months after treatment with “60 mg s.c. [subcutaneous] over 5 weeks,” the patient’s “EDSS had improved to 7, and MRI head at this time did not show any evidence of new T₂ lesions and no Gd⁺ lesions [enhancing lesions].” *Id.*, 507. A POSA would have understood that a decrease in the patient’s EDSS correlates to an improvement in clinical symptoms. See ¶ 35, *infra*. A POSA would have also understood that a reduction in the number or size of enhancing lesions were indicative of a treatment response. See ¶

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36, *infra*. In light of the patient's response to treatment, Alvarez-Gonzalez deemed the cladribine therapy "[s]uccessful" and concluded that "[b]ased on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT [disease-modifying treatment] for pwPMS [people with progressive MS]." EX1009, 509. Alvarez-Gonzalez further concluded that their results "should encourage studies to more definitely investigate the effectiveness of immunosuppressive DMT in pwPMS." *Id.* Thus, a POSA would have understood from Alvarez-Gonzalez that the PPMS patient's activity was treated with cladribine.

92. A POSA would have also understood that the PPMS patient treated by Alvarez-Gonzalez had a progressive form of MS that "does not include Early Secondary Progressive Multiple Sclerosis (ESPMS)," as also recited by claim 1. Specifically, a POSA would have understood that the PPMS patient treated in Alvarez-Gonzalez could not have had ESPMS, by definition. A POSA would have known that the general knowledge in the art recognized ESPMS as the transition period between RRMS and SPMS. *See* ¶ 34, *infra*. Thus, patients with ESPMS necessarily started with RRMS. As I explain above, a POSA would have known that the PPMS form shows disease progression "from onset" without first

exhibiting a relapsing-remitting course. EX1014, 909. Thus, PPMS patients never had RRMS in the first place.

93. Accordingly, a POSA would have understood Alvarez-Gonzalez to teach treating “a progressive form of multiple sclerosis,” such as PPMS, with cladribine, “wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS),” as recited in claim 1.

2. Giovannoni teach orally administering a “fixed dose” of cladribine “in a range of 1.5 mg/kg to 4.0 mg/kg” “per patient, per body weight and per treatment year”

94. Giovannoni discloses administering a “fixed dose” of cladribine “in a range of 1.5 mg/kg to 4.0 mg/kg” “per patient, per body weight and per treatment year.” Giovannoni reports the results of a “96-week phase 3 trial of a short-course oral [cladribine] tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, Abstract. Giovannoni discloses results from the “Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study” in which “[e]ligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo.” *Id.*, 417. Giovannoni details the following dosing regimen:

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The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.

In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).

Id., 417-418; *see also* ¶ 56, *infra*. Thus, a POSA would have understood that the patients in the 3.5 mg/kg cohort received the total 3.5 mg/kg dose over four treatment courses. And because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have further understood that the most logical and obvious way to administer Giovannoni's disclosed dosing regimen would be to administer the same dose in each of the four courses—two courses of 0.875 mg/kg each (i.e., 1.75 mg/kg total) administered in the first 48-week treatment period and an additional two courses of 0.875 mg/kg each (i.e., 1.75 mg/kg total) administered in the second 48-week treatment period. A POSA would have also understood that 48 weeks constitutes a

“treatment year,” as defined by the ’919 patent. EX1001, 53:64-67. As such, Giovannoni would have taught a POSA to administer a “fixed dose” of 1.75 mg of “orally administer[ed]” cladribine “per patient, per body weight and per treatment year,” which is encompassed by the claimed range of “1.5 mg/kg to 4.0 mg/kg,” recited in claim 1.

3. A POSA would have been motivated to combine Alvarez-Gonzalez and Giovannoni

95. A POSA would have been motivated to combine the teachings of Alvarez-Gonzalez and Giovannoni to treat a PP-active patient by administering “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0 mg/kg” according to Giovannoni’s oral cladribine dosing regimen. Alvarez-Gonzalez hypothesizes that a DMT, or anti-inflammatory, immunomodulating treatment, like cladribine, would have a “reasonable likelihood of success” in treating PP-active patients, because of its demonstrated efficacy in RRMS in the phase III CLARITY trial, as well as the “evidence of efficacy” in progressive MS shown in earlier clinical trials. EX1009, 509-510; *see also* EX1033; EX1036; EX1025; EX1058. And, a POSA would have understood that Alvarez-Gonzalez did, in fact, effectively treat a PP-active patient with subcutaneous cladribine, as explained above. Specifically, Alvarez-Gonzalez teaches that subcutaneous cladribine “led to effective suppression of inflammatory

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activity and partial recovery with no short-term safety issues or adverse events” in a PP-active patient (i.e., a relapsing PPMS patient). EX1009, Abstract. Alvarez-Gonzalez further reports that the patient “improved to EDSS 7, with no disease activity detected on follow-up MRI,” which a POSA would have understood was indicative of a treatment response. EX1009, 509; *See* ¶¶ 35-36, *infra*. As discussed above, a PP-active patient, by definition, cannot have ESPMS (since ESPMS is the transition state between RRMS and SPMS, and a PP-active patient never had RRMS in the first place). *See* ¶ 30, *infra*. As such, a POSA would have been motivated from the teachings of Alvarez-Gonzalez to treat a patient that had a progressive form of MS (i.e., PP-active) that is not ESPMS, as recited in claim 1.

96. Giovannoni and the general knowledge in the art also recognizes a preference for oral dosage forms over parenteral dosage forms. EX1007, 417; EX1026, 2:9-11. In fact, Giovannoni expressly teaches such a preference: “parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.” EX1007, 417. Thus, a POSA would have had a reason to substitute oral cladribine for Alvarez-Gonzalez’s subcutaneous cladribine because oral dosage forms were preferable to parenteral forms. A POSA would have also recognized that Alvarez-Gonzalez administered subcutaneous cladribine therapy “off-label” to their patient because

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of the “lack of any licensed options” (e.g., oral cladribine) available to them. For example, Merck’s previously disclosed cladribine tablets were not FDA-approved until March 2019 (EX1069). EX1009, 506, 509. Accordingly, Alvarez-Gonzalez’s use of subcutaneous cladribine would not have contradicted a POSA’s general understanding that oral cladribine was preferred over subcutaneous administration.

97. As such, a POSA would have been motivated to substitute Alvarez-Gonzalez’s parenteral dosing regimen with Giovannoni’s oral dosing regimen (i.e., dose and administration scheme) because Alvarez-Gonzalez explains that their subcutaneous dosing regimen was based (“resembles bioequivalence”) on the “oral dose used in the pivotal CLARITY MS study” (i.e., Giovannoni’s study). *Id.*, 509. Thus, a POSA wanting to modify Alvarez-Gonzalez’s dosing regimen with oral cladribine would have naturally looked to Giovannoni, since Alvarez-Gonzalez based their own parenteral dosing regimen on Giovannoni’s oral dosing regimen.

98. A POSA would have had a reason to utilize Giovannoni’s dosing regimen, which orally administers 3.5 mg/kg over 2 years in four treatment courses. A POSA would have found it logical and convenient to use Giovannoni’s entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract. Because Giovannoni does not differentiate between the four treatment courses (instead

describing them identically), a POSA would have been motivated to administer Giovannoni's 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year³) because that would have been the most logical and obvious dosing regimen. Thus, a POSA would have had a reason to administer 1.75 mg/kg of cladribine per treatment year with a specific administration schedule, to treat a PP-active patient. Because Alvarez-Gonzalez's parenteral dosing regimen resembles bioequivalence to Giovannoni's dosing regimen, a POSA would have had a reason to maintain Giovannoni's dosing regimen—i.e., specific doses and administration schedule. A POSA would have understood that in order to administer oral cladribine that provides a similar cladribine pharmacokinetic profile (i.e., “resembles bio-equivalence”) to the cladribine pharmacokinetic profile provided by Alvarez-Gonzalez's dosing regimen, Giovannoni's dosing schedule would need to be followed.

99. As such, a POSA would have been motivated to treat a PP-active patient, a progressive form of MS that is not ESPMS, with “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0

³ 3.5 mg/kg ÷ 4 treatment courses = 0.875 mg/kg per treatment course; 3.5 mg/kg ÷ 2 treatment years = 1.75 mg/kg per treatment year.

mg/kg” or oral cladribine with the same dosing regimen taught by Giovannoni, thus arriving at the method recited in claim 1.

4. A POSA would have had a reasonable expectation of successfully combining Alvarez-Gonzalez and Giovannoni

100. A POSA would have had a reasonable expectation of successfully treating a PP-active patient by orally administering “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0 mg/kg” of cladribine according to Giovannoni’s oral cladribine dosing regimen. As explained above, Alvarez-Gonzalez reports that three months after treatment with “60 mg s.c. [subcutaneous] over 5 weeks,” the patient’s “EDSS had improved to 7, and MRI head at this time did not show any evidence of new T₂ lesions and no Gd⁺ lesions [enhancing lesions],” both measures that indicate a patient’s positive response to therapy. EX1009, 507; *see also* ¶¶ 35-36, *infra*. Alvarez-Gonzalez explains that its subcutaneous cladribine dosing regimen (i.e., 10 mg s.c. was given on days 1, 2 and 3 in week one and again in week five) “resembles bio-equivalence” to Giovannoni’s oral dosing regimen, meaning Alvarez-Gonzalez’s subcutaneous dosing regimen provides a similar cladribine pharmacokinetic profile as Giovannoni’s oral dosing regimen *in vivo*. EX1039, generally. As such, a POSA would have reasonably expected Giovannoni’s oral dosing regimen to provide a similar cladribine pharmacokinetic profile as Alvarez-Gonzalez’s subcutaneous

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dosing regimen in a PP-active patient, and thus, a similar therapeutic effect.

EX1009, 509; EX1039, generally.

101. A POSA would have also reasonably expected to successfully substitute Alvarez-Gonzalez's subcutaneous dosing regimen for an oral dosing regimen, as disclosed by Giovannoni because Giovannoni provides the specific details for its oral dosing regimen—e.g., the timeframe for administering the tablets, the tablet strength, the number of tablets to administer, and the cumulative dose based on bodyweight. EX1007, 417-418, Supplementary Appendix FIG.1. Thus, by administering oral cladribine according to Giovannoni's dosing regimen, a POSA would have reasonably expected a PP-active patient to have a cladribine pharmacokinetic profile, which was shown by Alvarez-Gonzalez to “effective[ly] suppress[] inflammatory activity” in a PP-active patient. Accordingly, a POSA would have reasonably expected Giovannoni's oral cladribine dosing regimen to successfully treat PP-active.

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

B. Claim 2

103. Claim 2 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 2 further recites, “wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg.”

104. As explained above, a POSA would have been motivated to treat a PP-active patient orally administering “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0 mg/kg” of cladribine according to Giovannoni’s oral cladribine dosing regimen, with a reasonable expectation of success. A POSA would have found it logical and convenient to use Giovannoni’s entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract. As such, Giovannoni’s dosing regimen would have taught a POSA to administer a fixed dose of 1.75 mg/kg of cladribine per patient per treatment year. Thus, a POSA would have been motivated to administer 1.75 mg/kg per treatment year with Giovannoni’s oral cladribine dosing regimen to treat a PP-active patient would have administered, with a reasonable expectation of success.

105. Accordingly, a POSA would have arrived at the method of claim 2 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

C. Claim 3

106. Claim 3 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 3 further recites, “wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.”

107. As explained above for claim 1, a POSA would have been motivated to treat a PP-active patient orally administering “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0 mg/kg” of cladribine according to Giovannoni’s oral cladribine dosing regimen, with a reasonable expectation of success.

108. Accordingly, for the same reasons discussed for claim 1, a POSA would have arrived at the method of claim 3 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

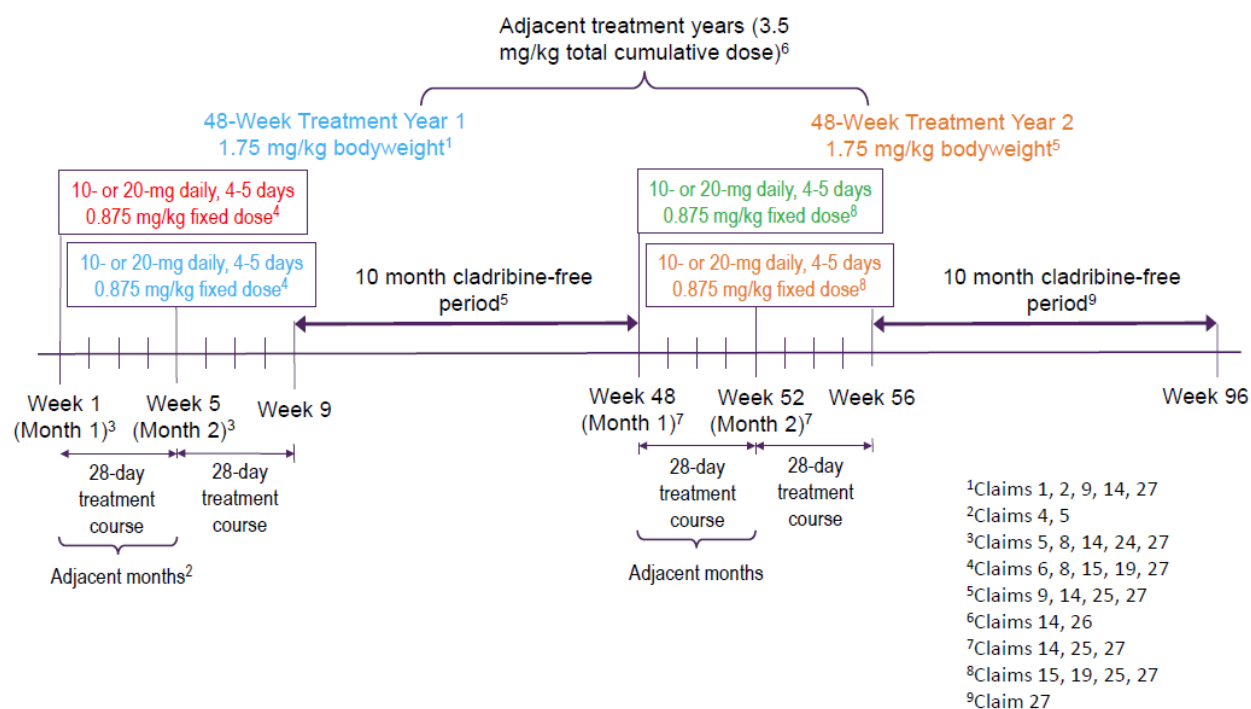
D. Claims 4-6

109. Claim 4 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 5 depends from claim 4 and thus, contains each and every limitation of claims 1 and 4. Claim 6 depends from claim 5 and thus, contains each and every limitation of claims 1, 4, and 5. Claim 4 further recites, “wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.” Claims 5 and 6 further recite “wherein said

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fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months” and “wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks,” respectively.

110. Giovannoni’s previously disclosed dosing regimen includes each of the additional dosing regimen elements of claims 4-6. I have prepared the following graphic to demonstrate how a POSA would have understood how Giovannoni’s 2-year dosing regimen corresponds to the claimed methods:



Schematic 1.

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As explained above, Giovannoni's dosing regimen would have taught a POSA to orally administer 0.875 mg/kg of cladribine over 4-5 days beginning on day 1 and again on week 5—i.e., 4-5 days of one week at the beginning of each one of two adjacent months, as recited in claims 4-6. Also, as explained above, a POSA would have been motivated to treat a PP-active patient orally administering “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0 mg/kg” of cladribine according to Giovannoni's oral cladribine dosing regimen, which comprises the additional dosing regimen limitations of claims 4-6, with a reasonable expectation of success. A POSA would have usedd Giovannoni's entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract.

111. Accordingly, a POSA would have arrived at the methods of claims 4-6 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

E. Claim 8

112. Claim 8 depends from claim 1 and thus, contains each and every limitation of claim 36. Claim 8 further recites “wherein each treatment year comprises: (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days

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each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.”

113. Giovannoni’s dosing regimen comprises each of the additional dosing elements of claim 8. *See, e.g., ¶ 110, infra.* As explained above, Giovannoni administers “short courses [of cladribine], each consisting of one or two 10-mg cladribine tablets” “for the first 4 or 5 days of a 28-day period.” EX1007, 417. In the 3.5 mg/kg patient cohort, Giovannoni administers two courses of cladribine on day 1 and week 5, and another two courses at weeks 48 and 52. *Id.*, 418. A POSA would have understood that no cladribine was administered to patients between weeks 5 and 48 (43 weeks or 10 months). *See ¶ 110, infra.* As such, Giovannoni’s dosing regimen contains all the additional dosing regimen limitations of claim 8. And as explained above, a POSA would have been motivated to treat a PP-active patient by administering a fixed dose of 1.75 mg/kg per treatment year according to Giovannoni’s oral cladribine dosing regimen, which included the additional limitations of claim 8, with a reasonable expectation of success. A POSA would have used Giovannoni’s entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract.

114. Accordingly, a POSA would have arrived at the method of claim 8 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

F. Claim 9

115. Claim 9 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 9 further recites “wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive Multiple Sclerosis, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.”

116. As explained above, a POSA would have been motivated to treat a PP-active patient by administering a fixed dose of 1.75 mg/kg per treatment year according to Giovannoni’s oral cladribine dosing regimen, with a reasonable expectation of success. Also, as explained above, Giovannoni’s oral cladribine dosing regimen comprises administering a fixed dose of 1.75 mg/kg per year for two years. EX1007, 418, Supplementary Appendix FIG.1; *see also* ¶ 110, *infra*. Thus, a POSA would have been motivated to treat a PP-active patient with 1.75 mg/kg per treatment year for at least two years, with a reasonable expectation of success. A POSA would have used Giovannoni’s entire 2-year-long dosing

regimen because it was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract.

117. Accordingly, a POSA would have arrived at the method of claim 9 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

G. Claim 12

118. Claim 12 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 12 further recites, "wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule."

119. As explained above, a POSA would have been motivated to treat a PP-active patient by administering a fixed dose of 1.75 mg/kg per treatment year according to Giovannoni's oral cladribine dosing regimen, with a reasonable expectation of success. Also, as explained above, Giovannoni's oral cladribine dosing regimen comprises administering oral tablets. EX1007, 417-418, Supplementary Appendix FIG.1. Thus, a POSA would have been motivated to treat a PP-active patient by administering a fixed dose of 1.75 mg/kg per treatment year of cladribine tablets according to Giovannoni's dosing regimen, with a reasonable expectation of success.

120. Accordingly, a POSA would have arrived at the method of claim 12 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

H. Claim 14

121. Claim 14 is directed to a “method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis” comprising “orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg ± 0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.” Claim 14 specifies that “the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis” and that “the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” EX1001, 65:59-66:11.

122. As explained above for claim 1, and as shown in Appendix A and explained in detail below, a POSA would have been motivated to combine the

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teachings of Alvarez-Gonzalez and Giovannoni to treat a PP-active patient (who, by definition, did not have ESPMS) by administering oral cladribine according to Giovannoni's dosing regimen. Claim 14 differs from claim 1 by requiring administering to a patient "a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year." *Id.* As explained in detail below, these additional limitations are elements of Giovannoni's prior art dosing regimen.

123. In addition to the reasons described for claim 1, which I will not reiterate here but which are applicable for claim 14, a POSA would have had a reason to administer a cumulative dose of cladribine of about 3.5 mg/kg body weight according to the claimed dosing regimen (i.e., administered as one treatment course of about 1.75 mg/kg per year for two years, wherein each treatment course consists 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year), with a reasonable expectation of success.

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124. Giovannoni would have taught “orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.” Giovannoni reports the results of a “96-week phase 3 trial of a short-course oral [cladribine] tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, Abstract. Giovannoni discloses that “[e]ligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo.” *Id.*, 417. A POSA would have understood that 96 weeks was equivalent to two years, as defined by the ’919 patent. EX1001, 53:64-67; *see also* ¶ 81, *infra*. Thus, Giovannoni explicitly discloses administering “a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years,” as recited in claim 14.

125. Giovannoni discloses the following dosing regimen:

The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.

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In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).

Id., 417-418. Thus, a POSA would have understood that the patients in the 3.5 mg/kg treatment arm received the total 3.5 mg/kg dose over four treatment courses—two courses were given in two consecutive months in the first 48-week treatment period and an additional two courses were given in two consecutive months in the second 48-week treatment period. *Id.* Because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni’s 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. As such, a POSA would have understood that Giovannoni “administered in each year as 1 treatment course of about 1.75 mg/kg±0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the

beginning of the first month and one at the beginning of the second month of the respective treatment year,” as recited in claim 14.

1. A POSA would have been motivated to combine Alvarez-Gonzalez and Giovannoni

126. A POSA would have been motivated to combine the teachings of Alvarez-Gonzalez and Giovannoni to treat PPMS (which by definition is not ESPMS), by orally administering a cumulative dose of 3.5 mg/kg over two years according to Giovannoni’s dosing regimen. Alvarez-Gonzalez’s hypothesizes that a DMT, or anti-inflammatory, immunomodulating treatment, like cladribine would have “a reasonable likelihood of success” in treating PP-active, including because of its demonstrated efficacy in RRMS in the phase III CLARITY trial as well as the “evidence of efficacy” in progressive MS shown in earlier clinical trials.

EX1009, 509-510; EX1033; EX1036; EX1025; EX1058. And, a POSA would have understood that Alvarez-Gonzalez did effectively treat a PP-active patient with subcutaneous cladribine, as explained above. Specifically, Alvarez-Gonzalez teaches that subcutaneous cladribine “led to effective suppression of inflammatory activity and partial recovery with no short-term safety issues or adverse events.”

EX1009, Abstract.

127. Giovannoni and the general knowledge in the art recognizes a preference for oral dosages forms over parenteral dosage forms. EX1007, 417;

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EX1026, 2:9-11. In fact, Giovannoni teaches such a preference: “parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.” EX1007, 417. Thus, a POSA would have had a reason to substitute oral cladribine for Alvarez-Gonzalez’s subcutaneous cladribine because oral dosage forms were preferable to parenteral forms. A POSA would have also recognized that Alvarez-Gonzalez administered subcutaneous cladribine therapy “off-label” to the patient because of the “lack of any licensed options” (e.g., oral cladribine) available to them at the time, as Merck’s previously disclosed cladribine tablets were not FDA-approved until March 2019 (EX1069). EX1009, 506, 509. Accordingly, Alvarez-Gonzalez’s use of subcutaneous cladribine would not have contradicted a POSA’s general understanding that oral cladribine was preferred over subcutaneous administration. EX1009, 506, 509.

128. As such, a POSA would have been motivated to substitute Alvarez-Gonzalez’s parenteral dosing regimen with Giovannoni’s oral dosing regimen (i.e., dose and administration scheme) because Alvarez-Gonzalez explains that their subcutaneous dosing regimen was based on the “oral 3.5 mg/kg dose used in the pivotal CLARITY MS study” (i.e., Giovannoni’s study). EX1009, 509. Thus, a POSA wanting to substitute Alvarez-Gonzalez’s subcutaneous cladribine with oral

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cladribine would have naturally looked to Giovannoni, since Alvarez-Gonzalez based their own parenteral dosing regimen on Giovannoni's oral dosing regimen.

129. A POSA would have had a reason to utilize Giovannoni's dosing regimen, which orally administers 3.5 mg/kg over 2 years in four treatment courses. A POSA would have found it logical and convenient to use Giovannoni's entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract.

130. Because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni's 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. Thus, a POSA would have had a reason to administer 1.75 mg/kg of cladribine per treatment year with a specific administration schedule, to treat a PP-active patient. Because Alvarez-Gonzalez's parenteral dosing regimen "resembles bio-equivalence" to Giovannoni's dosing regimen, a POSA would have had a reason to maintain Giovannoni's dosing regimen—i.e., specific doses and administration schedule. Based on a POSA's general knowledge of pharmacokinetics, a POSA would have understood that in order to administer oral cladribine that provides a similar

cladribine pharmacokinetic profile (i.e., “resembles bio-equivalence”) to the cladribine pharmacokinetic profile provided by Alvarez-Gonzalez’s dosing regimen, Giovannoni’s dosing schedule would need to be followed. As such, a POSA would have been motivated to treat a PP-active patient, a progressive form of MS that is not ESPMS, with 1.75 mg/kg per treatment year by orally administering cladribine with the same dosing regimen taught by Giovannoni, thus arriving at the method recited in claim 1.

2. A POSA would have had a reasonable expectation of successfully combining Alvarez-Gonzalez and Giovannoni

131. A POSA would have had a reasonable expectation of successfully treating a PP-active patient by orally administering a fixed dose of 1.75 mg/kg per treatment year according to Giovannoni’s oral cladribine dosing regimen. As explained above, Alvarez-Gonzalez reports that three months after treatment with “60 mg s.c. [subcutaneous] over 5 weeks,” the patient’s “EDSS had improved to 7, and MRI head at this time did not show any evidence of new T₂ lesions and no Gd⁺ lesions [enhancing lesions],” both measures that indicate a patient’s positive response to therapy. EX1009, 507; *see also* ¶¶ 35-36, *infra*. Alvarez-Gonzalez explains that its subcutaneous cladribine dosing regimen (i.e., 10 mg s.c. was given on days 1, 2 and 3 in week one and again in week five) “resembles bio-equivalence” to Giovannoni’s oral dosing regimen, meaning Alvarez-Gonzalez’s

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subcutaneous dosing regimen provides a similar cladribine pharmacokinetic profile as Giovannoni's oral dosing regimen *in vivo*. EX1039, generally. As such, a POSA would have reasonably expected Giovannoni's oral dosing regimen to provide a similar cladribine pharmacokinetic profile as Alvarez-Gonzalez's subcutaneous dosing regimen in a PP-active patient, and thus, a similar therapeutic effect. EX1009, 509; EX1039, generally.

132. A POSA would have also reasonably expected to successfully substitute Alvarez-Gonzalez's subcutaneous dosing regimen for an oral dosing regimen, as disclosed by Giovannoni because Giovannoni provides the specific details for its oral dosing regimen—e.g., the timeframe for administering the tablets, the tablet strength, the number of tablets to administer, and the cumulative dose based on bodyweight. EX1007, 417-418, Supplementary Appendix FIG.1. Thus, by administering oral cladribine according to Giovannoni's dosing regimen, a POSA would have reasonably expected a PP-active patient to have a cladribine pharmacokinetic profile, which was shown by Alvarez-Gonzalez to “effective[ly] suppress[] inflammatory activity” in a PP-active patient. Accordingly, a POSA would have reasonably expected Giovannoni's oral cladribine dosing regimen to successfully treat PP-active.

133. In sum, Alvarez-Gonzalez and Giovannoni would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

I. Claims 15 and 16

134. Claim 15 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 16 depends from claim 15 and thus, contains each and every limitation of claims 14 and 15. Claims 15 and 16 further recite, “wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient” and “wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule,” respectively.

135. Giovannoni’s dosing regimen comprises each of the additional dosing regimen elements of claims 15 and 16. As explained above, Giovannoni discloses administering “one or two 10-mg cladribine tablets [i.e., 10- or 20-mg] or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. Also, as explained above, a POSA would have been motivated to treat a PP-active patient by administering oral cladribine per Giovannoni's dosing regimen, which comprises the additional elements of claims 15 and 16, with a reasonable

expectation of success. A POSA would have used Giovannoni's entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract.

136. Accordingly, a POSA would have arrived at the methods of claims 15 and 16 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

J. Claim 18

137. Claim 18 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 18 further recites, "where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis."

138. For the same reasons discussed above for claim 14, a POSA would have been motivated to treat a PP-active patient by orally administering a cumulative dose of 3.5 mg/kg over two years according to Giovannoni's dosing regimen, with a reasonable expectation of success.

139. Accordingly, a POSA would have arrived at the method of claim 18 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

K. Claim 19

140. Claim 19 depends from claim 18, which depends from claim 14, and thus, contains each and every limitation of claims 14 and 18. Claim 19 further recites, “wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.”

141. Giovannoni’s dosing regimen comprises the additional dosing regimen element of claim 19. As explained above, Giovannoni discloses administering “one or two 10-mg cladribine tablets [i.e., 10- or 20-mg] or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. Also, as explained above, a POSA would have been motivated to treat a PP-active patient by administering oral cladribine per Giovannoni's dosing regimen, which comprises the additional elements of claim 19, with a reasonable expectation of success. A POSA would have found it logical and convenient to use Giovannoni’s entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract.

142. Accordingly, a POSA would have arrived at the methods of claim 19 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

L. Claim 20

143. Claim 20 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 20 further recites, “wherein said patient is between 18 and 65 years old.”

144. Both Alvarez-Gonzalez and Giovannoni disclose treating MS patients aged 18-65 years old. Specifically, Alvarez-Gonzalez discloses that the PPMS patient treated exhibited disease onset at the age of 28, was enrolled in a clinical trial five years after disease onset (in 2011), and developed disease activity about four years after enrollment (in 2015), and thus was approximately 38 when administered cladribine. Thus, Alvarez-Gonzalez discloses treating a PP-active patient between 18 and 65 years old as claimed. EX1009, 506-507. And Giovannoni discloses that patients in the 3.5 mg/kg treatment arm ranged from 18-65 years old, as well. EX1007, 419, Table 1. As such, a POSA would have been motivated to treat a PP-active patient between 18 and 65 years old by administering a fixed dose of 1.75 mg/kg per treatment year according to Giovannoni’s oral cladribine dosing regimen, with a reasonable expectation of success.

145. Accordingly, a POSA would have arrived at the method of claim 20 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

M. Claim 24

146. Claim 24 is directed to a “method of treating a patient suffering from a progressive form of Multiple Sclerosis” comprising “orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each.” Claim 24 specifies that “tablets or capsules are administered during a treatment year comprising the following regimen: (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient.” Claim 24 further specifies the number of 10-mg capsules or tablets patients should receive in both months based on patients’ weight—e.g., “wherein patients having a bodyweight ... in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course.”

EX1001, 66:51-67:39.

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147. As explained above for claim 1, a POSA would have been motivated to combine the teachings of Alvarez-Gonzalez and Giovannoni to treat a PP-active patient by administering a fixed dose of 1.75 mg/kg of cladribine per treatment year according to Giovannoni's dosing regimen. Claim 24 differs from claim 1 by:

a) by requiring “administering to said patient tablets or capsules containing about 10 mg of Cladribine ... during a treatment year,”

b) by further specifying that the administration during a “treatment year ... compris[es] the following regimen: (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient,” and

c) by specifying the number of 10-mg capsules or tablets patients should receive in both months based on patients’ weight—e.g., “wherein patients having a bodyweight ... in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course.” EX1001, 66:65-67:39.

148. In addition to the reasons described for claim 1, which I will not reiterate here but which are applicable for claim 24, a POSA would have had a reason to administer 10-mg cladribine tablets during a treatment year comprising the following regimen: (i) a treatment course lasting 2 months, wherein cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a cladribine-free period lasting 10 months wherein no Cladribine is administered. A POSA would have also had a reason to administer the claimed number of 10-mg cladribine tablets based on a patient's weight.

1. Giovannoni teaches administering the claimed oral cladribine dosing regimen

149. A POSA would have understood that Giovannoni discloses each and every limitation of the claimed dosing regimen. Giovannoni reports the results of a "96-week phase 3 trial of a short-course oral [cladribine] tablet therapy in patients with relapsing-remitting multiple sclerosis." EX1007, Abstract. Giovannoni discloses that "[e]ligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo." *Id.*, 417.

(a) Giovannoni teaches "a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20

mg of Cladribine on a treatment week of from 3 to up to 6 days each month”

150. As explained in detail above for claim 14, a POSA would have understood that Giovannoni teaches that some patients in their study (the 3.5 mg/kg treatment group) received a daily dose of 10 or 20 mg of Cladribine (i.e., one or two 10-mg cladribine tablets) for the first 4 or 5 days of a 28-day period starting on day 1 and again at week 5 (i.e., two consecutive months). A POSA would have understood that the “4 or 5 days of a 28-day period,” taught by Giovannoni is encompassed by “from 3 to up to 6 days each month,” recited in claim 24. And a POSA would have understood that two of Giovannoni’s “courses” administered in two consecutive months were equivalent to a “treatment course lasting 2 months,” as recited in claim 27.

151. Thus, Giovannoni expressly discloses a cladribine dosing regimen that constitutes “a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month,” as recited in claim 24.

(b) Giovannoni instructs administering a specific number of 10-mg cladribine tablets to patients based on their weight

152. Giovannoni teaches administering a total of 3.5 mg/kg as four “short courses” (i.e., “one or two 10-mg cladribine tablets ... given once daily for the first

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4 or 5 days of a 28-day period”) to MS patients. EX1007, 417-418. Giovannoni explains that patients in the 3.5 mg/kg cohort received two courses in the “first 48-week treatment period” and an additional two courses during the “second 48-week period.” As discussed above, because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni’s 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen.

153. Giovannoni’s disclosures regarding its 3.5 mg/kg dosing regimen, discussed above, would have also allowed a POSA to use simple mathematical calculations to determine the number of 10-mg cladribine tablets to administer to any patient, based on their bodyweight, in order to provide approximately 1.75 mg/kg of cladribine over a two-month period for that patient (or 0.875 mg/kg each treatment week in the two-month period), as I explain in further detail below.

154. Giovannoni discloses that the average patient weight in the 3.5 mg/kg cohort was 68.1 ± 14.6 kg, or 53.5 kg to 82.7 kg. EX1007, 419, Table 1. A POSA would have been able to determine how many 10-mg cladribine tablets a patient weighing approximately 57 kg (or 126 lbs.) should receive per Giovannoni’s 3.5 mg/kg regimen by the following calculation:

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$$\text{Dose of cladribine needed (in mg)} = 0.875 \frac{\text{mg}}{\text{kg}} \times 57 \text{ kg} = 49.9 \text{ mg}$$

155. With the knowledge that each patient received one or two 10-mg tablets daily for 4 to 5 treatment days, a POSA would have rounded the dose to the nearest 10-mg dose. Since a 49.9 mg dose is about 50 mg, a POSA would have known to administer five 10-mg cladribine tablets to achieve the total cumulative dose (50 mg ÷ 10 mg/tablet = 5 tablets). Thus, in order to administer a cumulative 1.75 mg/kg over a two-month period, a 57 kg patient, who falls within the claimed range of “50 to less than 60 kg,” a POSA would have understood Giovannoni to teach administering “1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course,” as recited in claim 24.

(c) Giovannoni teaches a cladribine-free period of 10 months

156. Giovannoni’s dosing regimen includes a “Cladribine-free period lasting 10 months wherein no Cladribine is administered.” Giovannoni discloses that during the first 48-week period of the study, the 3.5 mg/kg patient cohort received “two courses of cladribine, followed by two courses of placebo” “starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment).” EX1007, 418. A

POSA would have understood that “placebo” meant tablets that did not contain cladribine. EX1067, 3; EX1007, 418. During the second 48-week period, the patients received “two courses of cladribine” “starting at weeks 48 and 52 (8 to 10 days of treatment).” *Id.* Thus, a POSA would have understood that patients in the 3.5 mg/kg cohort did not receive cladribine for 43 weeks, or 10 months, between weeks 5 and 48 of the study. Accordingly, Giovannoni discloses a cladribine dosing regimen that includes “a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient,” as recited in claim 24.

2. A POSA would have been motivated to combine Alvarez-Gonzalez and Giovannoni

157. A POSA would have been motivated to combine the teachings of Alvarez-Gonzalez and Giovannoni to treat a PP-active patient by administering 10-mg cladribine tablets according to Giovannoni’s oral cladribine dosing regimen. And, a POSA would have understood that Alvarez-Gonzalez did, in fact, effectively treat a PP-active patient with subcutaneous cladribine, as explained above. Specifically, Alvarez-Gonzalez teaches that subcutaneous cladribine “led to effective suppression of inflammatory activity and partial recovery with no short-term safety issues or adverse events” in a PP-active patient (i.e., a relapsing PPMS patient). EX1009, Abstract. Alvarez-Gonzalez further reports that the patient “improved to EDSS 7, with no disease activity detected on follow-up MRI,” which

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a POSA would have understood was indicative of a treatment response. EX1009, 509; *See* ¶¶ 35-36, *infra*. Further, Alvarez-Gonzalez’s hypothesizes that a DMT, or anti-inflammatory, immunomodulating treatment, like cladribine would have “a reasonable likelihood of success” in treating PP-active, including because of its demonstrated efficacy in RRMS in the phase III CLARITY trial as well as the “evidence of efficacy” in progressive MS shown in earlier clinical trials. EX1009, 509.

158. For similar reasons, a POSA would have been motivated from the teachings of Alvarez-Gonzalez to treat a patient that had a progressive form of MS that is not ESPMS as covered by claim 1. Specifically, Alvarez-Gonzalez would have taught a POSA to treat PP-active; and, as discussed above, by definition a PP-active patient cannot have ESPMS (since ESPMS is the transition state between RRMS and SPMS, and a PP-active patient never had RRMS in the first place).

159. Giovannoni and the general knowledge in the art recognizes a preference for oral dosages forms over parenteral dosage forms. EX1007, 417; EX1026, 2:9-11. In fact, Giovannoni teaches such a preference: “parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.” EX1007, 417. Thus, a POSA would have had a reason to substitute oral cladribine for Alvarez-Gonzalez’s

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subcutaneous cladribine because oral dosage forms were preferable to parenteral forms. A POSA would have also recognized that Alvarez-Gonzalez administered subcutaneous cladribine therapy “off-label” to the patient because of the “lack of any licensed options” (e.g., oral cladribine) available to them at the time, as I understand that Merck’s previously disclosed cladribine tablets were not FDA-approved until March 2019 (EX1069). EX1009, 506, 509. Accordingly, Alvarez-Gonzalez’s use of subcutaneous cladribine would not have contradicted a POSA’s general understanding that oral cladribine was preferred over subcutaneous administration. EX1009, 506, 509.

160. As such, a POSA would have been motivated to substitute Alvarez-Gonzalez’s subcutaneous dosing regimen with Giovannoni’s oral dosing regimen (i.e., dose and administration scheme) because Alvarez-Gonzalez explains that their subcutaneous dosing regimen was based on the “oral 3.5 mg/kg dose used in the pivotal CLARITY MS study” (i.e., Giovannoni’s study). *Id.*, 509. Thus, a POSA wanting to substitute Alvarez-Gonzalez’s subcutaneous cladribine with oral cladribine would have naturally looked to Giovannoni, since Alvarez-Gonzalez based their own parenteral dosing regimen on Giovannoni’s oral dosing regimen.

161. A POSA would have had a reason to utilize Giovannoni’s dosing regimen, which orally administers 3.5 mg/kg over 2 years in four treatment

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courses. A POSA would have found it logical and convenient to use Giovannoni's entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract. Because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni's 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. Thus, a POSA would have had a reason to administer 1.75 mg/kg of cladribine per treatment year with a specific administration schedule, to treat a PP-active patient. Because Alvarez-Gonzalez's parenteral dosing regimen "resembles bio-equivalence" to Giovannoni's dosing regimen, a POSA would have had a reason to maintain Giovannoni's dosing regimen—i.e., specific doses and administration schedule. A POSA would have understood that in order to administer oral cladribine that provides a similar cladribine pharmacokinetic profile (i.e., "resembles bio-equivalence") to the cladribine pharmacokinetic profile provided by Alvarez-Gonzalez's dosing regimen, Giovannoni's dosing schedule would need to be followed. As such, a POSA would have been motivated to treat a PP-active patient, a progressive form

of MS, with the claimed dosing regimen, as taught by Giovannoni, thus arriving at the method recited in claim 1.

3. A POSA would have had a reasonable expectation of successfully combining Alvarez-Gonzalez and Giovannoni

162. A POSA would have had a reasonable expectation of successfully treating a PP-active patient by orally administering 10 mg cladribine tablets according to Giovannoni's oral cladribine dosing regimen. As explained above, Alvarez-Gonzalez reports that three months after treatment with "60 mg s.c. [subcutaneous] over 5 weeks," the patient's "EDSS had improved to 7, and MRI head at this time did not show any evidence of new T₂ lesions and no Gd⁺ lesions [enhancing lesions]," both measures that indicate a patient's positive response to therapy. EX1009, 507; *see also* ¶¶ 35-36, *infra*. Alvarez-Gonzalez explains that its subcutaneous cladribine dosing regimen (i.e., 10 mg s.c. was given on days 1, 2 and 3 in week one and again in week five) "resembles bio-equivalence" to Giovannoni's oral dosing regimen, meaning Alvarez-Gonzalez's subcutaneous dosing regimen provides a similar cladribine pharmacokinetic profile as Giovannoni's oral dosing regimen *in vivo*. EX1039, generally. As such, a POSA would have reasonably expected Giovannoni's oral dosing regimen to provide a similar cladribine pharmacokinetic profile as Alvarez-Gonzalez's subcutaneous

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dosing regimen in a PP-active patient, and thus, a similar therapeutic effect.

EX1009, 509; EX1039, generally.

163. A POSA would have also reasonably expected to successfully substitute Alvarez-Gonzalez's subcutaneous dosing regimen for an oral dosing regimen, as disclosed by Giovannoni because Giovannoni provides the specific details for its oral dosing regimen—e.g., the timeframe for administering the tablets, the tablet strength, the number of tablets to administer, and the cumulative dose based on bodyweight. EX1007, 417-418, Supplementary Appendix FIG.1. Thus, by administering oral cladribine according to Giovannoni's dosing regimen, a POSA would have reasonably expected a PP-active patient to have a cladribine pharmacokinetic profile, which was shown by Alvarez-Gonzalez to “effective[ly] suppress[] inflammatory activity” in a PP-active patient. Accordingly, a POSA would have reasonably expected Giovannoni's oral cladribine dosing regimen to successfully treat PP-active.

164. In sum, Alvarez-Gonzalez and Giovannoni would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

N. Claim 25

165. Claim 25 depends from claim 24 and thus, contains each and every limitation of claim 24. Claim 25 further recites, “wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.”

166. Giovannoni’s dosing regimen comprises the additional dosing elements of claim 25. A POSA would have understood that Giovannoni taught an oral cladribine dosing regimen that comprises administering cladribine in two identical treatment years. Giovannoni teaches that “[i]n the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group,” and [i]n the second 48-week period, both cladribine groups received two courses of cladribine” “starting at weeks 48 and 52 (8 to 10 days of treatment).” EX1007, 418. As discussed above, because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni’s 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. As such, Giovannoni would have taught a POSA to orally administer a cladribine dosing regimen that “comprises at

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least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.” A POSA would have found it logical and convenient to use Giovannoni’s entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract.

167. Accordingly, a POSA would have arrived at the method of claim 25 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

O. Claim 26

168. Claim 26 depends from claim 25, which depends from claim 24, and thus, contains each and every limitation of claims 24 and 25. Claim 26 further recites, “wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.”

169. As explained above for claim 25, Giovannoni discloses a cladribine dosing regimen that “comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.” Specifically, Giovannoni discloses administering oral cladribine on day 1, week 5, week 48, and week 52. A POSA would have understood that the treatment

courses of year 1 (i.e., on day 1 and week 5) were “directly adjacent” to the treatment courses administered in year 2 (i.e., weeks 48 and 52). As such, a POSA would have understood that Giovannoni’s dosing regimen includes an “additional treatment year [that] is directly adjacent to said treatment year.” And, as discussed above, a POSA would have been motivated to treat a PP-active patient by administering oral cladribine per Giovannoni’s dosing regimen, which comprises the additional elements of claim 26, with a reasonable expectation of success. A POSA would have found it logical and convenient to use Giovannoni’s entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract.

170. Accordingly, a POSA would have arrived at the method of claim 26 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

P. Claim 27

171. Claim 27 is directed to a “method of treating a patient suffering from a progressive form of Multiple Sclerosis” comprising “orally administering to said patient tablets or capsules containing about 10-mg of Cladribine each.” Claim 27 specifies that “the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary

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Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis” and that “the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” Claim 27 also specifies that “tablets or capsules are administered during a treatment year comprising the following regimen: (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient; (iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient.” Claim 27 further specifies the number of 10-mg capsules or tablets patients should receive in both months based on patients’ weight—e.g., “wherein patients having a bodyweight in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course.” EX1001, 66:51-67:39.

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172. As explained above for claim 1, a POSA would have been motivated to combine the teachings of Alvarez-Gonzalez and Giovannoni to treat a PP-active patient by administering Giovannoni's oral cladribine dosing regimen. As I explained above for claim 24, a POSA, would have been motivated to administer Giovannoni's oral cladribine tablets according to Giovannoni's dosing regimen, which Alvarez-Gonzalez teaches "resembles bioequivalence" to its subcutaneous dosing regimen, to treat patients with active PPMS. A POSA would have understood Giovannoni's dosing regimen to comprise "(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient" in which "all patients within a weight range received the same number of tablets."

173. Claim 27 only differs from claims 1 and 24 in that claim 27 recites a second treatment course following the first cladribine-free period, wherein the two treatment courses are identical, followed by a second cladribine-free period. Specifically, claim 27 differs from claims 1 and 24 by requiring a dosing regimen that comprises the following regimen:

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- (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;
- (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;
- (iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and
- (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient.

EX1001, 67:61-68:7.

174. In addition to the reasons described for claims 1 and 24, which I will not reiterate here but which are applicable for claim 27, a POSA would have had a reason to administer a second cladribine treatment course lasting 2 months, followed by a second cladribine-free period lasting 10 months, as taught by Giovannoni.

175. As explained above, Giovannoni discloses administering 3.5 mg/kg of cladribine in four “short courses” over two treatment years. EX1007, 417-418. In the first treatment year, two courses were administered over two consecutive months (a first treatment course) followed by a first cladribine-free period of 10

months. *Id.*; see also ¶ 110, *infra*. A POSA would have understood that two of Giovannoni's "courses" administered over two consecutive months were equivalent to a "treatment course lasting 2 months," as recited in claim 27. A POSA would have also understood that patients in the 3.5 mg/kg cohort did not receive cladribine for 43 weeks, or 10 months, between weeks 5 and 48 of the study. *Id.*; see also ¶ 110, *infra*.

176. Giovannoni expressly discloses administering a second treatment course after the first 10-month cladribine-free period. Specifically, Giovannoni teaches that "[i]n the second 48-week period, both cladribine groups [3.5 mg/kg and 5.25 mg/kg] received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment)." EX1007, 418. Because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni's 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. A POSA would have also understood the "two courses" administered in the second 48-week refers to the same treatment courses administered in the first 48-week period because Giovannoni makes no mention of the treatment courses being

different between the first and second 48-week periods. Thus, a POSA would have understood Giovannoni to administer cladribine with the same dosing regimen in both treatment years. As such, Giovannoni discloses a dosing regimen comprising “a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month,” as recited in claim 27.

177. Giovannoni’s dosing regimen includes a “second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient.” Giovannoni discloses that during the second 48-week period of the study, patients received “two courses of cladribine” “starting at weeks 48 and 52 (8 to 10 days of treatment).” *Id.* In other words, a POSA would have understood that patients did not receive cladribine for 44 weeks, or about 10 months, between weeks 52 and 96 of the study. Accordingly, Giovannoni discloses a cladribine dosing regimen that includes “a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient,” as recited in claim 27.

1. A POSA would have been motivated to combine Alvarez-Gonzalez and Giovannoni

178. A POSA would have been motivated to combine the teachings of Alvarez-Gonzalez and Giovannoni to treat a PP-active patient with disease activity by administering 10-mg cladribine tablets according to Giovannoni's oral

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cladribine dosing regimen. Alvarez-Gonzalez's hypothesizes that a DMT, or anti-inflammatory, immunomodulating treatment, like cladribine would have "a reasonable likelihood of success" in treating PP-active, including because of its demonstrated efficacy in RRMS in the phase III CLARITY trial as well as the "evidence of efficacy" in progressive MS shown in earlier clinical trials. EX1009, 509. As explained above, a POSA would have understood from Alvarez-Gonzalez that subcutaneous cladribine effectively treated a PP-active patient. Specifically, Alvarez-Gonzalez teaches that subcutaneous cladribine "led to effective suppression of inflammatory activity and partial recovery with no short-term safety issues or adverse events." EX1009, Abstract.

179. For similar reasons, a POSA would have been motivated from the teachings of Alvarez-Gonzalez to treat a patient that had a progressive form of MS that is not ESPMS as covered by claim 1. Specifically, Alvarez-Gonzalez would have taught a POSA to treat PP-active; and, as discussed above, by definition a PP-active patient cannot have ESPMS (since ESPMS is the transition state between RRMS and SPMS, and a PP-active patient never had RRMS in the first place).

180. Giovannoni and the general knowledge in the art recognizes a preference for oral dosages forms over parenteral dosage forms. EX1007, 417; EX1026, 2:9-11. In fact, Giovannoni teaches such a preference: "parenteral

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administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.” EX1007, 417. Thus, a POSA would have had a reason to substitute oral cladribine for Alvarez-Gonzalez’s subcutaneous cladribine because oral dosage forms were preferable to parenteral forms. A POSA would have also recognized that Alvarez-Gonzalez administered subcutaneous cladribine therapy “off-label” to the patient because of the “lack of any licensed options” (e.g., oral cladribine) available to them at the time, as I understand that Merck’s previously disclosed cladribine tablets were not FDA-approved until March 2019 (EX1069). EX1009, 506, 509. Accordingly, Alvarez-Gonzalez’s use of subcutaneous cladribine would not have contradicted a POSA’s general understanding that oral cladribine was preferred over subcutaneous administration. EX1009, 506, 509.

181. As such, a POSA would have been motivated to modify Alvarez-Gonzalez’s parenteral dosing regimen with Giovannoni’s oral dosing regimen (i.e., dose and administration scheme) because Alvarez-Gonzalez explains that their subcutaneous dosing regimen was based on the “oral 3.5 mg/kg dose used in the pivotal CLARITY MS study” (i.e., Giovannoni’s study). EX1009, 509. Thus, a POSA wanting to modify Alvarez-Gonzalez’s dosing regimen with oral cladribine

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would have naturally looked to Giovannoni, since Alvarez-Gonzalez based their own parenteral dosing regimen on Giovannoni's oral dosing regimen.

182. A POSA would have had a reason to utilize Giovannoni's dosing regimen, which orally administers 3.5 mg/kg over 2 years in four treatment courses. A POSA would have found it logical and convenient to use Giovannoni's entire 2-year-long dosing regimen because it was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract. A POSA would have understood from Giovannoni that this dosing regimen was found in a large, phase III trial to effectively treat disease activity in RRMS, and was just as effective as the other, higher 5.25 mg/kg dosing regimen used in CLARITY.

183. Because Giovannoni does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Giovannoni's 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. Thus, a POSA would have had a reason to administer 1.75 mg/kg of cladribine per treatment year with a specific administration schedule, to treat a PP-active patient. Because Alvarez-Gonzalez's parenteral dosing regimen "resembles bioequivalence" to Giovannoni's dosing regimen, a POSA would have had a reason to maintain Giovannoni's

dosing regimen—i.e., specific doses and administration schedule. A POSA would have understood that in order to administer oral cladribine that provides a similar cladribine pharmacokinetic profile (i.e., “resembles bioequivalence”) to the cladribine pharmacokinetic profile provided by Alvarez-Gonzalez’s dosing regimen, Giovannoni’s dosing schedule would need to be followed. As such, a POSA would have been motivated to treat a PP-active patient, a progressive form of MS that is not ESPMS, with the claimed dosing regimen, as taught by Giovannoni, thus arriving at the method recited in claim 1.

2. A POSA would have had a reasonable expectation of successfully combining Alvarez-Gonzalez and Giovannoni

184. A POSA would have had a reasonable expectation of successfully treating a PP-active patient by orally administering 10 mg cladribine tablets according to Giovannoni’s oral cladribine dosing regimen. As explained above, Alvarez-Gonzalez reports that three months after treatment with “60 mg s.c. [subcutaneous] over 5 weeks,” the patient’s “EDSS had improved to 7, and MRI head at this time did not show any evidence of new T₂ lesions and no Gd⁺ lesions [enhancing lesions],” both measures that indicate a patient’s positive response to therapy. EX1009, 507; *see also* ¶¶ 35-36, *infra*. Alvarez-Gonzalez explains that its subcutaneous cladribine dosing regimen (i.e., 10 mg s.c. was given on days 1, 2 and 3 in week one and again in week five) “resembles bio-equivalence” to

Giovannoni's oral dosing regimen, meaning Alvarez-Gonzalez's subcutaneous dosing regimen provides a similar cladribine pharmacokinetic profile as Giovannoni's oral dosing regimen *in vivo*. EX1039, generally. As such, a POSA would have reasonably expected Giovannoni's oral dosing regimen to provide a similar cladribine pharmacokinetic profile as Alvarez-Gonzalez's subcutaneous dosing regimen in a PP-active patient, and thus, a similar therapeutic effect. EX1009, 509; EX1039, generally.

185. A POSA would have also reasonably expected to successfully substitute Alvarez-Gonzalez's subcutaneous dosing regimen for an oral dosing regimen, as disclosed by Giovannoni because Giovannoni provides the specific details for its oral dosing regimen—e.g., the timeframe for administering the tablets, the tablet strength, the number of tablets to administer, and the cumulative dose based on bodyweight. EX1007, 417-418, Supplementary Appendix FIG.1. Thus, by administering oral cladribine according to Giovannoni's dosing regimen, a POSA would have reasonably expected a PP-active patient to have a cladribine pharmacokinetic profile, which was shown by Alvarez-Gonzalez to “effective[ly] suppress[] inflammatory activity” in a PP-active patient. Accordingly, a POSA would have reasonably expected Giovannoni's oral cladribine dosing regimen to successfully treat PP-active.

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186. In sum, Alvarez-Gonzalez and Giovannoni would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

Q. Claim 34

187. Claim 34 depends from claim 27 and thus, contains each and every limitation of claim 27. Claim 34 further recites, “wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis,” respectively.

188. For the same reasons discussed above for claim 27, a POSA would have been motivated to treat a PP-active patient by orally 10 mg tablets of cladribine according to Giovannoni’s oral cladribine dosing regimen, with a reasonable expectation of success. And a POSA would have easily been able to determine the total number of cladribine tablets to administer in each treatment week to a patient depending on their body weight.

189. Accordingly, a POSA would have arrived at the method of claim 34 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

XI. Claims 11, 23, and 33 would have been obvious over Alvarez-Gonzalez, Giovannoni, and Montalban

190. As shown in Appendix B and as I explain in detail below, Alvarez-Gonzalez, Giovannoni, and Montalban together disclose every limitation of claims 11, 23, and 33, and a POSA would have been motivated to combine their teachings with a reasonable expectation of success to arrive at the method recited in claims 11, 23, and 33. Claim 11 depends from claim 1, claim 23 depends from claim 14, and claim 33 depends from claim 27. For the reasons explained above, claims 1, 14, and 27 would have been obvious to a POSA in light of Alvarez-Gonzalez and Giovannoni. I incorporate my analysis for claims 1, 14, and 27 herein. Claims 11, 23, and 33 further recite, “wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient,” “wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses,” and “wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4,” respectively. In summary, claims 11, 23, and 33 specify that after patients have completed 2 years of treatment, no further cladribine is administered for “at least

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one year (claim 11),” for a “subsequent 1 or 2 years (claim 23),” or for the “subsequent 3 or 4 years (claim 33)”.

191. As explained above for claims 1, 14, and 27, would have been motivated to substitute Alvarez-Gonzalez’s subcutaneous cladribine with Giovannoni’s oral cladribine dosed at 1.75 mg/kg/year (cumulative dose of 3.5 mg/kg), administered in two treatment years (one course/year), to treat PPMS, with a reasonable expectation of success. EX1009, 509, 510; EX1007, 416, 417-418, Supplementary FIG. 1. Also, as explained above, Giovannoni discloses an oral cladribine dosing regimen implemented in a phase III clinical study, CLARITY, in which 3.5 mg/kg of cladribine was orally administered to MS patients over two years. Montalban explains that in a CLARITY Extension study, “the clinical benefits of 2-years of cladribine treatment (3.5mg/kg bodyweight) were maintained in the study for 4 years or more without further active treatment.” EX1006, 1.

192. A POSA would have understood from Montalban 2016 that the patients in the CLARITY trial continued to see a beneficial effect of 3.5 mg/kg of cladribine for “4 years or more” (i.e., at least one or two years) after the study, during which no cladribine was administered. Thus, a POSA would have been motivated to refrain from administering cladribine for at least one or two years to a patient who had completed two years of treatment because Montalban teaches that

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Giovannoni's 3.5 mg/kg regimen maintains its efficacy against disease activity for at least that long.

193. Because the general knowledge in the art also recognized cladribine was associated with some toxicity (e.g., Stelmasiak reports that in an earlier cladribine study, "dangerous marrow depression were [sic] reported in some multiple sclerosis patients," EX1035, 7), a POSA would have been motivated to provide cladribine-free periods to reduce toxicity. In light of Montalban's teachings, a POSA would have understood that patients could take an extended break from cladribine therapy, thus reducing its toxicity, while benefiting from cladribine's therapeutic effects. And a POSA would have reasonably expected to successfully treat patients for two years with cladribine, followed by one or two cladribine-free years, because Montalban expressly teaches that such a course of therapy was effective. EX1006, 1.

194. Accordingly, a POSA would have arrived at the methods of claims 11, 23, and 33 in light of Alvarez-Gonzalez and Giovannoni, with a reasonable expectation of success.

XII. Claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, and 34 would have been obvious over Clinicaltrials.gov, Schreiber, and Giovannoni

A. Claim 1

195. Claim 1 is directed to a “method of treating a progressive form of Multiple Sclerosis” comprising the “orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg.” Claim 1 specifies that “the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis” and that “the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” EX1001, 64:45-56.

196. As shown in Appendix C and as I explain in detail below, Clinicaltrials.gov, Schreiber, and Montalban together disclose every limitation of claim 1, and a POSA would have been motivated to combine their teachings with a reasonable expectation of success to arrive at the method of treatment recited in claim 1. Thus, claim 1 would have been obvious to a POSA over the combination of Clinicaltrials.gov, Schreiber, and Montalban before November 24, 2017.

**1. Clinicaltrials.gov would have taught a POSA to treat a
progressive form of multiple sclerosis with oral cladribine
that is not ESPMS**

197. A POSA would have understood that Clinicaltrials.gov teach treating a fully transitioned SPMS-active patient, a progressive form of MS, using cladribine. The regimen taught in Clinicaltrials.gov was designed to “evaluated the safety, tolerability and effectiveness of oral cladribine” in patients “who have experienced at least one relapse while taking IFN-beta therapy within 48 weeks prior to Screening, irrespective of disability progression,” including “[s]econdary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses.” *Id.* The eligibility criteria for the study – i.e., the guidelines to be used to determine what types of patients should be administered the cladribine treatment to be studied – (a) includes patients with “definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses” (b) but excludes patients with “PPMS [] or SPMS without relapses.” *Id.* A POSA would have understood from the general knowledge in the art that relapses were an indicator of disease activity. *See* Section VI.A, *infra*. As such, a POSA would have understood Clinicaltrials.gov broadly teaches treating patients who have forms of

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MS that: (a) exhibit relapses (or activity) and (b) that are not “PPMS [] or SPMS without relapses.” EX1005, 11.

198. Thus, Clinicaltrials.gov would have taught a POSA that RRMS patients, ESPMS patients, and fully transitioned SPMS patients may be treated with the cladribine therapy to be studied in the trial so long as they also exhibited activity. In other words, Clinicaltrials.gov would have taught a POSA to treat fully transitioned SPMS-active patients. As explained above, the term “a progressive form of [MS]” should be construed as encompassing SPMS-active. See ¶¶ 75-76.

199. Accordingly, Clinicaltrials.gov would have taught a POSA to treat an SPMS-active patient using cladribine, which falls under the scope of claim 1 as understood by a POSA at the time of the invention.

200. A POSA would have understood Clinicaltrials.gov to also teach treating of a progressive form of MS (namely, SPMS-active) that “does not include Early Secondary Progressive Multiple Sclerosis (ESPMS),” as also recited by claim 1. As explained above, the eligibility criteria for the ONWARD trial would have taught a POSA to administer the disclosed cladribine dosing regimen to treat a patient with any of RRMS, ESPMS, or SPMS, so long as that patient had disease activity. Thus, a POSA reviewing the teachings of Clinicaltrials.gov would have understood the disclosed dosing regimen may be used to treat an SPMS-active

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patient who did not have the distinct ESPMS form. For example, Clinicaltrials.gov's disclosure would have motivated a POSA to use the disclosed cladribine dosing regimen to treat a patient who had fully transitioned from RRMS to SPMS (and thus did not by definition have the distinct, transitional ESPMS form, but instead had SPMS and not ESPMS) so long as that patient had disease activity.

201. I also note that the '919 patent's description of the patients to be included in the ONWARD trial is effectively identical to Clinicaltrials.gov's (e.g., both Clinicaltrials.gov and the '919 patent teach the treatment of patients with both relapsing and secondary progressive forms of MS); thus, like Clinicaltrials.gov, the '919 patent specification also teaches a POSA that the claimed cladribine dosing regimen may be used to treat patients with any of RRMS, ESPMS, or SPMS so long as they had ongoing disease activity. *Compare* EX1005, 11 with EX1001, 3:25-35, 54:33-62, 55:18-24. Accordingly, I understand that the '919 patent claims simply elect the treatment of a progressive form of MS that is not ESPMS. In the same way, Clinicaltrials.gov would have taught a POSA to elect to treat an SPMS patient (namely SPMS-active) who does not have ESPMS, as discussed above.

202. Accordingly, a POSA would have understood Clinicaltrials.gov to teach treating "a progressive form of multiple sclerosis," such as SPMS, with oral

cladribine, “wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS),” as recited in claim 1.

2. Clinicaltrials.gov and Schreiber both teach “orally administering” a “fixed dose” of cladribine “in a range of 1.5 mg/kg to 4.0 mg/kg” “per patient, per body weight and per treatment year”

203. A POSA would have understood that Clinicaltrials.gov teaches administering a “fixed dose” of cladribine “in a range of 1.5 mg/kg to 4.0 mg/kg” “per patient, per body weight and per treatment year.” Clinicaltrials.gov discloses administering “cladribine tablets orally as [a] cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Weeks 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. A POSA would have understood that a dose of 0.875 mg/kg in Weeks 1, 5, 48, and 52 was equivalent to a dose of 1.75 mg/kg in the first 48-week treatment period (i.e., year 1) and another 1.75 mg/kg in the second 48-week treatment period (i.e., year 2). In other words, a POSA would have understood that the patients received a “fixed dose” of 1.75 mg of cladribine “per patient, per body weight and per treatment year,” which is encompassed by the claimed range of “1.5 mg/kg to 4.0 mg/kg” recited in claim 1.

204. Schreiber also discloses the implementation of this exact same dosing regimen that is the same as the dosing regimen recited in claim 1, using 10-mg

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tablets. Specifically, Schreiber discloses the oral cladribine dosing regimen used in the CLARITY study, which, based on a simple comparison with the disclosed dosing regimen of Clinicaltrials.gov (e.g., each disclose the use of cladribine tablets administered in the same 3.5 mg/kg cumulative dosage over the 96-week treatment period, and each disclose the exact same timing for administration of the cladribine tablets)⁴, a POSA would have understood was the same oral cladribine dosing regimen disclosed in Clinicaltrials.gov. *Compare* EX1008, 320 with EX1005, 11. Schreiber also specifies, “[e]ach course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4-5 days of a 28-day period.” EX1008, 320. Schreiber concludes that “[t]reatment with cladribine tablets significantly reduced the annual relapse rates,” and cladribine reduced active lesions detected on MRI. EX1008, 320, 324, 326.

⁴ Specifically, Schreiber teaches that during the phase III, placebo-controlled CLARITY study, MS patients were assigned to receive “one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year).” EX1008, 320.

**3. A POSA would have been motivated to combine
Clinicaltrials.gov, Schreiber, and Montalban**

205. A POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a fully transitioned SPMS-active patient by orally administering a fixed dose of 1.75 mg/kg of cladribine per treatment year. The disclosures of Clinicaltrials.gov would have given a POSA a reason to treat a patient who had fully transitioned from RRMS to SPMS (i.e., an SPMS-active patient), and thus, by definition, did not have ESPMS. Clinicaltrials.gov discloses treating a SPMS patient with “superimposed relapses.” EX1005, 12. As I explain above, a POSA would have understood relapses to be an indicator of disease activity. *See* Section VI.A, *infra*. Also, as explained above, the eligibility criteria for the ONWARD trial would have taught a POSA to administer the disclosed cladribine dosing regimen to treat a patient with any of RRMS, ESPMS, or SPMS, so long as that patient had disease activity. As such, a POSA would have also had a reason to orally administer 1.75 mg/kg of per treatment year to a SPMS-active patient because Clinicaltrials.gov expressly teaches administering the same dose to SPMS patients with disease activity.

206. Moreover, the Montalban reference would have confirmed to a POSA that the cladribine dosing regimen disclosed in Clinicaltrials.gov (which includes a fixed dose per patient per bodyweight of 1.75 mg/kg) would have in fact treated

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disease activity in SPMS-active patients, and thus would have been further motivated to treat an SPMS-active patient with Clinicaltrials.gov's dosing regimen. Specifically, a POSA would have understood Clinicaltrials.gov disclosed the treatment regimen to be used in the ONWARD trial, and would have further understood that Montalban discloses the actual results of that same trial, namely that: (a) the "mean number of qualifying relapses on study was lower (0.23) in patients treated with cladribine 3.5mg/kg plus IFN- β (N=124) vs. patients who received placebo plus IFN- β (0.56, N=48); (b) the "respective ARRs [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45)"; (c) the study results demonstrate that "[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse (P<0.001)"; and finally, (d) "[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits."

Id. Further, the "The mean numbers of new T1-Gd+, active T2 and CUA lesions/patient/scan were reduced in the combined treatment arm Thus, a POSA would have understood that the cladribine treatment disclosed in Clinicaltrials.gov would indeed be effective in treating disease activity, including in patients with SPMS-active. *Id.*

207. Finally a POSA would have recognized that Clinicaltrials.gov and Montalban were both silent regarding the specific strength of the cladribine tablets to use in Clinicaltrials.gov's regimen to achieve the disclosed 1.75 mg/kg/year dose of cladribine. A POSA would have thus recognized the need to determine the specific tablet strength to administer to the patient to achieve the 1.75 mg/kg/year dose of cladribine. Specifically, a POSA would have been motivated to use the 10-mg tablets disclosed in Schreiber because (as discussed above), a POSA would have understood that the 10-mg tablets disclosed in Schreiber were used in a dosing regimen that was identical to the dosing regimen disclosed by Clinicaltrials.gov, and were further described by Schreiber as providing a "very convenient short course" dosing regimen. EX1008, 324.

208. Accordingly, in light of the teachings of Clinicaltrials.gov, Montalban, and Schreiber, a POSA would have been motivated to treat a SPMS-active patient, a progressive form of MS, by orally administering a fixed dose of 1.75 mg/kg per treatment year.

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

209. A POSA would have had a reasonable expectation of successfully treating a SPMS-active patient by orally administering a fixed dose of 1.75 mg/kg per treatment year with Schreiber's 10 mg tablets. As explained above, Montalban

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reports the results of the ONWARD clinical trial, which orally administered 1.75 mg/kg of cladribine per treatment year to patients with “relapsing forms of MS,” including SPMS-active patients. EX1006, 1. Specifically, Montalban reports that the “[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)” and the “respective ARRs [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45).” *Id.* Montalban concludes that “[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits.” *Id.*

210. A POSA would have understood that a reduction in the number of relapses was a measure of a positive response to treatment. *See* ¶ 49, *infra*. Thus, a POSA would have reasonably expected to treat patients who had fully transitioned from RRMS to SPMS (i.e., SPMS-active patients), and thus, by definition, did not have ESPMS, by orally administering a fixed dose of 1.75 mg/kg of cladribine per treatment year, as taught by Clinicaltrials.gov, because Montalban expressly teaches that such treatment was successful in treating such patients. This reasonable expectation of success was confirmed by the general knowledge in the art, as reported by Schreiber. EX1008, 320, 324. Schreiber reported that early

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cladribine trials in progressive MS, e.g., by Sipe and Rice, demonstrated that active lesions “were markedly reduced” in “cladribine-treated groups,” i.e., cladribine treated disease activity in progressive MS. EX1008, 320.

211. Finally, a POSA would have had a reasonable expectation of success in using the 10-mg tablets disclosed by Schreiber to implement Clinicaltrials.gov’s dosing regimen to treat SPMS-active. Specifically, Schreiber disclosed that 10-mg cladribine tablets were given once daily in the same dosing regimen as disclosed in Clinicaltrials.gov (as discussed above) and provided a “very convenient” dosing regimen. EX1008, 320, 324. And Schreiber reports that “[t]reatment with cladribine tablets significantly reduced the annual relapse rates,” and cladribine reduced active lesions detected on MRI. EX1008, 320, 324, 326. Thus, a POSA with a high level of skill in treating MS patients would have easily followed Schreiber’s teachings to utilize a 10-mg cladribine tablet when administering Clinicaltrials.gov’s dosing regimen to a SPMS-active patient.

212. In sum, the teachings of Clinicaltrials.gov, Montalban, and Schreiber would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

B. Claim 2

213. Claim 2 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 2 further recites, “wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg.”

214. As explained above, a POSA would have been motivated to treat a SPMS-active patient by orally administering fixed dose of 1.75 mg/kg/year of cladribine with Schreiber’s 10-mg tablets, with a reasonable expectation of success. A POSA would have found it logical and convenient to use Clinicaltrial.gov’s entire 2-year-long dosing regimen because it was specifically designed and successfully shown to treat SPMS-active. EX1005, 10; EX1006, 1. Thus, a POSA would have been motivated to treat a SPMS-active patient by administering a fixed dose of 1.75 mg/kg of oral cladribine according to Clinicaltrials.gov's dosing regimen, with a reasonable expectation of success.

215. Accordingly, a POSA would have arrived at the method of claim 2 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

C. Claim 3

216. Claim 3 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 3 further recites, “wherein said progressive form of

multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.”

217. For the same reasons discussed above for claim 1, a POSA would have been motivated to treat a SPMS-active patient by orally administering fixed dose of 1.75 mg/kg/year of cladribine with Schreiber’s 10-mg tablets, with a reasonable expectation of success.

218. Accordingly, a POSA would have arrived at the method of claim 3 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

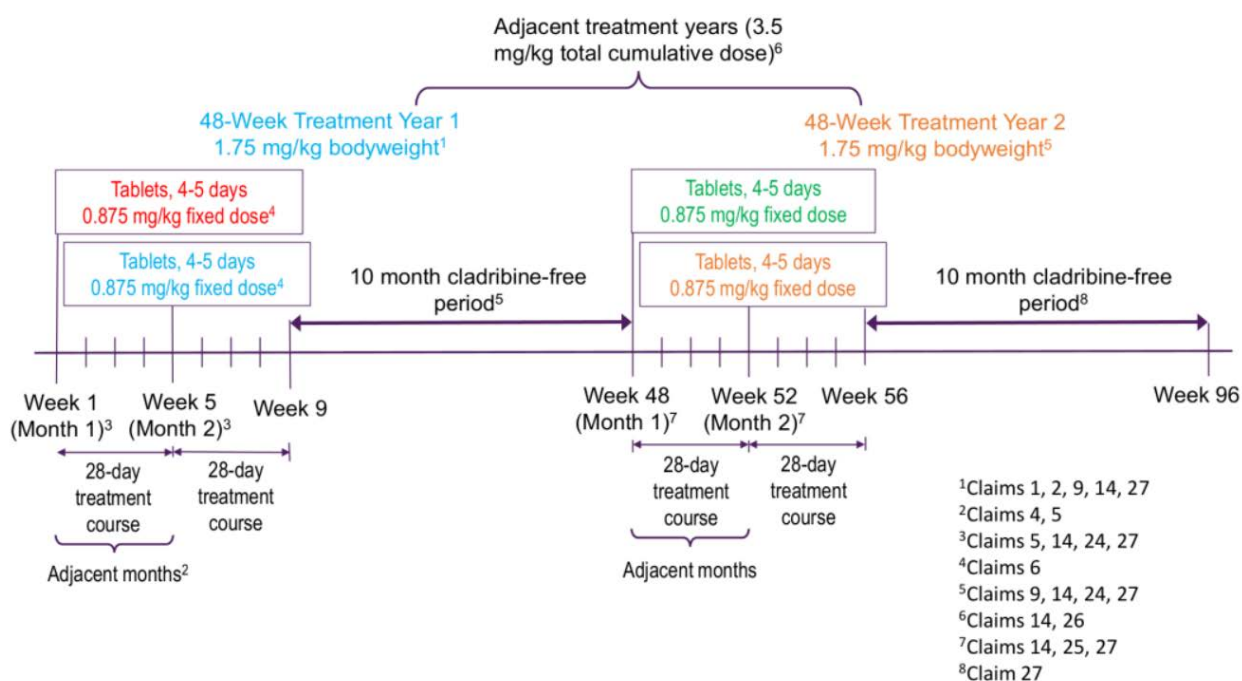
D. Claims 4-6

219. Claim 4 depends from claim 1 and thus, contain each and every limitation of claim 1. Claim 5 depends from claim 4 and thus, contains each and every limitation of claims 1 and 4. Claim 6 depends from claim 5 and thus, contains each and every limitation of claims 1, 4, and 5. Claim 4 further recites, “wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.” Claims 5 and 6 further recite “wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months” and “wherein

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said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks,” respectively.

220. Clinicaltrials.gov’s dosing regimen comprises each of the additional dosing regimen elements of claims 4-6. As explained above, Clinicaltrials.gov discloses administering “cladribine tablets orally as [a] cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Weeks 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. I have prepared the following graphic to demonstrate how a POSA would have understood how Clinicaltrials.gov’s 2-year dosing regimen corresponds to the claimed methods:



Schematic 4.

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A POSA would have understood that weeks 1 and 5 and weeks 48 and 52 were “two adjacent months within [a] treatment year.” Also, as explained above, a POSA would have been motivated to treat a SPMS-active patient by orally administering fixed dose of 1.75 mg/kg/year of cladribine with Schreiber’s 10-mg tablets, which comprises the additional elements of claims 4-6, with a reasonable expectation of success. A POSA would have found it logical and convenient to use Clinicaltrial.gov’s entire 2-year-long dosing regimen because it was specifically designed and successfully shown to treat SPMS-active. EX1005, 10; EX1006, 1.

221. Accordingly, a POSA would have arrived at the method of claims 4-6 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

E. Claim 8

222. Claim 8 depends from claim 1 and thus, contain each and every limitation of claim 36. Claim 8 further recites “wherein each treatment year comprises: (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.

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223. Clinicaltrials.gov's dosing regimen comprises each of the additional dosing regimen elements of claim 8. As explained above, Clinicaltrials.gov discloses administering "cladribine tablets orally as [a] cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Weeks 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks." EX1005, 11. Clinicaltrials.gov does not disclose what strength the administered cladribine tablets were. However, a POSA would have looked to Schreiber for the cladribine tablet strength (i.e., 10 mg) because it provides a review of oral cladribine dosing regimens. Specifically, Schreiber discloses that during the CLARITY clinical trial, MS patients were assigned to receive "one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year)," wherein "[e]ach course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4-5 days of a 28-day period." EX1008, 320. A POSA would have found it logical and convenient to use Clinicaltrial.gov's entire 2-year-long dosing regimen because it was specifically designed and successfully shown to treat SPMS-active. EX1005, 10; EX1006, 1.

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224. A POSA would have recognized that Schreiber’s dosing regimen was the same as Clinicaltrials.gov. A POSA would have had a reasonable expectation of successfully using Schreiber’s 10-mg tablets in Clinicaltrials.gov dosing regimen because Schreiber teaches that its dosing regimen “significantly reduced the annual relapse rates” and patients had “fewer lesions per patient per scan for: T1 gadolinium-enhancing lesions (mean 0.12 and 0.11 vs 0.91), active T2 lesions (mean 0.38 and 0.33 vs 1.43); and combined unique lesions (mean 0.43 and 0.38 vs 1.72).” EX1008, 320. A POSA would have understood that reduction in both relapses and MRI lesions constituted a positive treatment response. See ¶¶ 36, 49, *infra*. Thus, a POSA with a high level of skill in treating MS patients would have easily followed Schreiber’s teachings to utilize a 10-mg cladribine tablet when administering Clinicaltrials.gov’s dosing regimen to a SPMS-active patient.

225. Accordingly, a POSA would have arrived at the method of claim 8 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

F. Claim 9

226. Claim 9 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 9 further recites “wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive

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Multiple Sclerosis, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.”

227. As explained above, a POSA would have been motivated to treat a SPMS-active patient by administering oral cladribine according to Clinicaltrials.gov’s dosing regimen, with a reasonable expectation of success. Also, as explained above, Clinicaltrials.gov’s oral cladribine dosing regimen comprises administering a fixed dose of 1.75 mg/kg per year for two years. A POSA would have found it logical and convenient to use Clinicaltrial.gov’s entire 2-year-long dosing regimen because it was specifically designed and successfully shown to treat SPMS-active. EX1005, 10; EX1006, 1. Thus, a POSA would have been motivated to treat a SPMS-active patient with 1.75 mg/kg per treatment year for at least two treatment years, with a reasonable expectation of success.

228. Accordingly, a POSA would have arrived at the method of claim 9 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

G. Claim 11

229. Claim 11 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 11 further recites, “wherein orally administering

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Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient.”

230. As explained above, both Clinicaltrials.gov’s and Schreiber’s dosing regimens comprise administering oral cladribine for two treatment years. Schreiber further explains that in a CLARITY Extension study, over half of the patients enrolled in the CLARITY study “continued in the 96-week, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIIb extension study” in which “patients originally treated with cladribine tablets [in the CLARITY study] will be randomized to either cladribine tablets 3.5 mg/kg or placebo.” *Id.*, 321. In other words, some patients who received two years of cladribine treatment received placebo for another 96-week, meaning they did not receive additional cladribine therapy for at least 2 years. Montalban reports that “[i]n CLARITY Extension, the clinical benefits of 2-years of cladribine treatment (3.5mg/kg bodyweight) were maintained in the study for 4 years or more without further active treatment.”

EX1006, 1.

231. Because the general knowledge in the art also recognized cladribine was associated with some toxicity (e.g., Stelmasiak reports that in an earlier cladribine study, “dangerous marrow depression were [sic] reported in some

multiple sclerosis patients,” EX1035, 7), a POSA would have been motivated to provide cladribine-free periods to reduce toxicity. In light of Montalban’s teachings, a POSA would have understood that patients could take an extended break from cladribine therapy, thus reducing its toxicity, while benefiting from cladribine’s therapeutic effects. And a POSA would have reasonably expected to successfully treat patients for two years with cladribine, followed by one or two cladribine-free years, because Montalban expressly teaches that such a course of therapy was effective. EX1006, 1.

232. Accordingly, a POSA would have arrived at the method of claim 11 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

H. Claim 12

233. Claim 12 depends from claim 1 and thus, contains each and every limitation of claim 1. Claim 12 further recites, “wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.”

234. Clinicaltrials.gov, Schreiber, and Montalban expressly teach a POSA to administer “cladribine tablets” to MS patients, including SPMS patients with relapses. EX1005, 11; EX1008, 320; EX1006, 1. Thus, a POSA would have been motivated to treat a SPMS-active patient by administering oral cladribine tablets

according to Clinicaltrials.gov's dosing regimen, with a reasonable expectation of success.

235. Accordingly, a POSA would have arrived at the method of claim 12 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

I. Claim 14

236. Claim 14 is directed to a “method of treating a progressive form of Multiple Sclerosis” comprising “orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.” Claim 14 specifies that “the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis” and that “the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” EX1001, 65:59-66:11.

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237. As explained above for claim 1, and as shown in Appendix A and explained in detail below, a POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a SPMS-active patient by administering oral cladribine according to Clinicaltrials.gov's dosing regimen. Claim 14 differs from claim 1 by requiring administering to a patient "a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year." *Id.*, 65:62-66:3.

238. In addition to the reasons described for claim 1, which I will not reiterate here but which are applicable for claim 14, a POSA would have had a reason to administer a cumulative dose of cladribine of about 3.5 mg/kg body weight according to the claimed dosing regimen (i.e., administered as one treatment course of about 1.75 mg/kg per year for two years, wherein each treatment course consists 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year).

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239. A POSA would have understood that Clinicaltrials.gov teaches “orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.” Clinicaltrials.gov discloses administering “cladribine tablets orally as [a] cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Weeks 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.”

EX1005, 11. A POSA would have understood that a dose of 0.875 mg/kg in Weeks 1, 5, 48, and 52 was equivalent to a “cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years.” Clinicaltrials.gov expressly teaches administering that cumulative dose in both years as “1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month [i.e., Weeks 1 and 48] and one at the beginning of the second month [i.e., Weeks 5 and 52] of the respective treatment year.”

240. Schreiber also discloses the implementation of this exact same dosing regimen, which is also the same as the one recited in claim 1, using 10-mg tablets. Specifically, Schreiber discloses the oral cladribine dosing regimen used in the CLARITY study, which, based on a simple comparison with the disclosed dosing regimen of Clinicaltrials.gov (e.g., each disclose the use of cladribine tablets administered in the same 3.5 mg/kg cumulative dosage over the 96-week treatment period, and each disclose the exact same timing for administration of the cladribine tablets)⁵, a POSA would have understood was the same oral cladribine dosing regimen disclosed in Clinicaltrials.gov. *Compare* EX1008, 320 with EX1005, 11.

**1. A POSA would have been motivated to combine
Clinicaltrials.gov, Schreiber, and Montalban**

241. A POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a SPMS-active patient by

⁵ Specifically, Schreiber teaches that during the phase III, placebo-controlled CLARITY study, MS patients were assigned to receive “one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year).” EX1008, 320.

orally administering 3.5 mg/kg of cladribine over 2 years according to Clinicaltrials.gov's dosing regimen. The disclosures of Clinicaltrials.gov would have given a POSA a reason to treat a progressive form of MS—specifically, SPMS with disease activity. Clinicaltrials.gov discloses treating a SPMS patient with “superimposed relapses.” EX1005, 12. As I explain above, a POSA would have understood relapses to be an indicator of disease activity. *See* Section VI.A, *infra*. A POSA would have also had a reason to orally administer a “cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year” according to the claimed dosing regimen to a SPMS-active patient because Clinicaltrials.gov expressly teaches administering cladribine according to the claimed dosing regimen to SPMS-active patients.

242. Moreover, the Montalban reference would have confirmed to a POSA that the cladribine dosing regimen disclosed in Clinicaltrials.gov (which includes a fixed dose per patient per bodyweight of 1.75 mg/kg) would have in fact treated disease activity in SPMS-active patients, and thus would have been further

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motivated to treat an SPMS-active patient with Clinicaltrials.gov's dosing regimen. Specifically, a POSA would have understood Clinicaltrials.gov disclosed the treatment regimen to be used in the ONWARD trial, and would have further understood that Montalban discloses the actual results of that same trial, namely that: (a) the "mean number of qualifying relapses on study was lower (0.23) in patients treated with cladribine 3.5mg/kg plus IFN- β (N=124) vs. patients who received placebo plus IFN- β (0.56, N=48); (b) the "respective ARR[s] [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45)"; (c) the study results demonstrate that "[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)"; and finally, (d) "[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits." *Id.* Thus, a POSA would have understood that the cladribine treatment disclosed in Clinicaltrials.gov would indeed be effective in treating disease activity, including in patients with SPMS-active.

243. Finally a POSA would have recognized that Clinicaltrials.gov and Montalban were both silent regarding the specific strength of the cladribine tablets to use in Clinicaltrials.gov's regimen to achieve the disclosed 1.75 mg/kg/year

dose of cladribine. A POSA would have thus recognized the need to determine the specific tablet strength to actually administer to the patient. Specifically, a POSA would have been motivated to use the 10-mg tablets disclosed in Schreiber because (as discussed above), a POSA would have understood that the 10-mg tablets disclosed in Schreiber were used in a dosing regimen that was identical to the dosing regimen disclosed by Clinicaltrials.gov, and were further described by Schreiber as providing a “very convenient short course” dosing regimen. EX1008, 324.

244. Accordingly, in light of the teachings of Clinicaltrials.gov, Montalban, and Schreiber, a POSA would have been motivated to treat a SPMS-active patient, a progressive form of MS, by orally administering oral cladribine according to Clinicaltrials.gov’s dosing regimen.

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

245. A POSA would have had a reasonable expectation of successfully treating a SPMS-active patient by orally administering cladribine according to Clinicaltrials.gov’s dosing regimen. As explained above, Montalban reports the results of the ONWARD clinical trial, which orally administered a “cumulative dose of Cladribine of about 3.5 mg/kg body weight ... over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg+/-0.2 mg/kg per year,

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wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year” to patients with “relapsing forms of MS,” including SPMS-active patients. EX1005, 12. Specifically, Montalban reports that the “[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)” and the “respective ARR[s] [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45).” *Id.* Montalban concludes that “[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits.” *Id.*

246. A POSA would have understood that a reduction in the number of relapses was a measure of a positive response to treatment. *See* ¶ 49, *infra*. Thus, a POSA would have reasonably expected to treat SPMS patients with disease activity by orally administering cladribine according to Clinicaltrials.gov’s dosing regimen, because Montalban expressly teaches that such treatment was successful in treating disease activity. This reasonable expectation of success was confirmed by the general knowledge in the art, as reported by Schreiber. EX1008, 320, 324. Schreiber reported that early cladribine trials in progressive MS, e.g., by Sipe and Rice, demonstrated that active lesions “were markedly reduced” in “cladribine-

treated groups,” i.e., cladribine treated disease activity in progressive MS. EX1008, 320.

247. Finally, a POSA would have had a reasonable expectation of success in using the 10-mg tablets disclosed by Schreiber to implement Clinicaltrials.gov’s dosing regimen to treat SPMS-active. Specifically, Schreiber disclosed that 10-mg cladribine tablets were given once daily with the same dosing regimen as disclosed in Clinicaltrials.gov (as discussed above) and provided a “very convenient” dosing regimen. EX1008, 320, 324. Thus, a POSA with a high level of skill in treating MS patients would have easily followed Schreiber’s teachings to utilize a 10-mg cladribine tablet when administering Clinicaltrials.gov’s dosing regimen to a SPMS-active patient.

248. In sum, the teachings of Clinicaltrials.gov, Montalban, and Schreiber would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

J. Claims 15 and 16

249. Claim 15 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 16 depends from claim 15 and thus, contains each and every limitation of claims 1 and 15. Claims 15 and 16 further recite, “wherein

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each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient” and “wherein said patient receives the 10-mg or 20 mg of Cladribine for oral administration as a tablet or capsule,” respectively.

250. Clinicaltrials.gov’s dosing regimen comprises each of the additional dosing regimen elements of claims 15 and 16. *See also* ¶ 220, *infra*. Specifically, Clinicaltrials.gov instructs administering “cladribine tablets orally as [a] cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Weeks 1, 5, 48, and 52.” EX1005, 11. A POSA would have found it logical and convenient to use Clinicaltrial.gov’s entire 2-year-long dosing regimen because it was specifically designed and successfully shown to treat SPMS-active. EX1005, 10; EX1006, 1. A POSA would have understood from Schreiber that the dosing regimen employed in Clinicaltrials.gov is the same dosing regimen that was used in the CLARITY study. *See* EX1008, 319. Schreiber discloses that 10-mg cladribine tablets were administered in the CLARITY study. *Id.* Thus, a POSA would have been motivated to treat a SPMS-active patient by orally administering 3.5 mg/kg of cladribine over 2 years according to Clinicaltrials.gov’s dosing regimen, with a reasonable expectation of success.

251. Accordingly, a POSA would have arrived at the method of claims 15 and 16 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

K. Claim 18

252. Claim 18 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 18 further recites, “where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.”

253. As explained above for claim 14, Clinicaltrials.gov discloses treating patients with “[s]econdary progressive multiple sclerosis (SPMS), who are still experiencing relapses.” EX1005, 10. Montalban 2016 reports that 14.5% of the patients enrolled in the study “had SPMS at baseline,” and that the oral cladribine dosing regimen demonstrates “significant efficacy benefits,” in the patients with “SPMS with ongoing relapses.” EX1006, 1. A POSA would have found it logical and convenient to use Clinicaltrial.gov’s entire 2-year-long dosing regimen because it was specifically designed and successfully shown to treat SPMS-active. EX1005, 10; EX1006, 1. As such, a POSA would have been motivated to treat a fully transitioned SPMS-active patient by orally administering 3.5 mg/kg of

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cladribine over 2 years according to Clinicaltrials.gov's dosing regimen, with a reasonable expectation of success.

254. Accordingly, a POSA would have arrived at the method of claim 18 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

L. Claim 19

255. Claim 19 depends from claim 18, which depends from claim 14, and thus, contains each and every limitation of claims 14 and 18. Claim 19 further recites, "wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration."

256. Clinicaltrials.gov's dosing regimen comprises each of the additional dosing regimen elements of claim 19. Specifically, Clinicaltrials.gov instructs administering "cladribine tablets orally as [a] cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Weeks 1, 5, 48, and 52." EX1005, 11. A POSA would have understood from Schreiber that the dosing regimen employed in Clinicaltrials.gov is the same dosing regimen that was used in the CLARITY study. See EX1008, 319. Schreiber discloses that 10-mg cladribine tablets were administered in the CLARITY study. *Id.* Thus, a POSA would have been motivated to treat a SPMS-active patient by orally administering

3.5 mg/kg of cladribine over 2 years according to Clinicaltrials.gov's dosing regimen.

257. Accordingly, a POSA would have arrived at the method of claim 19 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

M. Claim 20

258. Claim 20 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 20 further recites, "wherein said patient is between 18 and 65 years old."

259. Both Clinicaltrials.gov and Montalban disclose treating MS patients aged 18-65 years old. Specifically, Clinicaltrials.gov discloses the inclusion criteria for the ONWARD study included patients "18 to 65 years of age." EX1005, 11. Montalban 2016 discloses treating "patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN- β therapy." EX1006, 1. As explained above for claim 14, Montalban 2016 reports the cladribine therapy disclosed in Clinicaltrials.gov was efficacious in patients with progressive forms of MS, such as fully transitioned SPMS-active. As such, a POSA would have been motivated to treat patients aged 18 to 65 years old with SPMS-active by orally administering 3.5

mg/kg of cladribine over 2 years according to Clinicaltrials.gov’s dosing regimen, with a reasonable expectation of success.

260. Accordingly, a POSA would have arrived at the method of claim 20 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

N. Claim 23

261. Claim 23 depends from claim 14 and thus, contains each and every limitation of claim 14. Claim 23 further recites, “wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.”

262. Schreiber explains that in a CLARITY Extension study, over half of the patients enrolled in the CLARITY study “continued in the 96-week, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIIb extension study” in which “patients originally treated with cladribine tablets [in the CLARITY study] will be randomized to either cladribine tablets 3.5 mg/kg or placebo.” *Id.*,

321. In other words, some patients who received 2 years of cladribine treatment received placebo for another 96-week, meaning they did not receive additional cladribine therapy for at least 2 years. Montalban 2016 reports that “[i]n CLARITY

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Extension, the clinical benefits of 2-years of cladribine treatment (3.5mg/kg bodyweight) were maintained in the study for 4 years or more without further active treatment.” EX1006, 1.

263. Because the general knowledge in the art also recognized cladribine was associated with some toxicity (e.g., Stelmasiak reports that in an earlier cladribine study, “dangerous marrow depression were [sic] reported in some multiple sclerosis patients,” EX1035, 7), a POSA would have been motivated to provide cladribine-free periods to reduce toxicity. In light of Montalban’s teachings, a POSA would have understood that patients could take an extended break from cladribine therapy, thus reducing its toxicity, while benefiting from cladribine’s therapeutic effects. And a POSA would have reasonably expected to successfully treat patients for two years with cladribine, followed by one or two cladribine-free years, because Montalban expressly teaches that such a course of therapy was effective. EX1006, 1.

264. Accordingly, a POSA would have arrived at the method of claim 23 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

O. Claim 24

265. Claim 24 is directed to a “method of treating a patient suffering from a progressive form of Multiple Sclerosis” comprising “orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each.” Claim 24 specifies that “tablets or capsules are administered during a treatment year comprising the following regimen: (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient.” Claim 24 further specifies the number of 10-mg capsules or tablets patients should receive in both months based on patients’ weight—e.g., “wherein patients having a bodyweight ... in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course.”

EX1001, 66:51-67:39.

266. As explained above for claim 1, a POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a SPMS-active patient by administering a fixed dose of 1.75 mg/kg of cladribine per

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treatment year according to Clinicaltrials.gov’s dosing regimen. Claim 24 differs from claim 1 in three ways:

- a) by requiring “administering to said patients tablets or capsules containing about 10 mg of Cladribine... during a treatment year,”
- b) by further specifying that the administration during a “treatment year compris[es] the following regimen: (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient,” and
- c) by specifying the number of 10-mg capsules or tablets patients should receive in both months based on patients’ weight—e.g., “wherein patients having a bodyweight ... in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course.” EX1001, 66:51-67:39.

267. In addition to the reasons described for claim 1, which I will not reiterate here but which are applicable for claim 24, a POSA would have had a

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reason to administer 10-mg cladribine tablets during a treatment year comprising the following regimen: (i) a treatment course lasting 2 months, wherein cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a cladribine-free period lasting 10 months wherein no Cladribine is administered. A POSA would have also had a reason to administer the claimed number of 10-mg cladribine tablets based on a patient's weight.

1. Clinicaltrials.gov and Schreiber teach administering the claimed oral cladribine dosing regimen

268. A POSA would have understood that Clinicaltrials.gov and Schreiber disclose each and every limitation of the claimed dosing regimen.

(a) Clinicaltrials.gov teaches “a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily ... on a treatment week of from 3 to up to 6 days each month;” Schreiber teaches the same dosing regimen with 10-mg cladribine tablets

269. As explained in detail above for claim 14, a POSA would have understood that Clinicaltrials.gov teaches administering “cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52.” EX1005, 11. A POSA would have understood that the “4 or 5 days of a 28-day period,” taught by Clinicaltrials.gov is encompassed by “from 3 to up to 6 days each month,” recited in claim 24,

rendering it obvious. And a POSA would have understood that the doses administered at weeks 1 and 5 and weeks 48 and 52 were constituted a “treatment course lasting 2 months,” as recited in claim 24.

270. Thus, Clinicaltrials.gov expressly discloses a cladribine dosing regimen that constitutes “a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily ... on a treatment week of from 3 to up to 6 days each month,” as recited in claim 24.

271. Schreiber also discloses the implementation of this exact same dosing regimen, that is also the same as the one recited in claim 1, using 10-mg tablets. Specifically, Schreiber discloses the oral cladribine dosing regimen used in the CLARITY study, which, based on a simple comparison with the disclosed dosing regimen of Clinicaltrials.gov (e.g., each disclose the use of cladribine tablets administered in the same 3.5 mg/kg cumulative dosage over the 96-week treatment period, and each disclose the exact same timing for administration of the cladribine tablets)⁶, a POSA would have understood was the same oral cladribine dosing regimen disclosed in Clinicaltrials.gov. *Compare* EX1008, 320 *with* EX1005, 11.

⁶ Specifically, Schreiber teaches that during the phase III, placebo-controlled CLARITY study, MS patients were assigned to receive “one of two cumulative

(b) Schreiber instructs administering a specific number of 10-mg cladribine tablets to patients based on their weight

272. Schreiber discloses administering “one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year).” EX1008, 320. Schreiber specifies, “[e]ach course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4-5 days of a 28-day period.” *Id.* Because Schreiber does not differentiate between the four treatment courses (instead describing them identically), a POSA would have been motivated to administer Schreiber’s 3.5 mg/kg in four equal treatment courses (0.875 mg/kg per treatment course or 1.75 mg/kg per treatment year) because that would have been the most logical and obvious dosing regimen. Accordingly, a POSA would have been able to determine that those patients received 1.75 mg/kg in each treatment year ($3.5 \text{ mg/kg} \div 2 \text{ treatment years} = 1.75$

doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year).” EX1008, 320.

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mg/kg per treatment year). Schreiber discloses that the 3.5 mg/kg dose, administered as 1.75 mg/kg over two years, “significantly reduced the annual relapse rates” and patients had “fewer lesions per patient per scan for: T1 gadolinium-enhancing lesions (mean 0.12 and 0.11 vs 0.91), active T2 lesions (mean 0.38 and 0.33 vs 1.43); and combined unique lesions (mean 0.43 and 0.38 vs 1.72).” EX1008, 320.

273. From this disclosure, a POSA would have been able to use routine calculations to determine the number of 10-mg cladribine tablets to administer to a patient to provide approximately 1.75 mg/kg of cladribine over a two-month period, as I explain in further detail below.

274. For example, a POSA would have been able to determine how many 10-mg cladribine tablets a patient weighing approximately 55 kg should receive by the following calculation:

$$\text{Dose of cladribine needed (in mg)} = 0.875 \frac{\text{mg}}{\text{kg}} \times 55 \text{ kg} = 48.1 \text{ mg}$$

275. With the knowledge that each patient received 10-mg tablets for 4 to 5 treatment days, a POSA would have rounded the dose to the nearest 10-mg dose. Since a 48.1 mg dose rounds to 50 mg, a POSA would have known to administer five 10-mg cladribine tablets to achieve the total cumulative dose. Thus, in order to administer a cumulative 1.75 mg/kg over a two-month period, a 55 kg patient, who

falls within the claimed range of “50 to less than 60 kg,” a POSA would have understood Schreiber to teach administering “1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course,” as recited in claim 24.

(c) Clinicaltrials.gov and Schreiber teaches a cladribine-free period of 10 months

276. Clinicaltrials.gov’s dosing regimen includes a “Cladribine-free period lasting 10 months wherein no Cladribine is administered.” Clinicaltrials.gov discloses that subjects received a “cumulative dose” of oral cladribine at “Week 1, 5, 48, and 52.” EX1005, 11. Thus, a POSA would have understood that subjects in the treatment arm of Clinicaltrials.gov did not receive cladribine for 43 weeks, or 10 months, between weeks 5 and 48 of the study. Accordingly, Clinicaltrials.gov discloses a cladribine dosing regimen that includes a “Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient,” as recited in claim 24.

277. Schreiber discloses the same dosing regimen, which also contains a “Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient.” Specifically, Schreiber discloses administering “one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or

placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year).” EX1008, 320. Thus, a POSA would have also understood that subjects in the treatment arm of the CLARITY study did not receive cladribine for 43 weeks, or 10 months, between weeks 5 and 48 of the study. Accordingly, Schreiber discloses a cladribine dosing regimen that includes a “Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient,” as recited in claim 24.

**2. A POSA would have been motivated to combine
Clinicaltrials.gov, Schreiber, and Montalban**

278. A POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a SPMS-active patient by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov’s dosing regimen. The disclosures of Clinicaltrials.gov would have given a POSA a reason to treat a progressive form of MS—specifically, a fully transitioned SPMS-active patient. Clinicaltrials.gov discloses treating a SPMS patient with “superimposed relapses.” EX1005, 12. As I explain above, a POSA would have understood relapses to be an indicator of disease activity. *See* Section VI.A, *infra*. A POSA would have also had a reason to orally administer 10-mg cladribine tablets, as taught by Schreiber, to a SPMS-active patient according to

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Clinicaltrials.gov's dosing regimen because the oral cladribine dosing regimens disclosed by Clinicaltrials.gov and Schreiber are the same. A POSA wanting to administer 0.875 mg/kg over 4-5 days, as taught by Clinicaltrials.gov, would have naturally looked to Schreiber for the daily cladribine dose because Schreiber also administers 0.875 mg/kg for 4-5 days.

279. Moreover, the Montalban reference would have confirmed to a POSA that the cladribine dosing regimen disclosed in Clinicaltrials.gov (which includes a fixed dose per patient per bodyweight of 1.75 mg/kg) would have in fact treated disease activity in SPMS-active patients, and thus would have been further motivated to treat an SPMS-active patient with Clinicaltrials.gov's dosing regimen. Specifically, a POSA would have understood Clinicaltrials.gov disclosed the treatment regimen to be used in the ONWARD trial, and would have further understood that Montalban discloses the actual results of that same trial, namely that: (a) the "mean number of qualifying relapses on study was lower (0.23) in patients treated with cladribine 3.5mg/kg plus IFN- β (N=124) vs. patients who received placebo plus IFN- β (0.56, N=48); (b) the "respective ARRs [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45)"; (c) the study results demonstrate that "[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)"; and

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finally, (d) “[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits.”

Id. Thus, a POSA would have understood that the cladribine treatment disclosed in Clinicaltrials.gov was, in fact, effective in treating disease activity, including in patients who have fully transitioned to SPMS-active.

280. Finally a POSA would have recognized that Clinicaltrials.gov and Montalban were both silent regarding the specific strength of the cladribine tablets to use in Clinicaltrials.gov’s regimen to achieve the disclosed 1.75 mg/kg/year dose of cladribine. A POSA would have thus recognized the need to determine the specific tablet strength to actually administer to the patient. Specifically, a POSA would have been motivated to use the 10-mg tablets disclosed in Schreiber because (as discussed above), a POSA would have understood that the 10-mg tablets disclosed in Schreiber were used in a dosing regimen that was identical to the dosing regimen disclosed by Clinicaltrials.gov, and were further described by Schreiber as providing a “very convenient short course” dosing regimen. EX1008, 324.

281. Accordingly, in light of the teachings of Clinicaltrials.gov, Montalban, and Schreiber, a POSA would have been motivated to treat a SPMS-active patient,

a progressive form of MS, by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov's dosing regimen.

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

282. A POSA would have had a reasonable expectation of successfully treating a SPMS-active patient by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov's dosing regimen. As explained above, Montalban reports the results of the ONWARD clinical trial, which orally administered 3.5 mg/kg of cladribine to patients with "relapsing forms of MS," including SPMS-active patients. EX1005, 12. Specifically, Montalban reports that the "[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)" and the "respective ARR[s] [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45)." *Id.* Montalban concludes that "[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits." *Id.*

283. A POSA would have understood that a reduction in the number of relapses was a measure of a positive response to treatment. *See* ¶ 49, *infra*. Thus, a POSA would have reasonably expected to treat SPMS patients with disease

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activity by orally administering the claimed dosing regimen, as taught by Clinicaltrials.gov, because Montalban expressly teaches that such treatment was successful in treating disease activity.Clinicaltrials.gov. This reasonable expectation of success was confirmed by the general knowledge in the art, as reported by Schreiber. EX1008, 320, 324. Schreiber reported that early cladribine trials in progressive MS, e.g., by Sipe and Rice, demonstrated that active lesions “were markedly reduced” in “cladribine-treated groups,” i.e., cladribine treated disease activity in progressive MS. EX1008, 320.

284. Finally, a POSA would have had a reasonable expectation of success in using the 10-mg tablets disclosed by Schreiber to implement Clinicaltrials.gov’s dosing regimen to treat SPMS-active. Specifically, Schreiber disclosed that 10-mg cladribine tablets were given once daily with the same dosing regimen as disclosed in Clinicaltrials.gov (as discussed above) and provided a “very convenient” dosing regimen. EX1008, 320, 324. Thus, a POSA with a high level of skill in treating MS patients would have easily followed Schreiber’s teachings to utilize a 10-mg cladribine tablet when administering Clinicaltrials.gov’s dosing regimen to a SPMS-active patient.

285. In sum, the teachings of Clinicaltrials.gov, Montalban, and Schreiber would have motivated a POSA to arrive at the claimed MS treatment method, with

a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

P. Claim 25

286. Claim 25 depends from claim 24 and thus, contains each and every limitation of claim 24. Claim 25 further recites, “wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.”

287. Clinicaltrials.gov’s dosing regimen comprises the additional dosing regimen element of claim 25. As explained above, Clinicaltrials.gov discloses an oral cladribine dosing regimen in which patients received a two-month course of cladribine, followed by a 10-month cladribine-free period in which they did not receive cladribine therapy. Clinicaltrials.gov teaches administering “cladribine tablets orally as cumulative dose of 0.875 milligrams per kilogram over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in [a] total cladribine dose of 3.5 mg/kg.” EX1005, 11. Thus, Clinicaltrials.gov discloses a cladribine dosing regimen that “comprises at least one subsequent additional treatment year [beginning at week 48], wherein said additional treatment year is substantially identical to said treatment year.” Also, as explained above, a POSA would have been motivated to treat a SPMS-active patient by administering 10-mg cladribine

tablets per Clinicaltrials.gov's dosing regimen, which comprises the additional elements of claim 25, with a reasonable expectation of success.

288. Accordingly, a POSA would have arrived at the method of claim 25 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

Q. Claim 26

289. Claim 26 depends from claim 25 and thus, contains each and every limitation of claims 24 and 25. Claim 26 further recites, "wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years."

290. As explained above for claim 25, Clinicaltrials.gov discloses a cladribine dosing regimen that "comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year." Specifically, Clinicaltrials.gov discloses administering oral cladribine on weeks 1, 5, 48, and 52. A POSA would have understood that the treatment courses of year 1 (i.e., on weeks 1 and 5) were "directly adjacent" to the treatment courses administered in year 2 (i.e., weeks 48 and 52). As such, a POSA would have understood that Clinicaltrials.gov's dosing regimen includes an "additional treatment year [that] is directly adjacent to said treatment year." Also,

as explained above, a POSA would have been motivated to treat a SPMS-active patient by administering 10-mg cladribine tablets per Clinicaltrials.gov's dosing regimen, which comprises the additional elements of claim 26, with a reasonable expectation of success.

291. Accordingly, a POSA would have arrived at the method of claim 26 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

R. Claim 27

292. Claim 27 is directed to a “method of treating a patient suffering from a progressive form of Multiple Sclerosis” comprising “orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each.” Claim 27 specifies that “the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis” and that “the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” Claim 27 also specifies that “tablets or capsules are administered during two treatment years comprising the following regimen: (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose

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of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient; (iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient.” Claim 27 further specifies the number of 10-mg capsules or tablets patients should receive in both months based on patients’ weight—e.g., “wherein patients having a bodyweight ... in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively.” EX1001, 67:48-68:64.

293. As explained above for claim 1, a POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a SPMS-active patient by orally administering a fixed dose of 1.75 mg/kg of cladribine per treatment year. As explained above for claim 24, A POSA would have been motivated to administer 10-mg cladribine tablets to treat SPMS-active

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patients according to Clinicaltrials.gov's dosing regimen comprising (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient. Also, as explained above for claim 24, a POSA would have understood Schreiber to teach administering "1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course."

294. Claim 27 only differs from claims 1 and 24 in that claim 27 recites a second treatment course following the first cladribine-free period, wherein the two treatment courses are identical, followed by a second cladribine-free period. Specifically, claim 27 differs from claims 1 and 24 by requiring a dosing regimen that comprises the following regimen:

- (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;
- (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;

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(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and

(iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient.

EX1001, 67:61-68:7.

295. In addition to the reasons described for claims 1 and 24, which I will not reiterate here but which are applicable for claim 27, a POSA would have had a reason to administer a second cladribine treatment course lasting 2 months, followed by a second cladribine-free period lasting 10 months, as taught by Clinicaltrials.gov.

296. As explained above for claim 24, Clinicaltrials.gov expressly discloses a cladribine dosing regimen that constitutes “a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily ... on a treatment week of from 3 to up to 6 days each month,” wherein the treatment course is administered on weeks 1, 5, 48, and 52. EX1005, 11; *see also* ¶ 220, *infra*. A POSA would have understood that administering cladribine on weeks 1 and 5 constituted a “first treatment course lasting 2 months,” as recited in claim 27,

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and the 43 weeks (or 10 months) between weeks 5 and 48, where no cladribine was administered, constituted a “first Cladribine-free period lasting 10 months.”

297. A POSA would have also understood that administering cladribine in weeks 48 and 52 constituted a “second treatment course lasting 2 months,” as recited in claim 27, and the 44 weeks (or about 10 months) between weeks 52 and 96 (i.e., the end of the study), where no cladribine was administered, constituted a “second Cladribine-free period lasting 10 months.” As such, Clinicaltrials.gov discloses administering cladribine tablets according to the following regimen: “(i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered ... on 3 to up to 6 days each month; (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient; (iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered ... on 3 to up to 6 days each month; and (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient.”

298. As also explained above, Schreiber also discloses the implementation of this exact same dosing regimen, which is also the same as the one recited in claim 1, using 10-mg tablets. Specifically, Schreiber discloses the oral cladribine dosing regimen used in the CLARITY study, which, based on a simple comparison

with the disclosed dosing regimen of Clinicaltrials.gov (e.g., each disclose the use of cladribine tablets administered in the same 3.5 mg/kg cumulative dosage over the 96-week treatment period, and each disclose the exact same timing for administration of the cladribine tablets)⁷, a POSA would have understood was the same oral cladribine dosing regimen disclosed in Clinicaltrials.gov. *Compare* EX1008, 320 *with* EX1005, 11.

**1. A POSA would have been motivated to combine
Clinicaltrials.gov, Schreiber, and Montalban**

299. A POSA would have been motivated to combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to treat a SPMS-active patient by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov's dosing regimen. The disclosures of Clinicaltrials.gov would have given a POSA a reason to treat a progressive form of MS—specifically, SPMS with disease

⁷ Specifically, Schreiber teaches that during the phase III, placebo-controlled CLARITY study, MS patients were assigned to receive “one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8-20 days/year).” EX1008, 320.

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activity. Clinicaltrials.gov discloses treating a SPMS patient with “superimposed relapses.” EX1005, 12. As I explain above, a POSA would have understood relapses to be an indicator of disease activity. *See* Section VI.A, *infra*. A POSA would have also had a reason to orally administer 10-mg cladribine tablets, as taught by Schreiber, to a SPMS-active patient according to Clinicaltrials.gov’s dosing regimen because the oral cladribine dosing regimens disclosed by Clinicaltrials.gov and Schreiber are the same. A POSA wanting to administer 0.875 mg/kg over 4-5 days, as taught by Clinicaltrials.gov, would have naturally looked to Schreiber for the daily cladribine dose because Schreiber also administers 0.875 mg/kg for 4-5 days.

300. Moreover, the Montalban reference would have confirmed to a POSA that the cladribine dosing regimen disclosed in Clinicaltrials.gov (which includes a fixed dose per patient per bodyweight of 1.75 mg/kg) would have in fact treated disease activity in SPMS-active patients, and thus would have been further motivated to treat an SPMS-active patient with Clinicaltrials.gov’s dosing regimen. Specifically, a POSA would have understood that Clinicaltrials.gov disclosed the treatment regimen to be used in the ONWARD trial, and would have further understood that Montalban discloses the actual results of that same trial, namely that: (a) the “mean number of qualifying relapses on study was lower (0.23) in

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patients treated with cladribine 3.5mg/kg plus IFN- β (N=124) vs. patients who received placebo plus IFN- β (0.56, N=48); (b) the “respective ARR[s] [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45)”;

(c) the study results demonstrate that “[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)”; and finally, (d) “[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN- β demonstrated significant efficacy benefits.”

Id. Thus, a POSA would have understood that the cladribine treatment disclosed in Clinicaltrials.gov would indeed be effective in treating disease activity, including in patients with SPMS-active.

301. Finally a POSA would have recognized that Clinicaltrials.gov and Montalban were both silent regarding the specific strength of the cladribine tablets to use in Clinicaltrials.gov’s regimen to achieve the disclosed 1.75 mg/kg/year dose of cladribine. A POSA would have thus recognized the need to determine the specific tablet strength to actually administer to the patient. Specifically, a POSA would have been motivated to use the 10-mg tablets disclosed in Schreiber because (as discussed above), a POSA would have understood that the 10-mg tablets disclosed in Schreiber were used in a dosing regimen that was identical to the

dosing regimen disclosed by Clinicaltrials.gov, and were further described by Schreiber as providing a “very convenient short course” dosing regimen. EX1008, 320, 324.

302. Accordingly, in light of the teachings of Clinicaltrials.gov, Montalban, and Schreiber, a POSA would have been motivated to treat a SPMS-active patient, a progressive form of MS, by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov’s dosing regimen.

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

303. A POSA would have had a reasonable expectation of successfully treating a SPMS-active patient by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov’s dosing regimen. As explained above, Montalban reports the results of the ONWARD clinical trial, which orally administered 3.5 mg/kg of cladribine to patients with “relapsing forms of MS,” including SPMS-active patients. EX1006, 1. Specifically, Montalban reports that the “[c]ladribine-treated patients were 63[percent] [sic] less likely to have a qualifying relapse ($P < 0.001$)” and the “respective ARR[s] [annual relapse rates] were 0.12 (95[percent] [sic] CI 0.08, 0.17) and 0.32 (95[percent] [sic] CI 0.20, 0.45).” *Id.* Montalban concludes that “[i]n patients with active relapsing MS with breakthrough disease while on IFN- β therapy (including SPMS with ongoing relapses), treatment with

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cladribine tablets added on to IFN- β demonstrated significant efficacy benefits.”

Id.

304. A POSA would have understood that a reduction in the number of relapses was a measure of a positive response to treatment. See ¶ 49, *infra*. Thus, a POSA would have reasonably expected to treat SPMS-active patients by orally administering the claimed dosing regimen (dose and administration schedule), as taught by Clinicaltrials.gov, because Montalban expressly teaches that such treatment was successful in treating disease activity. This reasonable expectation of success was confirmed by the general knowledge in the art, as reported by Schreiber. EX1008, 320, 324. Schreiber reported that early cladribine trials in progressive MS, e.g., by Sipe and Rice, demonstrated that active lesions “were markedly reduced” in “cladribine-treated groups,” i.e., cladribine treated disease activity in progressive MS. EX1008, 320.

305. Finally, a POSA would have had a reasonable expectation of success in using the 10-mg tablets disclosed by Schreiber to implement Clinicaltrials.gov’s dosing regimen to treat SPMS-active. Specifically, Schreiber disclosed that 10-mg cladribine tablets were given once daily with the same dosing regimen as disclosed in Clinicaltrials.gov (as discussed above) and provided a “very convenient” dosing regimen. EX1008, 320, 324. Thus, a POSA with a high level of skill in treating MS

patients would have easily followed Schreiber's teachings to utilize a 10-mg cladribine tablet when administering Clinicaltrials.gov's dosing regimen to a SPMS-active patient.

306. In sum, the teachings of Clinicaltrials.gov, Montalban, and Schreiber would have motivated a POSA to arrive at the claimed MS treatment method, with a reasonable expectation of success. As also explained in Section XIII, below, there is no objective evidence that weighs against the obviousness showing here.

S. Claims 30 and 34

307. Claims 30 and 34 depend from claim 27 and thus, contains each and every limitation of claim 27. Claims 30 and 34 further recite, "wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis" and "wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis," respectively.

308. As discussed above for claim 27, a POSA would have been motivated to treat a SPMS-active patient by orally administering 10-mg cladribine tablets according to Clinicaltrials.gov's dosing regimen, with a reasonable expectation of success. And a POSA would have easily been able to determine the total number of

cladribine tablets to administer in each treatment week to a patient depending on their body weight.

309. Accordingly, for the same reasons discussed above for claim 27, a POSA would have arrived at the method of claims 30 and 34 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

T. Claim 33

310. Claim 33 depends from claim 27 and thus, contains each and every limitation of claim 27. Claim 30 further recites, “wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.”

311. As explained above, both Clinicaltrials.gov’s and Schreiber’s dosing regimens comprise administering oral cladribine for two treatment years. Schreiber further explains that in a CLARITY Extension study, over half of the patients enrolled in the CLARITY study “continued in the 96-week, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIIb extension study” in which “patients originally treated with cladribine tablets [in the CLARITY study] will be randomized to either cladribine tablets 3.5 mg/kg or placebo.” EX1008, 321. In other words, some patients who received two years of cladribine treatment

received placebo for another 96-week, meaning they did not receive additional cladribine therapy for at least 2 years. Montalban reports that “[i]n CLARITY Extension, the clinical benefits of 2-years of cladribine treatment (3.5mg/kg bodyweight) were maintained in the study for 4 years or more without further active treatment.” EX1006, 1.

312. Because the general knowledge in the art also recognized cladribine was associated with some toxicity (e.g., Stelmasiak reports that in an earlier cladribine study, “dangerous marrow depression were [sic] reported in some multiple sclerosis patients,” EX1035, 7), a POSA would have been motivated to provide cladribine-free periods to reduce toxicity. In light of Montalban’s teachings, a POSA would have understood that patients could take an extended break from cladribine therapy, thus reducing its toxicity, while benefiting from cladribine’s therapeutic effects. And a POSA would have reasonably expected to successfully treat patients for two years with cladribine, followed by one or two cladribine-free years, because Montalban expressly teaches that such a course of therapy was effective. EX1006, 1.

313. Accordingly, a POSA would have arrived at the method of claim 33 in light of Clinicaltrials.gov, Schreiber, and Montalban, with a reasonable expectation of success.

XIII. No objective evidence of non-obviousness exist.

314. In reaching my opinions regarding obviousness described in this declaration, I considered whether there were any objective evidence of non-obviousness. For the reasons described below, I concluded that none of objective evidence that I reviewed supports the patentability of claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, and 34 of the '919 patent.

315. The '919 patent alleges that the claimed method supposedly demonstrated an “unexpected advantage for the SPMS patients” compared to RRMS patients. EX1001, 3:36-54. However, to the extent Merck intends to rely on these results as evidence of “unexpected results,” several issues preclude them from doing so. First, I understand that Merck must compare their supposed unexpected results to the closest prior art. However, patients with RRMS are not the closest prior art. In fact, Clinicaltrials.gov and Montalban, which reports that cladribine “demonstrated significant efficacy benefits” in patients with “active relapsing MS,” “including SPMS with ongoing relapses.” EX1006, 1. Alvarez-Gonzalez is also closer prior art than patients with RRMS because Alvarez-Gonzalez discloses successfully treating a patient with progressive disease (i.e., PP-active). Further, Merck did not disclose Clinicaltrials.gov, Montalban, or Alvarez-Gonzalez to the Patent Office during prosecution; nor did the Examiner

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find these references. EX1004. Thus, by the '919 patent filing date, there was nothing unexpected or surprising about treating a patient with a progressive form of MS with cladribine.

316. Second, the '919 patent itself concedes that “[t]here was no difference in annualized relapse rate between patients with [RRMS] and patients with [SPMS] with relapses” in the ONWARD study.⁸ EX1001, 47:60-48:1. Merck also made the same admission to the European Medicines Agency that “there was no difference in annualised relapse rate between patients with relapsing-remitting MS and patients with secondary progressive MS with relapses” in the ONWARD study. EX1023, 13.

317. Finally, any difference in efficacy of cladribine on patients with SPMS compared to RRMS in the ONWARD trial is one of degree, not kind.

⁸ Specifically, the '919 specification discusses a study involving “patients treated with Cladribine as an add-on to interferon-beta vs. placebo+interferon-beta” that “also included a limited number of patients with secondary progressive MS (26 patients),” which plainly refers to the ONWARD study as Montalban reports ONWARD involved cladribine added on to interferon-beta administered to 26 SPMS patients “at baseline. *Compare* EX1006, 1 *with* EX1001, 47:60-48:1.

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However, as explained above, Merck expressly stated there was no difference between in the efficacy of cladribine between SPMS and RRMS patients. Further, Merck only alleged unexpected results were seen in SPMS patients; however, the claims broadly recite PPMS and PRMS patients, as well. Thus, the unexpected results are not commensurate in scope with the claims.

318. I am unaware of Merck making any other arguments regarding secondary considerations in the '919 patent or during prosecution, and I am further unaware of any other evidence providing objective evidence of non-obviousness.

XIV. Conclusion

319. In view of the facts discussed above, and my understanding with respect to obviousness, claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, and 34 of the '919 patent would have been obvious over Clinicaltrials.gov, Schreiber, and Montalban 2016. It is also my opinion that claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 33, and 34 would have been obvious over Alvarez-Gonzalez and Giovannoni. It is further my opinion that claims 11, 23, and 33 would have been obvious over Alvarez-Gonzalez, Giovannoni, and Montalban 2016. Finally, it is my opinion there is no objective evidence establishing the non-obviousness of the claims.

Appendix A

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
1. A method of treating a progressive form of Multiple Sclerosis, said method comprising:	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb paresis to be the first manifestation of primary progressive MS (PPMS).” EX1009, 506.
orally administering Cladribine to a patient in need thereof	“In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study, we investigated the efficacy and safety of cladribine in a 96-week, phase 3, double-blind, placebo-controlled, multicenter trial involving patients with relapsing–remitting multiple sclerosis.” EX1007, 417.

⁹ Emphasis added throughout.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“Cladribine provides immunomodulation through selective targeting of lymphocyte subtypes. We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, Abstract. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.
at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg,	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, Abstract. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg

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	group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS),	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.” EX1009, 509. “Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM.” EX1009, 509.
and wherein the progressive form of Multiple Sclerosis does not include Early Secondary	“At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
Progressive Multiple Sclerosis (ESPMS)	henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb paresis to be the first manifestation of primary progressive MS (PPMS). ” EX1009, 506.
2. The method according to claim 1, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg.	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, Abstract. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	groups received two courses of cladribine , and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
3. The method according to claim 1, wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.” EX1009, 509. “Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM.” EX1009, 509.
4. The method according to claim 1, wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.	“In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine , and the placebo

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
5. The method according to claim 4, wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.	“ In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine , and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
6. The method according to claim 5, wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).”

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	EX1007, 416. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
8. The method according to claim 1, wherein each treatment year comprises:	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “A second treatment cycle is planned 11 months after the first.” EX1009, 509.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, 416. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416.
(i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month,	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment) . In the second 48-week period, both cladribine groups received two courses of cladribine , and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and	“The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period .” EX1007, 417.
(ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
9. The method according to claim 1, wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive Multiple Sclerosis,	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.” EX1009, 509. “Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM.” EX1009, 509.
wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg,	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted).

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
and wherein orally administering Cladribine comprises at least two treatment years.	“A second treatment cycle is planned 11 months after the first.” EX1009, 509.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
12. The method according to claim 1, wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.	“In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study, we investigated the efficacy and safety of cladribine in a 96-week, phase 3, double-blind, placebo-controlled, multicenter trial involving patients with relapsing–remitting multiple sclerosis.” EX1007, 417. “Cladribine provides immunomodulation through selective targeting of lymphocyte subtypes. We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, Abstract. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
14. A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising:	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb paresis to be the first manifestation of primary progressive MS (PPMS).” EX1009, 506.
orally administering to said patient a cumulative dose of Cladribine	“In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study, we investigated the efficacy and safety of cladribine in a 96-week, phase 3, double-blind, placebo-controlled, multicenter trial involving patients with relapsing–remitting multiple sclerosis.” EX1007, 417. “Cladribine provides immunomodulation through selective targeting of lymphocyte

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	subtypes. We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, Abstract. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.
of about 3.5 mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg± 0.2 mg/kg per year,	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year,	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “A second treatment cycle is planned 11 months after the first.” EX1009, 509. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS),	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract.

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.” EX1009, 509. “Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM.” EX1009, 509.
and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).	“At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb paresis to be the first manifestation of primary progressive MS (PPMS).” EX1009, 506.
15. The method according to claim 14, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	in week 5.” EX1009, 509 (footnote omitted). “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
16. The method according to claim 15, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.	“In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study, we investigated the efficacy and safety of cladribine in a 96-week, phase 3, double-blind, placebo-controlled, multicenter trial involving patients with relapsing–remitting multiple sclerosis.” EX1007, 417. “Cladribine provides immunomodulation through selective targeting of lymphocyte subtypes. We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, Abstract. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.
18. The method according to claim 14, where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract.

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.” EX1009, 509. “Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM.” EX1009, 509.
19. The method according to claim 18, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
20. The method according to claim 14, wherein said patient is between 18 and 65 years old.	“At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg.” EX1009, 506. “Cladribine 3.5 mg/kg (N – 433)” with “Mean” “Age — yr” of “37.9±10.3” and a “Range” for “Age — yr” of “18-65.” EX1007, 419.
24. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, comprising	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb paresis to be the first manifestation of primary progressive MS (PPMS).” EX1009, 506.
orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each,	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.
wherein said tablets or capsules are administered during a treatment	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
year comprising the following regimen:	resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416.
(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and

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	13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine , and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
(ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
wherein patients having a bodyweight in the range of 40 to less than 50 kg are administered	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted).

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 60 to less than 70 kg are administered	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “To maintain the double-blind nature of the study, all patients within a weight range received the same number of tablets (cladribine or matched placebo).” EX1007, 418. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 70 to less than 80 kg are administered 1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;	

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
in the range of 80 to less than 90 kg are administered 1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 90 to less than 100 kg are administered 1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of said treatment course;	

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
in the range of 100 to less than 110 kg are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of said treatment course; or in the range of 110 kg and above are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,	

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of said treatment course.	
25. The method according to claim 24, wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “A second treatment cycle is planned 11 months after the first.” EX1009, 509. “We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, 416. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
26. The method according to claim 25, wherein said additional treatment year is directly adjacent to said treatment year,	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416.

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.	This is an alternative limitation.
27. A method of treating a patient suffering from a progressive form of Multiple Sclerosis,	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract. “At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	paresis to be the first manifestation of primary progressive MS (PPMS). " EX1009, 506.
wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS),	"Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis." EX1009, Title. "We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label 'rescue' therapy." EX1009, Abstract. "In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration." EX1009, 509. "Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM." EX1009, 509.
and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS),	"At the age of 28, a woman of Afro-Caribbean origin first noticed weakness of her right leg. Neurological signs on examination were indicative of an upper motor neuron syndrome, which steadily deteriorated henceforth. Thorough diagnostic work-up including MRI head and spinal cord, and assessment of her cerebro-spinal fluid, revealed her lower limb paresis to be the first manifestation of primary progressive MS (PPMS)." EX1009, 506.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each,	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007 417.
wherein said tablets or capsules are administered during two treatment years comprising the following regimen:	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “A second treatment cycle is planned 11 months after the first.” EX1009, 509. “We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, 416 (Abstract). “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg

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	or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks , then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).” EX1007, 416.
(i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
(ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “A second treatment cycle is planned 11 months after the first.” EX1009, 509. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	given once daily for the first 4 or 5 days of a 28-day period." EX1007, 417. "In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix)." EX1007, 418.
wherein patients having a bodyweight in the range of 40 to less than 50 kg are administered 1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,	"Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5." EX1009, 509 (footnote omitted). "A second treatment cycle is planned 11 months after the first." EX1009, 509. "The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively[;] in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively[;] in the range of 60 to less than 70 kg are administered	given once daily for the first 4 or 5 days of a 28-day period." EX1007, 417. "To maintain the double-blind nature of the study, all patients within a weight range received the same number of tablets (cladribine or matched placebo)." EX1007, 418. "In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix)." EX1007, 418.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; in the range of 70 to less than 80 kg are administered 1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st	

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
and the 2nd treatment course, respectively; in the range of 80 to less than 90 kg are administered 1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; in the range of 90 to less than 100 kg are administered 1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of both the 1st	

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
and the 2nd treatment course, respectively, 2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; in the range of 100 to less than 110 kg are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; or	

Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
in the range of 110 kg and above are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively.	
34. The method according to claim 27, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.	“Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis.” EX1009, Title. “We report a case of rebound disease after fingolimod cessation in a pwPMS [progressive multiple sclerosis], who was successfully treated with Cladribine as an off-label ‘rescue’ therapy.” EX1009, Abstract.

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Claim	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007) ⁹
	“In conclusion, we report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.” EX1009, 509. “Based on its safety, convenience, and unique pharmacokinetics including CNS penetration Cladribine is a promising candidate DMT for pwPM.” EX1009, 509.

Appendix B

Claim	Alvarez-Gonzalez (EX1009), Giovannoni (EX1007), and Montalban (EX1006)
11. The method according to claim 1, wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year,	“Based on 100% bioavailability of Cladribine s.c. (versus 42% o[f] the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” EX1009, 509. “Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted). “A second treatment cycle is planned 11 months after the first.” EX1009, 509. “We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing-remitting multiple sclerosis.” EX1007, 416. “We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year).”

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Claim	Alvarez-Gonzalez (EX1009), Giovannoni (EX1007), and Montalban (EX1006)
	EX1007, 416. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
followed by at least one year in which no Cladribine is administered to said patient.	“Cladribine tablets given annually for 2 years in short-duration courses to RRMS patients significantly improved clinical and MRI outcomes (CLARITY). In CLARITY Extension, the clinical benefits of 2-years of cladribine treatment (3.5mg/kg bodyweight) were maintained in the study for 4 years or more without further active treatment.” EX1006, 1.
23. The method according to claim 14, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted).

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Claim	Alvarez-Gonzalez (EX1009), Giovannoni (EX1007), and Montalban (EX1006)
the completion of said 2 years with said 2 treatment courses.	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.
33. The method according to claim 27, wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.	“Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one. We then checked the total lymphocyte count in week 4 (Fig. 2F). After confirming the total lymphocyte count remained within normal limits we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5.” EX1009, 509 (footnote omitted).

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Claim	Alvarez-Gonzalez (EX1009), Giovannoni (EX1007), and Montalban (EX1006)
	“A second treatment cycle is planned 11 months after the first.” EX1009, 509. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417. “In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418.

Appendix C

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
1. A method of treating a progressive form of Multiple Sclerosis, said method comprising:	“A Phase 2 study of cladribine add-on to interferon-beta (INF-beta) therapy in multiple sclerosis (MS) patients with active disease (ONWARD).” EX1005, Title. “Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12.
orally administering Cladribine to a patient in need thereof	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“The Oral Cladribine Added onto IFN-β1a in Patients with Active Relapsing Disease (ONWARD) study will evaluate the safety and tolerability of cladribine tablets as an add-on therapy to IFN-β.” EX1008, 322.
at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg,	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320.
wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS),	experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
2. The method according to claim 1, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320.
3. The method according to claim 1, wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	cladribine tablets added on to IFN- β demonstrated significant efficacy benefits.” EX1006, 1.
4. The method according to claim 1, wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
5. The method according to claim 4, wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
6. The method according to claim 5, wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
8. The method according to claim 1, wherein each treatment year comprises:	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
(i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and	“To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
(ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
9. The method according to claim 1, wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive Multiple Sclerosis,	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 124. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
11. The method according to claim 1, wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
12. The method according to claim 1, wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “The Oral Cladribine Added onto IFN-β1a in Patients with Active Relapsing Disease (ONWARD) study will evaluate the safety and tolerability of cladribine tablets as an add-on therapy to IFN-β.” EX1008, 322.
14. A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising:	“A Phase 2 study of cladribine add-on to interferon-beta (INF-beta) therapy in multiple sclerosis (MS) patients with active disease (ONWARD).” EX1005, Title. “Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12.
orally administering to said patient a cumulative dose of Cladribine	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “The Oral Cladribine Added onto IFN-β1a in Patients with Active Relapsing Disease (ONWARD) study will evaluate the safety and tolerability of cladribine tablets as an add-on therapy to IFN-β.” EX1008, 322.
of about 3.5 mg/kg body weight, with a maximum deviation of +/-0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg +/-0.2 mg/kg per year,	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year,	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS),	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
15. The method according to claim 14, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
16. The method according to claim 15, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
18. The method according to claim 14, where the progressive form of Multiple Sclerosis is selected from	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.	treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
19. The method according to claim 18, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
20. The method according to claim 14, wherein said patient is between 18 and 65 years old.	“Ages Eligible for Study: 18 Years to 65 Years.” EX1005, 11. “Inclusion Criteria: Be male or female, 18 to 65 years of age (inclusive).” EX1005, 11. “ONWARD was a 2-year, randomized, double-blind Phase IIb study in patients aged 18-65 years, with ≥ 1 relapse during the prior 48 weeks while on IFN-β therapy, with EDSS scores 1.0-5.5 and normal blood cell counts within 28 days of baseline.” EX1006, 1.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
23. The method according to claim 14, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
24. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, comprising	“A Phase 2 study of cladribine add-on to interferon-beta (INF-beta) therapy in multiple sclerosis (MS) patients with active disease (ONWARD).” EX1005, Title.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12.
orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each,	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year)." EX1008, 320. "Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period." EX1008, 320. "The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen." EX1008, 324.
wherein said tablets or capsules are administered during a treatment year comprising the following regimen:	"Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks." EX1005, 11. "To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS." EX1006, 1. "A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year)." EX1008, 320.

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(Exhibit 1002)

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
(ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
wherein patients having a bodyweight in the range of 40 to less than 50 kg are administered 1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively,	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 60 to less than 70 kg are administered 1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 70 to less than 80 kg are administered 1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of said treatment course,	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 80 to less than 90 kg are administered 1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 90 to less than 100 kg are administered 1) 9 tablets or capsules (90 mg of Cladribine) in the 1st	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
treatment week of said treatment course, 2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of said treatment course; in the range of 100 to less than 110 kg are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of said treatment course; or in the range of 110 kg and above are administered	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of said treatment course.	
25. The method according to claim 24, wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
26. The method according to claim 25, wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
27. A method of treating a patient suffering from a progressive form of Multiple Sclerosis,	“A Phase 2 study of cladribine add-on to interferon-beta (INF-beta) therapy in multiple sclerosis (MS) patients with active disease (ONWARD).” EX1005, Title. “Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12.
wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
Progressive Relapsing Multiple Sclerosis (PRMS),	“Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS),	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses." EX1005, 11-12. "Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms." EX1005, 12. "14.5[percent] of patients (N=172) had SPMS at baseline." EX1006, 1. "In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits." EX1006, 1.
said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each,	"Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks." EX1005, 11. "To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS." EX1006, 1. "A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year)." EX1008, 320. "Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period." EX1008, 320. "The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen." EX1008, 324.
wherein said tablets or capsules are administered during two treatment years comprising the following regimen:	"Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks." EX1005, 11. "To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS." EX1006, 1. "A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year)." EX1008, 320.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
(i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
	“The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
(ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11. “To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.
wherein patients having a bodyweight	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
in the range of 40 to less than 50 kg are administered 1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively[;] in the range of 50 to less than 60 kg are administered 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,	“To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS.” EX1006, 1. “A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year).” EX1008, 320. “Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period.” EX1008, 320. “The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen.” EX1008, 324.

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively[;] in the range of 60 to less than 70 kg are administered 1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; in the range of 70 to less than 80 kg are administered	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; in the range of 80 to less than 90 kg are administered 1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
and the 2nd treatment course, respectively; in the range of 90 to less than 100 kg are administered 1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; in the range of 100 to less than 110 kg are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
and the 2nd treatment course, respectively, 2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; or in the range of 110 kg and above are administered 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively, 2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively.	

Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
30. The method according to claim 27, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.	“Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.” EX1005, 10. “Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.
33. The method according to claim 27, wherein to the patients having	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive

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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.	days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks." EX1005, 11. "To assess the efficacy of cladribine tablets (3.5mg/kg) as an add-on to IFN-β in patients with active relapsing MS." EX1006, 1. "A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year)." EX1008, 320. "Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period." EX1008, 320. "The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen." EX1008, 324.
34. The method according to claim 27, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple	"Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled." EX1005, 10.

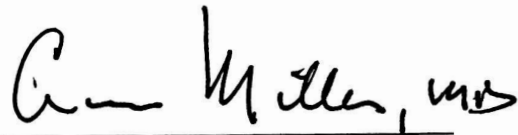
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Claim	Clinicaltrials.gov (EX1005), Schreiber (EX1008) and Montalban (EX1006)
Sclerosis and Secondary Progressive Multiple Sclerosis.	“Inclusion criteria: ... Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses.” EX1005, 11-12. “Exclusion criteria: Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms.” EX1005, 12. “14.5[percent] of patients (N=172) had SPMS at baseline.” EX1006, 1. “In patients with active relapsing MS with breakthrough disease while on IFN-β therapy (including SPMS with ongoing relapses), treatment with cladribine tablets added on to IFN-β demonstrated significant efficacy benefits.” EX1006, 1.

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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: 09/FEB/2023

A handwritten signature in black ink, appearing to read "A. E. Miller, MD", written over a horizontal line.

Dr. Aaron E. Miller, M.D.