UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, LLC,
Petitioner

v.

MERCK SERONO S.A.,
Patent Owner

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

SECOND DECLARATION OF AARON E. MILLER, MD

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. SUMMARY OF OPINIONS 2

III. LIST OF DOCUMENTS I CONSIDERED IN FORMULATING MY OPINIONS 10

V. STATE OF THE ART BEFORE DECEMBER 22, 2004 19

VI. CLAIM TERMS 23

A. The claims do not require any particular metric or degree of efficacy. 23

B. The claims do not require knowing a patient's weight before administering cladribine. 25

C. "About 1.7 mg/kg" 27

VII. BASIS OF MY ANALYSIS WITH RESPECT TO OBVIOUSNESS 28

VIII. CLAIMS 36, 38, 39, AND 41–46 WOULD HAVE BEEN OBVIOUS IN VIEW OF THE COMBINATION OF BODOR AND STELMASIAK. 33

A. A POSA would have been motivated to administer Bodor's oral cladribine tablets per Bodor's dosing regimen in an induction period followed by a 10 month cladribine-free period. 34

1. Before 2004, reducing inflammation by suppressing lymphocytes was a known goal of MS therapy. 34
2. Prior art studies demonstrated cladribine's efficacy and safety in treating MS. 35
3. A POSA would have used Bodor's oral cladribine tablets to treat MS. 40
4. A POSA would not have had to "convert" Bodor's regimen to a "weight-based" regimen to arrive at the claimed methods. 42

B. A POSA would have been motivated to re-treat with cladribine after Bodor's induction/cladribine-free period. 47

1. A POSA would have re-treated with cladribine because the art suggests as much. 47
2. A POSA would have re-treated because cladribine's suppression of lymphocytes was known to be

impermanent and MS is a chronic, lymphocyte-dependent autoimmune disease in which patients were expected to relapse. 48

3. A POSA would not have been dissuaded to re-treat with cladribine due to safety concerns because prior art studies demonstrated cladribine's safety in treating MS. 51

4. A POSA would have re-treated because the dosing of other MS drugs suggests re-treatment after a drug-free period. 55

C. A POSA would have routinely optimized the dose and dosing length of the maintenance period to arrive at a lower dose. 56

D. A POSA would have incorporated a second cladribine-free period after the re-treatment period. 60

E. A POSA would have had a reasonable expectation of success. 62

1. A POSA would have reasonably expected Bodor's induction/cladribine-free period to treat MS..... 62

2. A POSA would have reasonably expected to successfully re-treat patients with cladribine after Bodor's induction/cladribine-free period..... 66

F. Claims 38, 39, and 41–46 would have been obvious over the combination of Bodor and Stelmasiak.....68

IX. DR. LUBLIN'S OBJECTIVE EVIDENCE DO NOT SUPPORT NONOBVIOUSNESS OF THE CLAIMED METHODS. 69

A. Dr. Lublin does not demonstrate skepticism. 69

B. Dr. Lublin does not demonstrate unexpected results. 77

C. Dr. Lublin does not establish a long-felt, but unmet need.....83

I, Aaron E. Miller, MD, hereby declare as follows.

I. INTRODUCTION

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

2. I have previously provided a declaration dated January 23, 2023, (EX1002) in these proceedings in support of HOPEWELL PHARMA VENTURES, INC.'s ("HOPEWELL") Petition for the above-captioned *inter partes* review (IPR). The opinions I expressed in my first Declaration remain unchanged.

3. My professional background and qualifications discussed in ¶¶4–13 of EX1002, remain unchanged.

4. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is $790 per hour.

5. I understand that this Declaration accompanies the Petitioner's Reply to the Patent Owner's Response dated December 23, 2023.

6. In preparing this Declaration, I have reviewed the '947 patent and each of the documents cited herein, in light of general knowledge in the art. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art ("POSA"), which I defined in my first declaration (EX1002, ¶¶20–21) prior to December 22, 2004.

II. SUMMARY OF OPINIONS

7. Before 2004, the prior art reported that cladribine "shows promise as a treatment" for multiple sclerosis (MS) (EX1031, Abstract), contrary to Dr. Lublin's argument that the art was "skeptical about the utility of cladribine for treating MS" (EX2051, ¶68). Several pre-2004 publications reported that cladribine "impressively" decreased relapse rate in patients with relapsing-remitting MS (RRMS). EX1013, 7; *see also* EX1031, Abstract. Dr. Lublin agrees with me that a reduction in relapse rate is "important" in determining clinical efficacy of an MS drug, therefore, it is "included in almost all [MS] trials" as an endpoint. EX1061, 41:18–19; EX2011, 4. Treatment with cladribine also "virtually eliminated" enhancing brain lesions, which are current sites of inflammatory demyelination. EX1018, 1153; EX1006, 940. Such a response provides "strong evidence of treatment effects," with which Dr. Lublin agrees. EX2011, 4. And the adverse events reported with cladribine were "mild or moderate in severity," and "not treatment-limiting." EX1018, Abstract; EX1061, 104:7–12; *see also* EX1031, Abstract. Thus, I disagree with Dr. Lublin's conclusion that pre-2004 cladribine studies reported a "lack of cladribine clinical efficacy" and "safety concerns," and maintain that a POSA would have been motivated to treat MS with cladribine before 2004. EX2051, ¶68.

8. I also disagree with Drs. Lublin and Meibohm that a POSA would not have treated MS with Bodor's oral cladribine tablets because "a POSA would have understood that Stelmasiak's oral cladribine formulation has higher bioavailability than Bodor's." EX2051, ¶167; *see also* EX2052, ¶83. Drs. Lublin and Meibohm are not considering the art from the perspective of a POSA. Further, their opinions focus on oral bioavailability while ignoring other desirable characteristics of Bodor's tablets, including lower interpatient and intrapatient variability, higher stability, and better patient compliance and convenience compared to other oral and parenteral formulations. EX2051, ¶¶168–171; EX2052, ¶21. To be sure, Dr. Bodor himself admitted there were "many reasons," including "convenience, or cost, or compliance, [and] stability," why a POSA would prefer to use a solid tablet instead of an oral liquid. EX1059, 61:18–62:2. In fact, a POSA would have understood from Bodor that his oral tablets incorporate cladribine in "a high thermodynamic state," which results in "improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation." EX1002, ¶79; EX1022, 11:27–12:3, 23:9-20. And a POSA would not have had a reason to ignore Bodor's characterization of cladribine's tablet, given that it originated from Dr. Bodor, an accomplished inventor in 2004. EX1080, ¶34, FN 3. And in any event, as I explain in detail below, a POSA would have

understood that Stelmasiak's solution did not have a higher oral bioavailability than Bodor's tablets.

9. I have previously opined that it would have been obvious to administer Bodor's tablets to a patient of average weight (e.g., 70 kg), and in doing so, a POSA would have arrived at the claimed induction dose of 1.4 mg/kg to 2 mg/kg. EX1002, ¶83. Dr. Lublin "disagree[s] that Bodor's flat, fixed dosing is 'equivalent' to weight-based dosing of approximately 1.4 to 2 mg/kg." EX2051, ¶89. Dr. Lublin misrepresents my testimony on this issue. I did not base my opinions on "one very particular-weight patient, chosen with hindsight" from "any patient weight." EX2051, ¶¶89–90. Instead, I explained that POSA would have been able to determine that Bodor teaches administering a total of 100 to 140 mg of cladribine over a two-month induction period, which, when administered to an average adult weighing 70 kg, would have resulted in a dose of 1.4 mg/kg to 2 mg/kg. EX1002, ¶83.

10. To be sure, Dr. Lublin did not disagree with me that treating a MS patient of average weight would have been obvious to a POSA. A POSA reading Bodor certainly would have contemplated applying Bodor's method to a patient of average weight because a POSA would have understood that treatment regimens are designed for treating average patients unless they specifically indicate otherwise. Nothing in Bodor suggests that its teachings are irrelevant to a patient

of average weight, and Dr. Lublin never provides a reason to exclude an average-weight patient from Bodor's disclosure. To the contrary, as Dr. Lublin concedes, Stelmasiak also reported treating MS patients between 52–75 kg (median of 66 kg) with cladribine, without any weight-based exclusion. EX1013, 5; EX2051, ¶96. Further, the '947 patent claims do not recite administering cladribine to patients of a particular weight, nor do they exclude administering cladribine to patients of a particular weight, with which Dr. Lublin agrees. EX1001, 19:13–30, 20:3–7, 20:11–25; EX1061, 135:1–10. Further, as I explain in Section V.B, the claims do not require knowing a patient's weight or determining a patient's weight *before* administering cladribine. EX1001, 19:13–30, 20:3–7, 20:11–25.

11. Bodor expressly teaches an MS cladribine treatment regimen that included a 2-month induction period and a 10-month "no treatment" period, with which Dr. Lublin agrees. EX2051, ¶86. Dr. Lublin argues, however, that a POSA would not have "automatically re-treat[ed]" a patient after the cladribine-free period because "any subsequent re-treatment would have been based on a combination of factors, such as evidence of disease progression, time course of therapeutic effects, and safety considerations." EX2051, ¶113. But Dr. Lublin does not explain why a POSA would have disregarded Bodor's implied teaching to retreat. Indeed, what meaning would a POSA have assigned to Bodor's specified length of time (10 month) of the "no treatment" period other than to

resume the treatment after the 10 months? Dr. Lublin does not explain. But the most logical reading of Bodor would have included a re-treatment period, especially because such re-treatments were consistent with prior clinical studies and patients were known to relapse during or after cladribine treatment. EX1013, Abstract.

12. I have previously testified, and Dr. Lublin agreed with me, that treatment with cladribine results in a dose-related lymphocyte reduction in a patient, and that the safety of the treatment can be assessed using lymphocyte count. EX2051, ¶139; EX1061, 72:19–22; EX1002, ¶¶91, 92, 95, 102, 110. Dr. Lublin nevertheless contends that a POSA would not have optimized the maintenance period dose and length using a change in lymphocyte count because, allegedly, "it would require years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact clinical outcomes." EX2051, ¶127. But contemporaneously with the filing date of the '947 patent, Dr. Lublin was of the view that at least one clinical outcome, relapse rate, "is a routine measure of disease activity that is easy to quantify" and which is typically measured over one year. EX2011, 4; EX1061, 38:10–12. I agree that it is a routine measure of disease activity that is easy to quantify.

13. However, regardless of the time it takes to identify a clinical response, lymphocyte reduction induced by cladribine can be seen relatively quickly, within

a month or two. EX1018, FIG. 4; EX1013, FIG. 1; EX1031, FIG. 6 (Lymphocytes graph). Thus, a POSA would have understood that adjusting the cladribine dose or dosing length could be assessed by lymphocyte counts over the course of a few months, not years, as Dr. Lublin argues.

14. Dr. Lublin contends that a POSA would not have reasonably expected to successfully suppress lymphocytes with Bodor's modified dosing regimen, but I disagree. For example, Dr. Lublin argues that a POSA would not have expected to reduce lymphocytes below 1000 cells/μL with Bodor's maximum cladribine induction dose of 140 mg, because Stelmasiak's 150 mg dose did not achieve that level, despite Stelmasiak's "higher bioavailability." EX2051, ¶¶167, 183. However, as I made clear in my first declaration, lymphocytes do not need to be suppressed to *below* 1000 cells/μL to achieve a therapeutic effect—1000 cells/μL is merely an exemplary level. EX1002, ¶¶16, 32, 40, 90. As I explained in my first declaration, during treatment, neurologists commonly assessed the therapeutic effect of cladribine by monitoring a patient's lymphocyte count, with a sustained reduction of lymphocytes, e.g., to ≤ about 1000 cells/μL, being characteristic of a treatment response. EX1002, ¶16. I mentioned this 1000 cells/μL level because a POSA would have known that 1000 cells/μL was at the low end of the normal range of lymphocyte counts. EX1018, 1152, FIG. 4; EX2009, 31:19–20. I also explained during my deposition that 1000 cells/μL is an example of a lymphocyte

level that constitutes immune suppression. EX2009, 30:12–16, 31:16–32:12. However, I never argued that a POSA would have understood that lymphocytes must be suppressed to a level of ≤ about 1000 cells/μL or below to achieve a treatment response.

15. In any event, a POSA would have understood that Stelmasiak's solution did not have a higher oral bioavailability than Bodor's tablets. As I stated in my first declaration, the art taught that cladribine oral solution has a bioavailability of 37% to 51%. EX1002, ¶110; EX1048, 122. Bodor's oral tablets have a bioavailability of 35.7% to 52.1%. EX1002, ¶79; EX1022, Example 4, Table VI. Thus, Drs. Lublin and Meibohm are wrong when they contend that Bodor's oral tablets have a lower bioavailability than Stelmasiak's. A POSA would have understood Bodor's bioavailability to be at least comparable to Stelmasiak's. And Dr. Pinal agrees with me. EX1080, ¶77.

16. Further, a POSA would have reasonably expected Bodor's dose to treat MS. As I explained in my first declaration, Rice reported that patients receiving 0.7 mg/kg of subcutaneous cladribine—a dose that, as Dr. Pinal confirms, is comparable to Bodor's oral induction dose of 100–140 mg—exhibited a positive response to cladribine therapy because their enhancing lesions were eliminated. EX1080, ¶¶78–79; EX1018, 1153. A POSA would have thus expected to achieve a least similar results with Bodor's cumulative dose.

17. Drs. Lublin and Meibohm also narrowly focus on Stelmasiak's EDSS scores to contend that a POSA would not have looked to Bodor's dosing regimen to treat MS because Stelmasiak's "higher dose (300 mg) resulted in a better EDSS score than the lower dose (150 mg)." EX2051, ¶172; *see also* EX2052, ¶¶85, 87, 88. However, a POSA would have understood that Stelmasiak's 150 mg dose did, in fact, lower EDSS scores, which Dr. Lublin concedes is "important." EX1013, 5; EX2051, ¶60; *see also* EX1061, 49:10–15. As such, in light of Stelmasiak's data, a POSA would have at least expected Bodor's dosing regimen to reduce or maintain EDSS scores, both of which are metrics of efficacy.

18. Moreover, the majority of Stelmasiak's patients experienced a "very marked" reduction in relapse rate, which Dr. Lublin also concedes is a metric of efficacy. EX1013, 7; EX2051, ¶60; EX1061, 56:20–57:3. A POSA would also have reasonably expected Bodor's dose to reduce the number and volume of brain lesions based on Rice's study results, which showed just that with a similar dose of cladribine as Bodor's dose. And as Dr. Lublin conceded, the claims of the '947 patent do not recite a specific metric of efficacy, nor do the claims require a particular degree of efficacy. EX1061, 136:3–8. A single metric of efficacy would have been sufficient for a POSA to conclude cladribine's effectiveness. Therefore, a POSA would have expected a reasonable expectation of success in practicing the claimed methods.

19. Dr. Lublin's evidence of skepticism, unexpected results, and long-felt but unmet need does not support nonobviousness of the claimed methods. Dr. Lublin does not compare his evidence of unexpected results to the closest prior art, provide evidence that was roughly in line with the full scope of the claimed invention, or establish that the evidence is attributable to any unique characteristics of the claimed invention, which I understand is required, as I discuss in Section VI. When arguing that the art was skeptical of cladribine's efficacy in treating MS, Dr. Lublin cherry-picks prior-art studies in progressive MS patients and narrowly focuses on EDSS scores to argue cladribine's lack of efficacy, while disregarding other evidence that demonstrate cladribine's efficacy in RRMS patients (Stelmasiak (EX1013), Romine (EX1031)). And Dr. Lublin provides no evidence that an unmet need for an oral cladribine dosing regimen was recognized in the art before 2004.

III. LIST OF DOCUMENTS I CONSIDERED IN FORMULATING MY OPINIONS

20. In formulating my opinions, I have considered all the references and documents cited herein, including those listed below.

Exhibit No.	***Description***
1001	De Luca, G., et al., "Cladribine Regimen for Treating Multiple Sclerosis," U.S. Patent No. 7,713,947 B2 (filed June 18, 2007; issued May 11, 2010)

Exhibit No.	***Description***
1002	Declaration of Aaron E. Miller, M.D.
1004	File History for U.S. Patent No. 7,713,947
1006	Noseworthy, J.H., et al., "Multiple Sclerosis," *The New England Journal of Medicine*, 343(13):938-952 (2000)
1007	Neuhaus, O., et al., "Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection," *TRENDS in Pharmaceutical Sciences*, 24(3):131-138 (2003)
1008	Weiner, H.L., et al., "Immunotherapy of Multiple Sclerosis," *Annals of Neurology*, 23(3):211-222 (1988)
1009	Wingerchuk, D.M., et al., "Biology of Disease, Multiple Sclerosis: Current Pathophysiological Concepts," *Laboratory Investigation*, 81(3):263-281 (2001)
1010	Kurtzke, J.F., "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)," *Neurology*, 33:1444-1452 (1983)
1012	Whitaker, J.N., "Rationale for Immunotherapy in Multiple Sclerosis," *Annals of Neurology*, 36:S103-S107 (1994)
1013	Stelmasiak, Z., et al., "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis," *Medical Science Monitor*, 4(1):4-8 (1998)
1014	Beutler, E., et al., "The treatment of chronic progressive multiple sclerosis with cladribine," *Proceedings of the National Academy of Sciences*, USA 93:1716-1720 (1996)
1015	Tortorella, C., et al., "Cladribine Ortho Biotech Inc," *Current Opinion in Investigational Drugs*, 2(12):1751-1756 (2001)
1016	Langtry, H.D., et al., "Cladribine, A Review of its Use in Multiple Sclerosis," *BioDrugs*, 9(5):419-433 (1998)

Exhibit No.	***Description***
1017	Rudick, R.A., et al., "Management of Multiple Sclerosis," *The New England Journal of Medicine*, 337(22):1604-1611 (1997)
1018	Rice, G.P.A., et al., "Cladribine and progressive MS, Clinical and MRI outcomes of a multicenter controlled trial," *Neurology*, 54:1145-1155 (2000)
1019	Barkhof, R., et al., "Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis," *Neuroradiology*, 36:382-387 (1994)
1020	Pirko, I. and Rodriguez, M., "Pulsed Intravenous Methylprednisolone Therapy in Progressive Multiple Sclerosis: Need for a Controlled Trial," *Archives of Neurology*, 61:1148-1149 (2004)
1021	Weiner, H.L., et al., "Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: Final report of the Northeast Cooperative Multiple Sclerosis Treatment Group," *Neurology*, 43:910-918 (1993)
1022	Bodor, N. and Dandiker, Y., "Oral Formulations of Cladribine," International Publication No. WO 2004/087101 A2 (filed March 26, 2004; published October 14, 2004)
1023	Grieb, P., et al., "Effect of Repeated Treatments with Cladribine (2-Chlorodeoxyadenosine) on Blood Counts in Multiple Sclerosis Patients," *Archivum Immunologiae Experimentalis*, 43:323-327 (1995)
1024	Schultz, T.W., et al., "Cyclodextrine Cladribine Formulations," U.S. Patent No. 6,194,395 B1 (filed February 25, 1999; issued February 27, 2001)
1025	File History for U.S. Patent No. 8,377,903

Exhibit No.	***Description***
1026	Beutler, E., "Use of Substituted Adenine Derivatives for Treating Multiple Sclerosis," U.S. Patent No. 5,506,214 B2 (filed February 18, 1993; issued April 9, 1996)
1031	Romine, J. S., et al., "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis," *Proceedings of the Association of American Physicians*, 111(1):35-44 (1999)
1033	Bloom, P.M., "Treatment of Multiple Sclerosis With Lymphocytapheresis and Chemo-Immunosuppression," U.S. Patent No. 4,964,848 (filed June 27, 1988; issued October 23, 1990)
1036	Lassmann, H., et al., "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy," *TRENDS in Molecular Medicine*, 7(3):115-121 (March 2001)
1037	Lublin, F. D., et al., "Defining the clinical course of multiple sclerosis: Results of an international survey," *Neurology*, 46:907-911 (1996)
1038	Casanova, B., et al., "High clinical inflammatory activity prior to the development of secondary progression: a prospective 5-year follow-up study," *Multiple Sclerosis*, 8:59-63 (2002)
1042	Shurkovich, S., et al., "Randomized study of antibodies to INF-γ and TNF-α in secondary progressive multiple sclerosis," *Multiple Sclerosis*, 7:277-84 (2001)
1043	Khoury, S. J., "Multiple Sclerosis: What Have We Learned From Magnetic Resonance Imaging Studies?," *Archives of Internal Medicine*, 158:565-73 (1998)
1044	Roitt, I. M., "Essential Immunology, Sixth Edition," Blackwell Scientific Publications, 1-29 (1988) (Excerpt)

Exhibit No.	***Description***
1045	Filippi, M., et al., "The effect of cladribine on T1 'black hole' changes in progressive MS," *Journal of Neurological Sciences*, 176:42–44 (2000)
1046	Romine, J. S., et al., "Cladribine: Use in Therapy of Multiple Sclerosis," *Biodrugs*, 7(5):386-93 (1997)
1047	Selby, R., et al., "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis," *Canadian Journal of Neurological Sciences*, 25:295-99 (1998)
1048	Liliemark, J., "The Clinical Pharmacokinetics of Cladribine," *Clinical Pharmacokinetics*, 32(2):120-31 (1997)
1049	Barkhof, F., et al., "Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis," *Neuroradiology*, 36:382-387 (1994)
1050	Chumlea, W.C., "Total body water data for white adults 18 to 64 years of age: The Fels Longitudinal Study," *Kidney International*, 56:244-252 (1999)
1059	Transcript of the Deposition of Nicholas S. Bodor. Ph.D. (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
1061	Transcript of the Deposition of Fred D. Lublin, M.D.
1062	Transcript of the Deposition of Dr. Bernd Meibohm
1064	Albertioni, F. et al., "On the bioavailability of 2-chloro-2'-deoxyadenosine (CdA): The influence of food and omeprazole," *Eur. J. Clin. Pharmacol.*, 44:579–582 (1993)
1065	Gilbert S. Banker and Christopher T. Rhodes, *Modern Pharmaceutics*, 4th ed., 2002
1080	Declaration of Rodolfo Pinal, Ph.D. (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)

Exhibit No.	***Description***
1083	Sipe, J.C. et al., "A neurologic rating scale (NRS) for use in multiple sclerosis," *Neuro.*, 34:1368–1372 (1984)
2001	MAVENCLAD® (Cladribine) Package Insert (2022)
2004	H. El-Moslimany et al., *Escape Therapies and Management of Multiple Sclerosis* in C. S. Raine MULTIPLE SCLEROSIS A COMPREHENSIVE TEXT 333 (2008)
2005	A. E. Miller et al., *Treatment Issues* in R. C. Kalb MULTIPLE SCLEROSIS: THE QUESTION YOU HAVE – THE ANSWERS YOU NEED 43 (2d ed. 2000)
2006	M. J. Tullman et al., *Immunotherapy of Multiple Sclerosis – Current Practice and Future Directions*, 39 J. REHAB. RES. DEV. 273 (2002)
2007	Video: A. Miller, *What You Need to Know About Mavenclad®* (https://www.nationalmssociety.org/Treating-MS/Medications/Mavenclad) (2019)
2008	Transcript of Video, A. Miller, *What You Need to Know About Mavenclad®* (2019)
2009	Deposition Transcript of Dr. Aaron Miller (December 12, 2023)
2010	J. E. Joy et al., Multiple Sclerosis: Current Status and Strategies for the Future, 17 (2001)
2011	F. Lublin, *History of Modern Multiple Sclerosis Therapy*, 252 (SUPPL 3) J. NEUROL. III/3 (2005)
2013	D. S. Goodin et al., *Disease Modifying Therapies in Multiple Sclerosis*, 58 NEUROLOGY 169 (2002)
2014	Betaseron® (Interferon beta-1b) Package Insert (1993)
2015	Avonex™ (Interferon beta-1a) Package Insert (1996)

Exhibit No.	***Description***
2016	Rebif® (Interferon beta-1a) Package Insert (2003)
2017	Copaxone® (glatiramer acetate) Package Insert (2001)
2018	Novantrone® (mitoxantrone) Package Insert (2000)
2019	Tysabri® (natalizumab) Package Insert (2004)
2020	R. A. Rudick et al., *Natalizumab: α_4-Integrin Antagonist Selective Adhesion Molecule Inhibitors for MS*, 4 EXPERT REV. NEUROTHER. 571 (2004)
2021	R. A. Rudick et al., *Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis*, 354 NEW ENG. J. MED. 911 (2006)
2024	L. Durelli, *Dose and Frequency of Interferon Treatment Matter*, 250 J. NEUROL. (SUPPL 4) IV/9 (2003)
2025	D. S. Alberts et al., *Disposition of Mitoxantrone in Cancer Patients*, 45 CANCER RES. 1879 (1985)
2026	M. Caporro et al., *Two Decades of Subcutaneous Glatiramer Acetate Injection: Current Role of the Standard Dose, and New High-Dose Low-Frequency Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis Treatment*, 8 PATIENT PREFER. ADHERENCE 1123 (2014)
2030	J. C. Sipe et al., *Development of Cladribine Treatment in Multiple Sclerosis*, 1 MULT. SCLER. 343 (1996)
2031	J. Noseworthy et al., *Disease-Modifying Treatments in Multiple Sclerosis* in A. Compston MCALPINE'S MULTIPLE SCLEROSIS 729 (4th ed. 2005)

Exhibit No.	***Description***
2032	K. Rammohan et al., *The Development of Cladribine Tablets for the Treatment of Multiple Sclerosis: A Comprehensive Review*, 80 DRUGS 1901 (2020)
2033	G. Giovannoni et al., *A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis*, 362 NEW ENG. J. MED. 416 (2010)
2034	G. Giovannoni et al., Supplementary Appendix to *A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis*, 362 NEW ENG. J. MED. 416 (2010)
2035	G. Giovannoni et al., *Safety and Efficacy of Cladribine Tablets in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized Extension Trial of the CLARITY Study*, 24 MULT. SCLER. J. 1594 (2018)
2036	G. Giovannoni et al., *Long-Term Follow-Up of Patients with Relapsing Multiple Sclerosis from the CLARITY/CLARITY Extension Cohort of CLASSIC-MS: An Ambispective Study*, 29 MULT. SCLER. J. 719 (2023)
2037	A. Miller et al., *Current and Investigational Therapies Used to Alter the Course of Disease in Multiple Sclerosis*, 90 SOUTH. MED. J. 367 (1997)
2038	*Merck Receives Complete Response Letter From FDA on Cladribine Tablets New Drug Application*, FIERCEBIOTECH.COM (March 2, 2011) (https://www.fiercebiotech.com/biotech/merck-receives-complete-response-letter-from-fda-on-cladribine-tablets-new-drug- application) Accessed on November 24, 2023
2040	FDA News Release: *FDA Approves New Oral Treatment For Multiple Sclerosis* (March 29, 2019) (https://www.fda.gov/news-events/press- announcements/fda-approves-new-oral-treatment-multiple-sclerosis) Accessed on November 25, 2023

Exhibit No.	***Description***
2041	ClinicalTrials.gov publication and Record History, NCT00213135 *A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS) (CLARITY)* (2014) (https://clinicaltrials.gov/study/NCT00213135; https://clinicaltrials.gov/study/NCT00213135?tab=history&a=13) Accessed on November 25, 2023
2042	M. Hoffman, K. Rammohan Interview: *Short-Term Dosing Regimen Gives Cladribine an Advantage in MS*, NEUROLOGYLIVE (July 1, 2020) (https://www.neurologylive.com/view/shortcommitment-dosing-regimen-gives-cladribine-an-advantage-in-ms) Accessed on November 10, 2023
2043	J. Liliemark et al., On the Bioavailability of Oral and Subcutaneous 2-Chloro-2'-Deoxydenosine in Humans: Alternative Routes of Administration, 10 JOURNAL OF CLINICAL ONCOLOGY 1514 (1992)
2051	Declaration of Fred D. Lublin, M.D.
2052	Declaration of Bernd Meibohm, Dr.rer.nat.
2059	Copaxone® (glatiramer acetate) Package Insert (2014)
2060	A. Liu, *Better 8 Years Late Than Never: Merck KGaA Nabs FDA Nod for MS Drug MAVENCLAD*, FIERCEPHARMA.COM (April 1, 2019) (https://www.fiercepharma.com/pharma/better-8-years-late-than-never- merck-kgaa-nabs-fda-nod-for-ms-drug-mavenclad) Accessed on December 18, 2023
2061	The Canadian Cooperative Multiple Sclerosis Study Group, *The Canadian Cooperative Trial of Cyclophosphamide and Plasma Exchange in Progressive Multiple Sclerosis*, 337 Lancet 441 (1991)

Exhibit No.	***Description***
2062	Hainer JW, Barrett JS, Assaid CA, Fossler MJ, Cox DS, Leathers T, Leese PT. Dosing in heavy-weight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. Thromb Haemost. 2002 May; 87(5):817-23. PMID: 12038783
2063	Meibohm, B, Evans, WE: Clinical Pharmacodynamics & Pharmacokinetics. In: Helms, RA, Quan, DJ: Textbook of Therapeutics: Drug and Disease Management, 8th Ed., Lippincott Williams Wilkins 2006, ISBN 0-7817-5734, p. 1-31
2070	SAFETY & SIDE EFFECTS Learn about the possible risks of MAVENCLAD (https://www.mavenclad.com/en/home/why-mavenclad/safety-and-side-effects.html#:~:text=It) (last updated November 2022) Accessed on December 18, 2023

V. STATE OF THE ART BEFORE DECEMBER 22, 2004

21. In addition to my comments on the state of the art that I provided in ¶¶22–63 of my first declaration (EX1002), I provide the following additional comments on the state of the art related to the metrics used to assess MS treatment efficacy in response to Dr. Lublin's testimony.

22. Before 2004, clinicians used various outcomes to assess efficacy of disease-modifying therapies ("DMTs") in MS treatment. EX1002, ¶35; EX1013, Abstract; EX1018, Abstract; EX1031, Abstract; EX1061, 56:20–57:4, 62:3–5; EX2051, ¶¶60–61. One such outcome was relapse rate. EX1013, 7; EX1031, Abstract; EX1061, 38:19–22. A relapse is "associated with inflammation in a localized area," and includes "an acute onset of something," *e.g.*, "loss of vision in

one eye," "numbness, tingling, difficulty walking, slurred speech, double vision," "bladder dysfunction, cognitive dysfunction," as Dr. Lublin agrees. EX1061, 27:21–28:8. As I explained in my first declaration, a POSA would have understood the reduction in the frequency and severity of exacerbations (or relapses) was a "favorable effect of cladribine." EX1002, ¶44; EX1013, Abstract. Dr. Lublin agreed with me in his deposition, noting that relapses are a "measure of disease activity," and "it's important to decrease the number of relapses" in patients suffering from MS. EX1061, 41:18–19; EX2011, 4. This is because, as Dr. Lublin correctly noted, "patients don't like them," "they cause impairment," "they cause time away from work," "there's potential suffering." EX1061, 41:19–22. This is why relapse rate as an outcome measure is "included in almost all trials." EX2051, ¶60; EX2011, 4.

23. Physical disability status, which measures disease progression, was another measure of treatment efficacy in MS before 2004. EX2051, ¶60; EX2011, 4; *see also* EX1002, ¶26. A POSA would have known, and Dr. Lublin agrees, that the most common measure of physical disability is the Kurtzke Expanded Disability Status Scale (EDSS), which is based on a neurologic exam of different functional systems in the body. EX1010, 1445–49; EX1016, 425–26; EX2051,

¶60.[1] However, Dr. Lublin admitted during his deposition that there is a "subjective" element to the EDSS test due to the patient-reported parameters, such as "cognitive and mood assessment and the bladder assessment." EX1061, 47:16–18, 48:11–19. EDSS scoring is also "dependent on the examiner." EX1061, 49:19–20. Therefore, as Dr. Lublin admitted during his deposition, "the [EDSS] assessment from one person to the next may differ," and "intra- and inter-rater variabilities can occur with EDSS." EX1061, 49:19–21.

24. Magnetic resonance imaging ("MRI") was also commonly used to assess a patient's disease state before 2004, as Dr. Lublin conceded. EX2051, ¶61; EX1061, 42:16–18; EX1006, 940, 946. MRI scans show the difference between active and non-active brain lesions in MS patients. EX1061, 64:3–65:15, 66:6–12. Active lesions, also known as gadolinium-enhancing T1 lesions, appear in the scans as white patches when a contrast fluid containing gadolinium is injected, which highlights the "current sites of presumed inflammatory demyelination (active lesions)." EX1006, 940, 946; EX1002, ¶27; EX1061, 64:7–10, 66:3–9; EX2051, ¶61. Hypointense (or "dark") lesions, which can also be seen with a T1

[1] The Scripps Neurological Rating Scale ("SNRS") is an alternative neurologic rating scale developed by Scripps to clinically assess MS patients' impairment. EX1083.

MRI scan, are likely to be older lesions. EX1061, 65:14–15. Hyperintense, or bright, lesions can be seen with a T2 MRI scan. EX1061, 66:10–12. These hyper- and hypointense lesions are "the scar[s] of the MS," as Dr. Lublin correctly called them. EX1061, 65:14–15, 66:12. Old and new lesions seen on MRI provided "useful information about acute disease activity" and "strong evidence of treatment effects." EX2011, 4; EX1061, 34:3–15, 42:16–18, 44:1–14, 44:17–45:5, 61:22–62:5.

25. A POSA would have understood that measuring lymphocyte count was a way to ensure cladribine was effectively suppressing the immune system according to its mechanism of action. Before 2004, clinicians measured lymphocyte count in patients treated with some DMTs to assess the drug's pharmacologic effect. A POSA would have known that measuring lymphocytes in response to a DMT treatment (e.g., cladribine) was routinely practiced in the field, and Dr. Lublin does not disagree. EX1002, ¶52; EX2051, ¶¶139–141. Instead, Dr. Lublin contends that "a sustained decrease in lymphocyte count was not necessarily characteristic of [DMT] treatment response for MS." EX2051, ¶52 (quotation omitted). While not *all* known DMTs exerted their effect by suppressing lymphocytes, they all targeted inflammation, as Dr. Lublin conceded. EX1061, 63:20–63:1. Cladribine was an example of a DMT that reduced

inflammation by "induc[ing] a reduction in lymphocyte count." EX2051, ¶¶74, 137; EX1061, 58:7–11; 63:17–64:1; EX1016, 421; EX1046, Abstract.

26. A POSA would have understood improvements in one or more of relapse rate, EDSS score, brain lesions detected by MRI, or a reduction in lymphocyte counts would be indicative of a positive response to cladribine therapy. EX1013, Abstract; EX1018, Abstract; EX1031, Abstract; EX1061, 56:20–57:4, 62:3–5; EX2051, ¶¶60–61. A POSA would have also understood that patients do not have to demonstrate an improvement in every outcome metric in order to determine a cladribine's efficacy. EX1061, 52:10–15; EX1013, 7. And, as Dr. Lublin conceded, not every patient needs to demonstrate improvement in a given metric in order to demonstrate efficacy. EX1061, 51:9–14, EX1013, 7.

VI. CLAIM TERMS

27. My understanding of how to interpret terms of the claims is discussed in my first declaration. EX1002, ¶¶67, 71. I continue to use the same principles in interpreting these additional terms. In my first declaration, I construed the terms "total dose of cladribine," "induction period," and "maintenance period." EX1002, ¶¶68–70. I applied those same claim constructions to this current declaration.

A. The claims do not require any particular metric or degree of efficacy.

28. As I explained in my first declaration, I understand that the terms of the claims are to be given their plain and ordinary meaning from the point of a

POSA in question on December 22, 2004. EX1002, ¶67. I also understand that for any term I have not expressly interpreted, I should apply its plain and ordinary meaning.

29. Each of claims 36, 38, 39, and 41–46 of the ’947 patent recites a “method of treating multiple sclerosis,” and this term has its plain and ordinary meaning, as I stated in my first declaration. EX1002, ¶¶67, 70. The language of the claims of the ’947 patent does not contain any recitation of a specific metric of efficacy, nor do the claims require a particular degree of efficacy, as Dr. Lublin conceded. EX1061, 136:3–8. As such, a POSA would have understood that the claimed methods do not require an improvement in any particular metric of efficacy, nor do they require a particular degree of efficacy.

30. Also, while the claims do not define what “treating” means, the patent does define the term “efficacy.” The ’947 patent states the following:

> “Efficacy” of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the *frequency of relapses in RRMS* and the *presence or absence of new lesions in the CNS as detected using methods such as MRI technique*.

EX1001, 5:52–59 (emphasis added). The ’947 patent further states that the “observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced

lesions (thought to represent areas of active inflammation) gives a primary efficacy variable." EX1001, 5:60–63. The '947 patent lists the "Expanded Disability Status Scale score" ("EDSS") as one of several "secondary efficacy variables." EX1001, 5:64–6:6. Thus, a POSA would have understood that a reduction in the frequency of relapses (i.e., relapse rate) or a decrease in the number and/or volume of lesions detected by MRI are metrics of cladribine's treatment of MS. This is consistent with how clinicians treat MS in practice since, as Dr. Lublin conceded, "it's important to decrease the number of relapses" because "patients don't like them," "they cause impairment," "[t]hey cause time away from work," "[t]here's potential suffering." EX1061, 41:18–22; *see also* EX2011, 4. Dr. Lublin also admitted that lesions are measured because to "some degree [they are] a measure of severity" "of the illness." EX1061, 44:4–14.

B. The claims do not require knowing a patient's weight before administering cladribine.

31. According to Dr. Lublin, the "claims recite an induction period and a maintenance period during which cladribine is administered using a weight-based dosage (mg/kg)." EX2051, ¶79. Dr. Lublin argues that "when patients are administered a drug based on weight-based dosing, the prescriber determines the dose that each patient will get based on that individual's weight." EX2051, ¶91. In other words, a patient receives a dose in milligrams calculated *a priori* based on their weight and a previously determined mg/kg dose. However, a POSA would

have understood that claims 36, 38, 39, and 41–46 of the ’947 patent do not recite administering cladribine to patients of any particular weight. EX1001, 19:13–30, 20:3–7, 20:11–25. The claims also do not exclude administering cladribine to patients of any particular weight. EX1001, 19:13–30, 20:3–7, 20:11–25. Dr. Lublin conceded both points in his deposition. EX1061, 135:1–10. Nothing in the ’947 patent specification instructs that cladribine needs to be administered to patients of any weight, nor does it instruct not administering cladribine to patients of a particular weight. Nor did Merck make any such arguments during prosecution of the patent. EX1004.

32. Also, none of claims 36, 38, 39, and 41–46 require an active step of determining a patient’s weight before administering cladribine, nor do they require basing a dose to be administered on a patient’s weight. EX1001, 19:13–30, 20:3–7, 20:11–25. The ’947 patent also does not instruct weighing a patient before administering cladribine. While Table 3 of Example 1 of the ’947 patent discloses administering different amounts of cladribine to patients of different weights, the claims do not recite administering specific amounts of cladribine to patients of a specific weight. The claims do not preclude basing the cladribine dose on a patient’s weight provided that the method results in the mg/kg dose falling within the recite mg/kg range; however, they are not limited to such an administration.

Thus, while the claims of the ’947 patent encompass weight-based dosing, they are not limited to weight-based dosing.

C. “About 1.7 mg/kg”

33. Claim 39 recites that the total dose of cladribine reached at the end of the induction and maintenance periods is “about 1.7 mg/kg.” As I explain below, a POSA would understand the term “about” to mean a range of doses both higher and lower than 1.7 mg/kg. As such, the induction period and maintenance period doses can be within a range around 1.7 mg/kg.

34. As I explained in my first declaration, a POSA would have understood that the maintenance period dose must be lower than the induction period dose. EX1002, ¶70. As such, a POSA would construe claim 39 as requiring a maintenance period dose at the lower end of the range encompassed by “about 1.7 mg/kg” and the induction dose at the higher end of the range. During prosecution of the ’947 patent, Merck argued that none of the cited art taught “*lowering* treatment dosages with each successive use of the drug.” EX1004, 251. And during the prosecution of the ’903 patent, Merck argued that the maintenance period is characterized by administration of a *lower* total dose of cladribine compared to the induction period. EX1025, 151. These arguments were made in light of pending claims that recited “about 1.7 mg/kg” for both the induction period and maintenance periods doses. EX1004, 241, Claim 41; EX1025, 53,

Claim 20.

35. As such, claim 39 requires a total induction dose and total maintenance dose that are in the recited range, with the maintenance dose lower than the induction dose.

VII. BASIS OF MY ANALYSIS WITH RESPECT TO OBVIOUSNESS

36. As I explained in my first declaration, 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.

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

38. 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.

39. I further understand that a claimed range may be obvious if a prior art reference discloses a range that overlaps with or is encompassed by the claimed range. I further understand that even if a prior art reference does not disclose a particular value or range of values, the prior art would still render a claim obvious if it would require only routine experimentation to arrive at the claimed value or range of values.[2] I understand that a particular parameter must first be recognized as a result-effective variable, which I understand is a variable that achieves a recognized result, before the determination of the optimum or workable ranges of the variable may be characterized as routine experimentation. I also understand that the patentee may present evidence of teaching away, unexpected results, or criticality, or other pertinent objective evidence indicating that the overlapping range would not have been obvious in light of that prior art.

40. I understand that when considering the obviousness of an invention, one should also consider whether there is any objective evidence that supports the

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

nonobviousness of the invention. I understand that objective evidence of nonobviousness (also known as secondary considerations of nonobviousness) includes factors such as failure of others; unexpectedly superior results; skepticism followed by praise in the industry; long-felt, but unmet, need; copying; commercial acquiescence through licensing the of the patent; failure of others; teaching away; and commercial success.

41. I understand that in order to support an argument of nonobviousness, a patent owner may provide evidence that the invention achieves unexpectedly superior results relative to the closest prior art, which is the reference having the most in common with the claimed invention, bearing in mind the relative importance of particular limitations. I understand that there is no all-encompassing principle or test to determine the closest prior art. However, a comparison of the claimed invention with the disclosure of each prior art reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference. I also understand that the unexpectedly superior results must be reasonably in line with the full scope of the claims – i.e., roughly the full scope of the claimed invention should exhibit the unexpectedly superior results, not just one embodiment of the claimed invention. I further understand that a patent applicant does not need to show unexpectedly superior results for every single

embodiment within the scope of the claims, and that evidence that arises after the filing date of a patent is allowed to show unexpectedly superior results. And I understand that the unexpected results must be attributable to the unique characteristics of the claimed invention.

42. I understand that a long-felt, but unmet, need refers to a problem facing a particular technical area that has gone unsolved for a prolonged period. I understand that the mere passage of time is not sufficient to establish long-felt need; there needs to have been a technical reason that the need had not been satisfied. I also understand that the need must have been a persistent one that was recognized by those of ordinary skill in the art and must not have been satisfied by another before the claimed invention. I further understand that the claimed invention must, in fact, satisfy the long-felt need and that the filing date of the patent application is the relevant date for determining whether a long-felt need existed.

43. I understand that in order to demonstrate skepticism to support a nonobviousness argument, the evidence provided must (i) be in line with the full scope of the claims and (ii) have a connection to the unique features of the claimed invention.

44. I understand that in order to demonstrate commercial success, the evidence provided must have a connection to the unique features of the claimed

invention. I understand that the evidence must show that commercial success is in fact attributable to the claimed invention rather than to other, unrelated factors such as advertising or unclaimed features of the product. I also understand that when assessing commercial success, one must consider the patented product's market share, e.g., did the drug attain a large market share.

45. I understand that deference to the validity of a patient by a substantial portion of the competitors in a market – generally through acceptance of a license – may provide evidence of nonobviousness, provided there is a connection between the licensing activity and unique features of the claimed invention.

46. I understand that if others copied a patented invention, it may provide evidence that the claimed invention was nonobvious.

47. I understand that evidence showing that others tried but failed to develop the claimed invention may support an argument of nonobviousness, especially when the evidence indicates that others found the development of the claimed invention difficult and failed to achieve any success. I understand that when relying on the failure of others, a patent owner should provide details identifying actual failed attempts by others to develop features recited in the claims or to address problems solved by the claims. I further understand that a lack of competition in the marketplace alone is not enough to prove whether others "tried and failed" at developing a solution.

48. I also understand that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. I understand that a reference "teaches away" when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. I also understand that a teaching that an element only "sometimes works" or a mere expression of a general preference for an alternative invention without criticizing, discrediting, or otherwise discouraging in investigation into the invention claimed is not sufficient for teaching away.

VIII. CLAIMS 36, 38, 39, AND 41–46 WOULD HAVE BEEN OBVIOUS IN VIEW OF THE COMBINATION OF BODOR AND STELMASIAK.

49. In my first declaration, I concluded that claims 36, 38, 39, and 41–46 of the '947 patent would have been obvious in view of Bodor and Stelmasiak. EX1002, ¶¶78–119. I explained that a POSA would have had a reason to treat MS by administering Bodor's oral cladribine formulation for two months (an induction period), followed by a ten-month cladribine-free period. A POSA would have had a reason to re-treat a patient with another course of cladribine because MS is a chronic, progressive disease that typically requires periodic treatment and cladribine's therapeutic effects are impermanent. EX1002, ¶17. As I also explained in my first declaration, a POSA would have had a reasonable expectation of successfully modifying Bodor's dosing regimen in view of

Stelmasiak's teachings to arrive at the claimed method. EX1002, ¶¶111–119. My opinions regarding obviousness of the challenged claims have not changed. But I offer the following additional comments in rebuttal to Dr. Lublin's and Dr. Meibohm's testimony.

A. A POSA would have been motivated to administer Bodor's oral cladribine tablets per Bodor's dosing regimen in an induction period followed by a 10 month cladribine-free period.

1. Before 2004, reducing inflammation by suppressing lymphocytes was a known goal of MS therapy.

50. As I explained in my first declaration, and as Dr. Lublin conceded, before 2004, MS was known to be a lymphocyte-dependent autoimmune disease in which auto-reactive lymphocytes cross the blood-brain barrier and mediate the destruction of the myelin sheath. EX1002, ¶29; EX1007, 131; EX2051, ¶40; EX1061, 45:1–5. Given the inflammatory aspects of MS, reducing inflammation, either via suppression of auto-reactive lymphocytes or otherwise, was a goal of MS therapy before 2004. EX1061, 63:20–64:1. A common way to reduce inflammation in MS patients was with disease-modifying therapies ("DMTs", also referred to as "disease-modifying agents" or "DMAs"). EX1016, 420; EX1013, 6; EX2014, 1; EX2015, 1; EX2016, 1-2; EX2017, 1; EX2018, 3, 34; EX2019, 1, 5; EX1061, 58:7–11; EX2051, ¶50. Cladribine was an anti-inflammatory DMT, known to reduce lymphocytes by "apoptosis." EX2030, 343; *see also* EX1064, 579. Dr. Lublin does not dispute the fact that cladribine was known to cause a

"marked depletion" of lymphocytes in MS patients—a confirmation of cladribine's pharmacological activity. EX1014, 1718-19; EX1013, 7; EX1031, 41; EX1061, ¶73; EX2051, ¶137.

2. Prior art studies demonstrated cladribine's efficacy and safety in treating MS.

51. Before 2004, a POSA would have known that several prior art studies demonstrated cladribine's efficacy in treating MS. EX1002, ¶¶35–49. Specifically, these studies, which reflect the general knowledge in the art, demonstrated cladribine's efficacy by reducing relapse rate (EX1013, 7; EX1031, 38–39) and reducing lesions as detected by MRI (*see, e.g.,* EX1018, 1153), which Dr. Lublin does not dispute. EX2051, ¶¶60–61; EX1014, 1718–19; EX1061, 41:18–19, 62:4–5. For example, Stelmasiak reported a "very marked (almost five-fold on average) reduction in the relapse rate." EX1013, 7. Romine reported "a statistically significant favorable effect of cladribine on the joint frequency and severity of relapses" and that "MRI-enhancing lesions were completely suppressed in the cladribine patients by the sixth month of treatment." EX1031, Abstract. Rice reported that "[g]adolinium-enhancing lesions were virtually eliminated by treatment with cladribine" and "T2 burden of disease showed a modest improvement in cladribine-treated patients." EX1018, Abstract, 1153. Because reduction in relapse rates and enhancing lesions are measures cladribine's efficacy, as I explained above, a POSA would have considered cladribine to be a

"promis[ing] treatment" for MS; indeed, Romine expressly stated as much. EX1031, Abstract.

52. Dr. Lublin does not acknowledge, let alone reconcile, Stelmasiak's "very marked" reduction in relapse rate "during the 2 years after the initiation of the treatment." EX1013, 7. Dr. Lublin argues that before 2004, POSAs were "skeptical about the utility of cladribine for treating MS" because of "the reported lack of cladribine clinical efficacy," but Dr. Lublin downplays the improvements seen in relapse rates and brain lesions. EX2051, ¶¶67–70. For example, Dr. Lublin discounts Romine's results, in which patients' relapse rates "fell dramatically," and concludes that Romine didn't demonstrate efficacy because there were "no significant differences between the treatment groups in either EDSS or SNRS [i.e., Scripps Neurological Rating Scale] scores." EX2051, ¶67. Similarly, Dr. Lublin contends that after Stelmasiak's 9 months of no cladribine treatment, "EDSS scores worsened for both 'responders' and 'non-responders,'" "nearly returning to baseline for 'responders.'" EX2051, ¶183. Yet, a POSA would have understood that the fact that Stelmasiak's patients' EDSS scores at 24 months were the same as they were at baseline indicates a lack of overall disability worsening, which Dr. Lublin admits is a measure of efficacy. EX1061, 57:3–4. And, in fact, Stelmasiak reports that "[p]atients who experienced the reduced relapse rate also seemed to

show longer and more pronounced improvement in their neurological status." EX1013, Abstract.

53. A POSA would not have concluded that cladribine lacked efficacy based on EDSS scores alone when other metrics (reduced relapse rate, reduction in in the number and/or volume of brain lesions) established cladribine's positive effect on MS. In fact, Dr. Lublin admitted during his deposition that using EDSS to judge efficacy is "challeng[ing]." EX1061, 49:10–50:12. These "challenges" include "intra- and inter-rater variabilities," the fact that the "scale from zero to 10 is not linear," and that certain elements of the assessment are "subjective." EX1061, 48:11–15, 49:19–50:4. According to Dr. Lublin, the challenges of using EDSS scores to assess drug efficacy are why Dr. Lublin admitted that "we don't use things like mean EDSS anymore." EX1061, 49:11, 49:16–50:7. Thus, Dr. Lublin's conclusion that pre-2004 cladribine studies reported a "lack of cladribine clinical efficacy" is not supported by the art. EX2051, ¶68. I address Dr. Lublin's additional arguments regarding skepticism in the art in Section VIII.A below.

54. Dr. Lublin also admitted during his deposition that it would be "desirable to reduce a patient's relapse rate" even if a "patient's EDSS score doesn't change," which runs counter to his argument that "[a] study in which all outcomes point to the same effect, even if they are not all statistically significant, provides confidence that the outcomes observed are real." EX1061, 52:10–15;

EX2051, ¶62. Thus, a POSA would have understood that improvements in every outcome metric did not need to be seen in order to determine a drug's efficacy in treating MS.

55. Dr. Lublin also contends that the art was skeptical about cladribine in MS because of "safety concerns for long-term side effects of cladribine's lymphocytotoxic activity" (EX2051, ¶¶68, 72), but Dr. Lublin overinflates the concerns. Pre-2004 clinical studies, which administered 0.7 mg/kg to 2.8 mg/kg of cladribine, reported that adverse events were lower for 0.7 mg/kg and 2.1 mg/kg doses compared to a 2.8 mg/kg dose. For example, the earliest study in MS, which administered a total dose of 2.8 mg/kg of cladribine over four monthly courses, reported some patients developed thrombocytopenia and one patient developed severe bone marrow depression. EX1014, 1720. But subsequent pre-2004 studies using lower total doses of cladribine reported no such concerns. EX1013, 7; EX1047, Abstract; EX1031, 41; EX1018, 1153.

56. For example, Selby, which administered a total dose of 2.1 mg/kg, reported that cladribine "was remarkably well tolerated in CPMS [chronic progressive MS], with no significant myelosuppression." EX1047, Abstract. Romine, which administered a total dose of 2.1 mg/kg, reported that "there were no individual cases of significant thrombocytopenia, anemia, granulocytopenia, or generalized marrow suppression" and "no side effects that might have led to

unblinding of patients or examining neurologists." EX1031, 41. Rice, which administered a total dose of 0.7 mg/kg and 2.1 mg/kg, reported that "no serious adverse events could be attributed to cladribine treatment in this study." EX1018, 1153. Rice attributed the "improved tolerability and lower incidence of infections in this study" to the "dosing schedule." EX1018, 1153. Stelmasiak administered 2 mg/kg to 2.8 mg/kg to their subjects and reported that "[s]ide effects of the therapy are mild" and no "clinically significant hematological side effects" were seen over its two-year study. EX1013, 7.

57. Dr. Lublin also misconstrues Romine's disclosure when he argues that cladribine posed significant long-term safety concerns. EX2051, ¶72. Romine states that "[r]epeated treatment [with cladribine] raises long-term toxicity issues including: 1) susceptibility to opportunistic infection; 2) marrow stem cell depletion; and 3) an increase in the incidence of malignancy, known to occur in association with other long-term immunosuppressive treatments." EX1031, 43-44. However, Romine's comments are based on toxicity issues "known to occur in association with other long-term immunosuppressive treatments." EX1031, 44. Romine actually states that "there are few data on the safety of long-term retreatment with cladribine in a nonmalignant disease such as MS." EX1031, 43. A POSA would have understood that Romine's concerns are not related to cladribine, as confirmed by Romine's data and also Stelmasiak's data and their

conclusions, as I explained above. *See* ¶¶55–57. For example, Romine reports that in the patients who were re-treated with cladribine in their study, there were "no instances of marrow suppression or thrombocytopenia." EX1031, 43. And as I explained above, Stelmasiak's patients who were re-treated with cladribine experienced no "non-hematologic toxicity" or "clinically significant hematological side effects," despite repeated cladribine treatments. EX1013, 7. And a POSA would have understood that cladribine continued to be administered to MS patients before 2004, despite the "safety concerns" Dr. Lublin claims existed.

3. A POSA would have used Bodor's oral cladribine tablets to treat MS.

58. A POSA would have administered Bodor's oral cladribine tablets to treat MS, contrary to Drs. Lublin and Meibohm argument that a POSA would not have treated MS patients with Bodor's tablets because "a POSA would have understood that Stelmasiak's oral cladribine formulation has higher bioavailability than Bodor's." EX1002, ¶99; EX2051, ¶167; *see also* EX2052, ¶83. Drs. Lublin and Meibohm focus on the importance of bioavailability while ignoring other desirable characteristics of Bodor's tablets, including "lower interpatient and/or intrapatient variation of the drug" and "enhanced" patient compliance, and "reduced costs." EX1022, 2:9–19, 5:4–7. A POSA would have known that oral tablets were also preferred because they provide "increased stability" compared to

other oral dosage forms, such as oral solutions. EX1065, 287. In fact, Bodor discloses that its formulation was "uniquely well-suited for optimizing the oral bioavailability of cladribine." EX1022, 8:29–30. In addition, Dr. Bodor himself admitted there were "many reasons," including "convenience, or cost, or compliance, [and] stability," that a POSA would prefer to use a solid tablet instead of an oral liquid. EX1059, 61:18–62:2. Dr. Bodor also admitted that his tablets provided a "very important" reduction in interpatient and intrapatient variability. EX1059, 41:16–42:3. And Dr. Meibohm admitted during his deposition that the stability and interpatient variability of a dosage form are considerations when developing a dosing regimen. EX1062, 52:10–53:2, 53:12–16.

59. Dr. Pinal agrees with me and opines that Bodor's cladribine tablets have "host of benefits, such as an acceptable bioavailability, lower interpatient variability, increased stability, and greater potential for patient compliance and convenience than other cladribine dosage forms." EX1080, ¶¶60-65. Also, a POSA would have also preferred Bodor's tablets over an oral solution because tablets are preferable to liquid formulations, and Dr. Pinal agrees. EX1065, 287; EX1080, ¶66.

60. Drs. Lublin and Meibohm also mischaracterize the bioavailability of Stelmasiak's cladribine solution by ignoring the art that discloses a range of bioavailabilities ("37% to 51%") for oral cladribine solutions, such as that used in

Stelmasiak. EX1002, ¶110; EX1048, 122; EX1013, 5. Stelmasiak does not test the bioavailability of its solution; it only cites to a Lilliemark paper that discloses cladribine solutions have a bioavailability of "approximately 50%." EX2043, 1516. Drs. Lublin and Meibohm also fail to acknowledge that Bodor's tablets exhibited a range of bioavailabilities (between 35.7% and 52.1%). EX1002, ¶110; EX1022, Example 4, Table VI; EX2051, ¶150; EX2052, ¶84. Thus, as Dr. Pinal agrees, a POSA would have understood Bodor's oral tablets to have an at least comparable bioavailability to Stelmasiak's oral solution. EX1080, ¶77. As such, a POSA would have been motivated to select Bodor's oral cladribine tablets.

61. Accordingly, in light of the advantages of Bodor's tablets, a POSA would have been motivated to treat MS patients with Bodor's oral cladribine tablets.

4. A POSA would not have had to "convert" Bodor's regimen to a "weight-based" regimen to arrive at the claimed methods.

62. A POSA would not have found it inventive to administer Bodor's tablets to a patient of average weight (e.g., 70 kg), which would result in the patient receiving a dose (1.4 mg/kg to 2 mg/kg) that overlaps with the claimed range (about 1.7 mg/kg to 3.5 mg/kg). EX1002, ¶83. Dr. Lublin admits that a person weighing 70 kg would have received a dose of 1.4 mg/kg to 2 mg/kg per Bodor's dosing regimen. EX1061, 91:20–92:4. As I explained above, while the

claims of the ’947 patent encompass weight-based dosing, they are not limited to weight-based dosing. *See* Section VI.B. The claims don’t, for example, include a step of calculating a dose based on the patient’s weight prior to administering the dose. The claims merely require that the resulting total dose administered fall within the range of about 1.7 mg/kg to 3.5 mg/kg. EX1001, 19:13–30, 20:3–7, 20:11–25; *see* ¶¶31–32. Dr. Lublin is in agreement. EX1061, 135:1–10. The ’947 patent claims also do not require an active step of determining a patient’s weight before administering cladribine. While Dr. Lublin testified that the ’947 patent claims “require knowing a patient’s weight before cladribine is administered,” he points to no specific claim language in his declaration to support such a construction. EX1061, 145:4–8. Therefore, a POSA would not have needed to consider a patient’s weight to administer an amount of cladribine that overlaps with the claimed range in patients of a certain weight (e.g., an average-weight patient).

63. Drs. Lublin and Meibohm disagree with me that Bodor teaches the claimed total induction dose of cladribine because “Bodor’s flat, fixed dosing is [not] ‘equivalent’ to weight-based dosing of approximately 1.4 to 2 mg/kg.” EX2051, ¶89; EX2052, ¶69. And, according to Dr. Lublin, I based my opinions on “one very particular-weight patient, chosen with hindsight.” EX2051, ¶89. As I previously explained, a POSA would have been able to determine that Bodor

teaches administering a total of 100 to 140 mg of cladribine over a two-month induction period, which, when administered to an average adult weighing 70 kg, would have resulted in a dose of 1.4 mg/kg to 2 mg/kg. EX1002, ¶83. Thus, Dr. Lublin incorrectly concluded that my opinion was based on "one very particular-weight patient, chosen with hindsight." EX2051, ¶89.

64. Further, Drs. Lublin and Meibohm do not cite any evidence in the art to show that weight-based dosing for cladribine is not "equivalent" to flat, fixed dosing. For example, they provide no evidence that shows that a patient who receives a dose based on their weight would have any better results than a patient who received a dose based on Bodor's dosing regimen modified in light of Stelmasiak. At most, Dr. Meibohm cites to one reference regarding weight-based dosing of a low molecular weight heparin, a completely different drug than cladribine, used to treat a completely different indication (venous thromboembolism). EX2052, ¶34. A POSA would not have looked to a low molecular weight heparin when developing a cladribine dosing regimen because treating venous thromboembolisms has nothing to do with treating MS. At the same time, Dr. Meibohm admits that "[f]or some drugs, however, the variability in pharmacologic effect by weight may be minimal," but provides no evidence that cladribine's variability in pharmacologic effect is not "minimal." EX2052, ¶34.

65. As I previously explained, a POSA would not have found it inventive to administer Bodor's tablets to a patient of average weight (70 kg). EX1002, ¶83. A POSA would have thought to treat a patient of average weight in light of the prior art disclosures of cladribine dosing regimens, such as Stelmasiak. EX1002, ¶82; EX1013, 5. Dr. Lublin does not, and cannot, disagree because nothing in the art excludes treating average-weight patients. In fact, Stelmasiak reported administering cladribine to MS patients weighing 52–75 kg, which includes patients with average weight. EX1013, 5; EX2052, ¶71.[3]

66. As such, my opinion remains unchanged that a POSA would have been motivated to administer Bodor's MS dosing regimen to patients of average

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[3] If Bodor's dosing regimen had been administered to patients weighing 52–75 kg (median of 66 kg), the administered dose expressed in mg/kg is shown below:

$$100\ mg\ \div 52\ kg\ (or\ 75\ kg) = 1.9\frac{mg}{kg}(or\ 1.3\frac{mg}{kg})$$

$$140\ mg\ \div 52\ kg\ (or\ 75\ kg) = 2.7\frac{mg}{kg}(or\ 1.9\frac{mg}{kg})$$

As Drs. Lublin and Meibohm confirmed, a POSA could have readily performed these calculations and determined that those patients would have received total doses of 1.3 mg/kg to 2.7 mg/kg, which also overlaps with the claimed range. EX1061, 94:9–95:8; EX1062, 125:20–126:2, 127:15–22.

weight (70 kg), resulting in such patients receiving 1.4 mg/kg to 2 mg/kg of cladribine over two months.

67. According to Dr. Lublin, in 2019, I distinguished between weight-based and flat, fixed dosing by saying MAVENCLAD®'s dosing regimen was "rather unique" and MAVENCLAD® is "the only MS medicine that we have that is not given in a fixed dose but rather the dose is determined by how much the individual weighs." EX2051, ¶93; EX2008. However, Dr. Lublin took these comments regarding MAVENCLAD®'s dosing regimen out of context, and such comments do not contradict my testimony in this proceeding. My comments actually were made in the context of *approved* MS drugs, not *all* drugs or dosing regimens being investigated in the prior art, such as Bodor and Stelmasiak. To be sure, I started the video by saying, "[i]t's always exciting to have a new medication for the treatment of multiple sclerosis … we're going to be talking about a new medicine called Mavenclad … [which] has been approved to be used in patients with relapsing, remitting multiple sclerosis and secondary progressive MS with activity." EX2008, 2:1–8. However, my comments were not made from the standpoint of a POSA who was considering all the pertinent art in the field (e.g., Bodor and Stelmasiak), but rather from the standpoint of a practicing clinical expert. It's clear that I was only comparing MAVENCLAD®'s dosing regimen to that of other FDA-approved products. And just because MAVENCLAD®'s dosing

regimen is the first FDA-approved oral dosing regimen for MS does not make it nonobvious in view of the prior art.

68. Finally, Dr. Lublin incorrectly argues that Stelmasiak "teaches away" from a weight-based dosing regimen. EX2051, ¶96. While Stelmasiak states that "[t]here was no indication that a 'good response' is related to the actual cladribine dose per body weight," a POSA would have understood that to simply mean that "responders" in the study had different body weights. Indeed, Stelmasiak reports they were "unable to identify any factor which would differentiate between the 'responders' and the 'non-responders.'" EX1013, 7. As such, POSA would not have understood Stelmasiak to teach away from a weight-based dosing regimen. And again, Dr. Lublin provides no evidence that weight-based cladribine dosing was superior or not "equivalent" to flat, fixed dosing.

B. A POSA would have been motivated to re-treat with cladribine after Bodor's induction/cladribine-free period.

1. A POSA would have re-treated with cladribine because the art suggests as much.

69. Dr. Lublin agrees that Bodor expressly teaches an MS cladribine treatment regimen that included administering Bodor's oral tablets for a 2-month induction period followed by a 10-month "no treatment" period. EX2051, ¶86. Dr. Lublin contends, however, that a POSA would not have "automatically re-treat[ed]" a patient after the cladribine-free period because "any subsequent re-

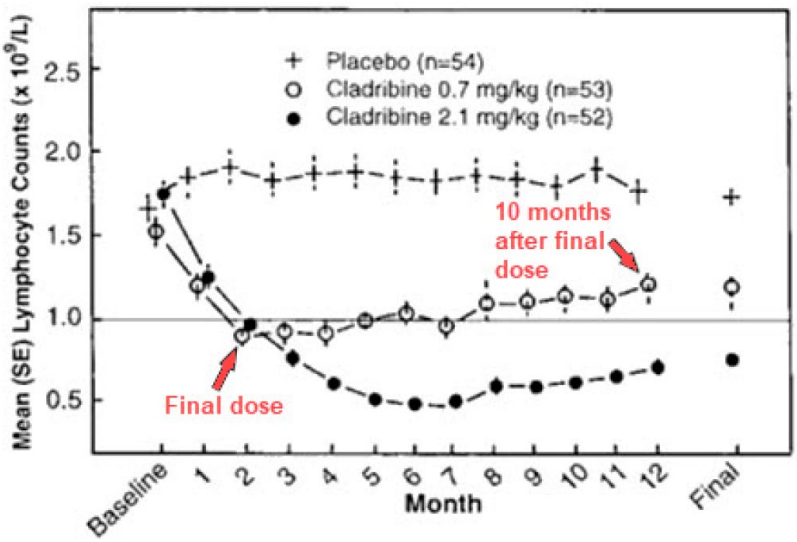
treatment would have been based on a combination of factors, such as evidence of disease progression, time course of therapeutic effects, and safety considerations." EX2051, ¶113. However, Dr. Lublin mischaracterizes my testimony by suggesting that I did not consider evidence of disease progression, the duration of cladribine's lymphocyte suppression, and safety. In fact, I discussed all three when explaining why a POSA would have re-treated after a 10-month cladribine-free period. EX1002, ¶¶51, 52, 91, 99–102.

70. Further, Dr. Lublin does not explain why a POSA would have disregarded Bodor's implied teaching to re-treat. As I explained in my first declaration, a POSA would have understood Bodor to teach re-treatment because otherwise, the specified length of time of the cladribine-free period (10 months) is meaningless. EX1002, ¶86. Dr. Lublin does not provide another explanation of why Bodor specifies the length of time of the cladribine-free period. The most logical reading of Bodor would have included a re-treatment period, especially because such re-treatments were consistent with prior clinical studies where patients relapsed during or after cladribine therapy, such as Stelmasiak. EX1013, Abstract; EX1031, 43.

2. A POSA would have re-treated because cladribine's suppression of lymphocytes was known to be impermanent

and MS is a chronic, lymphocyte-dependent autoimmune disease in which patients were expected to relapse.

71. As described, Dr. Lublin and I agree that reducing inflammation was one of the goals of MS therapy before 2004. EX2051, ¶50; EX1061, 58:7–11. Cladribine's anti-inflammatory activity was based on its lymphocytotoxic activity. EX1015, 1751. It was known in the art, as Dr. Lublin concedes, that cladribine did not cause a permanent reduction in lymphocyte counts—that is, lymphocyte counts would "rebound" or "return at some point after the cessation of cladribine treatment." EX1046, 392; EX1061, 71:9–16. Indeed, the prior art clinical studies consistently reported such rebound. EX1002, ¶95; EX1013, 5; EX1018, 1152, FIG. 4; EX1046, 392; EX1047, 296, 297. For example, as I annotated in the figure below, Rice's data demonstrates that after 10 months of no cladribine, patients who had received 0.7 mg/kg saw a rebound in their lymphocyte count, as shown below:



EX1018, 1152, FIG. 4 (annotated). And, in fact, Dr. Lublin recognizes that after 9 months of no cladribine therapy, Stelmasiak's patients saw an increase in lymphocyte counts. EX2051, ¶185. Because lymphocytes rebound, the art recognized that the "lengthy but impermanent duration of effect of cladribine means that retreatment will be necessary if cladribine is to become a practical long-term therapy for MS." EX1031, 43; *see also* EX1046, 392.

72. Despite the art's express recognition that lymphocytes rebound after a cladribine treatment, and thus the need to re-treat, Dr. Lublin insists that a POSA would not have done so because lymphocyte counts may not have returned to baseline after a 10-month cladribine-free period. EX2051, ¶116. Dr. Lublin misconstrues my argument that "lymphocyte counts eventually rebounded after a cladribine-free period" to mean that the lymphocyte counts returned to baseline. EX2051, ¶116; EX1002, ¶95. This was not my argument. Rather, I stated that "a POSA would have understood that a lower dose of cladribine was sufficient to *maintain* the lymphocyte suppression effected during an induction period"— i.e., before lymphocyte counts rebounded to baseline. EX1002, ¶18 (emphasis added); *see also* ¶¶90, 108, 117. Accordingly, a POSA would have been motivated to re-treat a patient with cladribine after a cladribine-free period to maintain lymphocyte suppression.

73. Dr. Lublin also contends that a POSA would not have re-treated with cladribine because "some clinicians will switch the patient to an alternative MS therapy" if they experience an inadequate response to a DMT. EX2051, ¶118. However, even if some clinicians might have switched drugs, it would not have been inventive to re-treat with cladribine. Indeed, the prior art expressly taught re-treating with cladribine after a cladribine-free period. EX1013, Abstract, 5; EX1031, 43.

3. A POSA would not have been dissuaded to re-treat with cladribine due to safety concerns because prior art studies demonstrated cladribine's safety in treating MS.

74. A POSA would not have been dissuaded to re-treat with cladribine, despite Dr. Lublin's argument that "a POSA would have been concerned about the safety of cladribine treatment." EX2051, ¶20. As I explained above, the earliest study in MS, which administered a total dose of 2.8 mg/kg of cladribine over four monthly courses, reported some patients developed thrombocytopenia and one patient developed severe bone marrow depression. EX1014, 1720. But subsequent pre-2004 studies using a lower total dose of cladribine reported no such concerns. EX1013, 7; EX1018, 1153; EX1047, Abstract; EX1031, 41.

75. Dr. Lublin argues that "if a POSA were to consider retreatment, a POSA would have looked to the studies in which cladribine was retreated, e.g., Rice and Romine" – limiting a POSA's review to Rice and Romine. EX2051,

¶180. I disagree, as a POSA would have also looked at Stelmasiak's study, which also discloses re-treatment with cladribine. EX2051, ¶180. Stelmasiak reports that "a two- to three-fold reduction of blood lymphocyte count can be achieved by the drug given subcutaneously without clinically significant hematological side effects." EX1013, 7. However, despite Dr. Lublin's argument that "Rice was concerned with lymphopenia," Rice actually reports a "relatively low number of serious infections in the presence of significant overall lymphocytopenia." EX2051, ¶114; EX1018, 1152. Rice also reports that "[m]ost adverse events were mild or moderate in severity and not treatment limiting." EX1018, Abstract. Accordingly, a POSA would have understood that Rice's own disclosure, as well as Stelmasiak's disclosure, does not support Dr. Lublin's argument.

76. Dr. Lublin also contends that a "POSA reading Bodor would not have assumed that it would have been safe to re-treat patients with cladribine ***at the end of*** the 10-month cladribine-free period" because "it was unclear how long cladribine-induced lymphocyte suppression would last." EX2051, ¶¶99–100 (emphasis is Dr. Lublin's). As I explained in my first declaration, a POSA would have known that Bodor's dosing regimen for treating MS, which includes a 10-month cladribine-free period and suggests re-treatment with cladribine, was specifically designed for Bodor's "instant solid dosage form." EX1002, ¶79; EX1022, 23:15–20. I also explained in my first declaration that a POSA would

have wanted to "*maintain* the lymphocyte suppression effected during an induction period" – i.e., before lymphocyte counts rebounded to baseline. EX1002, ¶18 (emphasis added); *see also* ¶¶90, 108, 117. Accordingly, a POSA would have been motivated to re-treat a patient with cladribine after a cladribine-free period to maintain lymphocyte suppression. And because a POSA would have understood that Bodor likely considered cladribine's toxicity when developing a dosing regimen that specified a 10-month cladribine-free period – a point that Dr. Lublin agrees with (EX2051, ¶99) – a POSA would have understood Bodor to suggest that it would be safe to re-treat with cladribine after 10 months of no treatment. Also, Dr. Lublin mischaracterizes comments I made in 2019 (EX2008) when I said "[a]nd some of the drugs" "that the person might have been on before Mavenclad may have suppressed the lymphocyte count, so "we may need to wait to get that lymphocyte count back into the safe range" before starting MAVENCLAD® therapy. EX2008, 12:4–9; EX2051, ¶100. My comments were not made with respect to re-treating with cladribine after an initial cladribine induction period followed by a cladribine-free period; my comments were made with respect to starting cladribine therapy after another immunosuppressive drug.

77. Dr. Lublin also argues that "a POSA would have understood that cladribine posed significant long-term safety concerns," but he misrepresents the prior art. According to Dr. Lublin, the concern comes from Romine's disclosure

that "[r]epeated treatment [with cladribine] raises long-term toxicity issues." EX2051, ¶72; EX1031, 43–44. However, Romine's comments are based on toxicity issues "known to occur in association with other long-term immunosuppressive treatments." EX1031, 44. Romine actually states that "there are few data on the safety of long-term retreatment with cladribine in a nonmalignant disease such as MS." EX1031, 43. A POSA would have understood that Romine's concerns are not related to cladribine, as confirmed by Romine's data and also Stelmasiak's data. *See* ¶¶55–57. For example, Romine reports that in the patients who were re-treated with cladribine in their study, there were "no instances of marrow suppression or thrombocytopenia." EX1031, 43. And as I explained above, Stelmasiak's patients who were re-treated with cladribine experienced no "non-hematologic toxicity" or "clinically significant hematological side effects," despite repeated cladribine treatments. EX1013, 7.

78. Dr. Lublin further mischaracterizes the disclosure in a book chapter I wrote, in which I explained that in light of cladribine's "profound and very long-lasting lymphopenia induced by the drug," patients should not concomitantly take other immunosuppressant agents. EX2051, ¶100; EX2004, 341. Dr. Lublin misconstrues my statements to suggest a POSA would have interpreted my statements as suggesting that re-treatment with cladribine would not have been safe. A POSA would simply have understood that concomitantly administering

another immunosuppressant with cladribine was not recommended. Indeed, others in the art also recognized the importance of avoiding concomitantly administering additional immunosuppressants with cladribine to mitigate the risk of toxicity. EX1047, 298. In any event, a POSA would have understood from the art I discussed above that continued lymphocyte suppression with cladribine was safe and effective. EX1013, Abstract; EX1018, Abstract; EX1031, Abstract.

4. A POSA would have re-treated because the dosing of other MS drugs suggests re-treatment after a drug-free period.

79. Dr. Lublin contends that the prior art corticosteroids, cyclophosphamide, and intravenous methylprednisone dosing regimens "would not have informed treatment with cladribine" (EX2051, ¶¶104–106), but Dr. Lublin doesn't deny that those drugs are examples of dosing regimens where an MS patient receives a drug for a period of time, stops taking the drug for a period of time, and then begins treatment again. EX2051, ¶¶105–106; EX1002, ¶54. Regardless, a POSA would have looked to art that specifically discloses re-treatment with cladribine (e.g., Bodor and Stelmasiak) to inform them of cladribine dosing regimens.

80. Indeed, several drugs were administered cyclically prior to 2004, despite Dr. Lublin's argument that these drugs were dosed "continuously." EX2051, ¶103. Mitoxantrone and natalizumab were both administered cyclically–each dosing regimen included an initial treatment period, a drug-free period, and

re-treatment periods. EX2018, 29; EX2019, 10. Mitoxantrone was administered as a "short (approximately 5 to 15 minutes) intravenous infusion every 3 months" (EX2018, 29) and natalizumab was administered as a one-hour IV infusion every 4 weeks (EX2019, 10). Dr. Lublin's opinion that these drugs were administered based on the drug's specific pharmacological effects, mechanism of action, therapeutic benefits, and safety risks (EX2051, ¶103) does not undermine my testimony as I have already addressed these considerations specific to cladribine in reaching the opinions of my first declaration. EX1002, ¶¶34–52.

C. A POSA would have routinely optimized the dose and dosing length of the maintenance period to arrive at a lower dose.

81. Dr. Lublin disagrees that a POSA would have routinely optimized the maintenance period dose or dosing length based on a change in lymphocyte counts because, according to Dr. Lublin, lymphocyte count or a change in lymphocyte count is "not a metric of efficacy." EX2051, ¶¶125–126. However, I never argued that lymphocyte counts are a measure of efficacy. I consistently argued that a POSA would have optimized the cladribine dose/dosing length because lymphocyte suppression is a recognizable result of the cladribine dose and dosing length. EX1002, ¶¶91, 117, 109. In fact, Dr. Lublin agrees that "cladribine induces a reduction in lymphocyte count as a pharmacological effect" and that Rice reports "[a] more marked, long-lasting, *dose-related* lymphocyte count reduction" in response to cladribine. EX2051, ¶¶137, 139 (emphasis added); EX1061, 74:15–

24. And lymphocytes do not need to be a measure of efficacy for a POSA to optimize the cladribine dose and dosing length based on a change in lymphocytes. Thus, a POSA would have been motivated to optimize the cladribine dose and dosing length based on the change in lymphocyte count because lymphocyte count is a measure of cladribine's suppression of the immune system. And as I explained in my first declaration, it was also general knowledge in the art that a direct correlation exists between the dose and length of administration of cladribine and level of lymphocyte suppression. EX1002, ¶91.

82. Dr. Lublin also contends that because some clinical studies reported lymphocyte data under a "safety evaluation" or "side effects" heading, a POSA would not have thought to optimize cladribine's dose and dosing length based on lymphocyte count. EX2051, ¶¶139–141. Regardless of how the authors decided to report lymphocyte levels, a POSA would have still understood the art to teach a "dose-related lymphocyte count reduction," which Dr. Lublin concedes. EX1018, 1152; EX1047, 297–298; EX2051, ¶¶137, 139; EX1061, 72:19–22. As such, a POSA would have been motivated to adjust the dose and/or dosing length of cladribine by measuring cladribine's effect on lymphocyte counts.

83. Dr. Lublin also contends that "it would require years to evaluate how changes made to an MS drug's dose and/or dosing schedule would impact clinical outcomes." EX2051, ¶127. I disagree. As I wrote in Exhibit 2005, the efficacy of

an MS drug is assessed in early clinical trials "typically of much shorter duration … many months to a year or longer." EX2005, 49. As such, a POSA would have understood that efficacy could be determined in as little as months to a year, not "years," as Dr. Lublin argues. Moreover, contemporaneously with the filing of the '947 patent, Dr. Lublin wrote in 2005 that at least one clinical outcome, relapse rate, "is a routine measure of disease activity that is easy to quantify." EX2011, 4. A POSA would have understood Dr. Lublin's 2005 statement to mean a POSA wouldn't have needed years to assess a drug's efficacy using relapse rate as an outcome measure. In fact, Dr. Lublin admitted during his deposition that relapse rates are typically measured over one year, not "years." EX1061, 38:10–12. And MRI scans can assess a positive treatment response in as little as 6 months. For example, Romine reports "complete suppression of enhancing lesions after study month 6 in the cladribine group." EX1031, 40.

84. While changes in relapse rate and lesions can be assessed in as little as 6 to 12 months, lymphocyte reductions induced by cladribine can be seen even quicker, within a month or two. For example, the patients in Rice's 0.7 mg/kg treatment arm reached their lymphocyte nadir 2 months after administering the first dose. EX1018, FIG. 4. Stelmasiak and Romine both reported similar responsiveness of lymphocyte counts to cladribine suppression. EX1013, FIG. 1; EX1031, FIG. 6 (Lymphocytes graph). Thus, a POSA would have understood that

adjusting the cladribine dose or dosing length could be assessed by lymphocyte counts over the course of a few months, not years as Dr. Lublin argues.

85. Dr. Lublin also does not disagree that a POSA would have been motivated to lower the dose in the re-treatment period. EX2051, ¶159. Rather, Dr. Lublin contends that a POSA may have instead considered decreasing the number of treatment courses to "lower" the dose. EX2051, ¶159. As I explained in my first declaration, a POSA would have known how to adjust a patient's cladribine dose depending on the patient's lymphocyte counts (e.g., by administering more or less cladribine) and/or the length of administration (e.g., administering cladribine for a shorter period of time to reduce the amount administered). EX1002, ¶93. In fact, Bodor instructs as much, stating:

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

EX1022, 24:1–9. Bodor is consistent with the general knowledge in the art, e.g., as reflected in Beutler, which teaches that "one can tailor the dosage and duration

for which [cladribine] is administered to the stage of the disease and the condition of the patient being treated." EX1026, 5:22-25. Thus, a POSA would have known that adjusting the dose or dosing length of cladribine would have been routine. Even if there were other ways to lower the maintenance period dose, that does not detract from the fact that a POSA would have optimized the dose and/or dosing length to lower the dose administered in the maintenance period.

86. Dr. Lublin also contends that "because Bodor does not consider patient weight, Bodor's suggestion to fine tune is with respect to its daily flat dosage of 10 mg." EX2051, ¶135. However, the claims encompass both weight-based and flat dosing, as I explain above. *See* ¶¶31–32. So, Dr. Lublin agrees with me that a POSA would have optimized Bodor's flat 10 mg dose, which, when given to an average-weight patient, would have resulted in the claimed dosage. EX1002, ¶83.

D. A POSA would have incorporated a second cladribine-free period after the re-treatment period.

87. Dr. Lublin "agree[s]" that "a POSA would have incorporated a cladribine-free period into an MS dosing regimen to mitigate side effects associated with cladribine toxicity," however, Dr. Lublin argues that I did not address how a 10-month cladribine-free period would have mitigated side effects. EX2051, ¶¶100, 160. However, as I explained previously, a POSA would have had the skill to monitor a patient's lymphocyte count and side effects associated

with lymphocyte and myelosuppression and optimize the length of time of the second cladribine-free period to mitigate side effects while maximizing lymphocyte suppression. EX1002, ¶¶104–105. I clearly explained that it was routine in the art to monitor a patient's lymphocyte counts when treating a patient with a known immunosuppressant, such as cladribine, because "cladribine causes prolonged, profound suppression of lymphocyte counts" and cladribine toxicity was a concern. EX1002, ¶¶91, 106, 118. Bodor teaches a 10-month cladribine-free period after administering their oral cladribine tablets, so it would have been logical for a POSA to optimize Bodor's cladribine-free period. EX1002, ¶104. And, in fact, Dr. Lublin argues that "a POSA would have understood that Bodor's 10-month cladribine-free period after a two-month dosing period likely relates to ***safety considerations***, i.e., to limit the potentially toxic effects of cladribine dosing." EX2051, ¶99 (emphasis in the original).

88. However, Dr. Lublin goes on to contend that "numerous possible combinations of … drug-free period length/number" exist "that a POSA could have 'optimized.'" EX2051, ¶¶160–161. But as I explained, a POSA would have used Bodor's 10-month cladribine-free period as a logical starting point for optimizing a second cladribine-free period. EX1002, ¶104. Dr. Lublin does not, however, explain why a POSA would not have started with Bodor's cladribine-free period. And as Dr. Lublin concedes, Bodor designed their dosing regimen to

"limit the potentially toxic effects of cladribine." EX2051, ¶99. And Bodor's dosing regimen was specifically designed for Bodor's cyclodextrin-cladribine tablets. EX1022, 23:15–20.

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

1. A POSA would have reasonably expected Bodor's induction/cladribine-free period to treat MS.

89. As I explained in my first declaration, a POSA would have reasonably expected Bodor's oral cladribine tablets administered with Bodor's induction dose and followed by a cladribine-free period to effectively suppress lymphocytes and treat MS by reducing relapse rates and/or brain lesions as detected by MRI. EX1002, ¶¶111, 112, 116. I disagree with Dr. Lublin's argument that Bodor's maximum cladribine dose of 140 mg is lower than Stelmasiak's 150 mg dose and has lower bioavailability than Stelmasiak's dosage form, which "likely would have been insufficient to reduce lymphocytes to a level below 1000 cells/μL." EX2051, ¶158; *see also* ¶150.

90. To begin with, Dr. Lublin is wrong to insist that lymphocyte counts must drop to 1000 cells/μL to "show efficacy." EX2051, ¶150. As I made clear in my first declaration, lymphocytes do not need to be suppressed to or below 1000 cells/μL to achieve a therapeutic effect—1000 cells/μL is merely an exemplary level of suppression. EX1002, ¶¶16, 32, 40, 90. As I also explained in my first declaration, during treatment, neurologists commonly assessed the therapeutic

effect of cladribine by monitoring a patient's lymphocyte count, with a sustained reduction of lymphocytes, *e.g.*, to ≤ about 1000 cells/μL, as being characteristic of a treatment response. EX1002, ¶16. I mentioned this 1000 cells/μL level because a POSA would have known that 1000 cells/μL was at the low end of the normal range of lymphocyte counts. EX1018, 1152, FIG. 4; EX2009, 31:19–20. It is also clear from my deposition that 1000 cells/μL is an example of a lymphocyte level that constitutes immune suppression. EX2009, 30:12–16, 31:16–32:12. However, a POSA would have understood that lymphocytes do not necessarily need to be suppressed to a level of 1000 cells/μL to determine a treatment response.

91. In an effort to rebut my testimony that a POSA would have used Bodor's oral cladribine tablets to treat MS, Drs. Lublin and Meibohm mischaracterize the bioavailability of Bodor's tablets. As I explained, a POSA would have understood Bodor's oral tablets to have an at least comparable bioavailability to Stelmasiak's oral solution. *See* ¶60; *see also* EX1080, ¶74. As such, a POSA would have reasonably expected Bodor's dose to sufficiently suppress lymphocyte counts, in light of Stelmasiak's and Rice's data, as explained below.

92. Further, in arguing that Bodor's maximum cladribine dose of 140 mg would have been "insufficient to reduce lymphocytes to a level below 1000 cells/μL," Dr. Lublin overlooks Rice, which – reported administering a similar

dose as Bodor and disclosed lymphocyte counts. EX2051, ¶158. A POSA would have reasonably expected Bodor's induction period dose to suppress lymphocytes to a similar level as Rice discloses. According to Dr. Pinal, Bodor's induction period administers about the same dose as Rice's lower-dose treatment arm over the same amount of time (a total of 0.7 mg/kg over two months). EX1080, ¶¶81–83. Dr. Lublin admits he did not consider comparing Bodor's induction period dose to Rice's 0.7 mg/kg dose (because he was unable to convert Bodor's dose to a subcutaneous dose) when forming his opinion that a POSA would not have expected Bodor's maximum cladribine induction dose of 140 mg to reduce lymphocytes to a level of approximately 1000 cells/µL or below. EX1080, ¶¶81–83; EX1018, Abstract; EX1061, 95:22–96:13. Rice plots the change in mean lymphocyte count over time in Figure 4. EX1018, 1152, FIG. 4. A POSA would have estimated that patients in the 0.7 mg/kg treatment group had an average baseline lymphocyte count of ~1500 cells/µL. EX1018, 1152, FIG. 4; *see also* EX1061, 77:8–21. Those patients reached a lymphocyte count nadir of ~950/µL. EX1018, 1152, FIG. 4; *see also* EX1061, 78:1–4. Because Rice's patients' lymphocytes were reduced by ~550 cells/µL to below 1000 cells/µL, a POSA would have reasonably expected Bodor's similar dose to induce the same level of suppression.

93. Dr. Lublin argues that Rice reports that "clinical efficacy was not shown," however, Rice discloses that the 0.7 mg/kg dose was "significantly superior to placebo with respect to the proportion of patients having detectable enhanced T1 lesions as well as to the mean volume and number of such lesions at 6 months and final evaluation." EX2051, ¶156; EX1018, 1153. A POSA would have understood that a reduction in the number and volume of such lesions was characteristic of cladribine's efficacy. *See* ¶24. The '947 patent also includes a reduction in the number and volume of such lesions is a metric of efficacy by stating that the "observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable." EX1001, 5:60–63. A POSA would have also reasonably expected Bodor's similar dose to have the same treatment effect on brain lesions.

94. Drs. Lublin and Meibohm also narrowly focus on Stelmasiak's EDSS scores to contend that a POSA would not have looked to Bodor's dosing regimen to treat MS because Stelmasiak's "higher dose (300 mg) resulted in a better EDSS score than the lower dose (150 mg)." EX2051, ¶172; EX2052, ¶¶85, 87, 88. However, a POSA would have understood that Stelmasiak's 150 mg dose did, in fact, lower EDSS scores, which Drs. Lublin and Meibohm agree with. EX1013, 5; EX1002, ¶172; EX2051, ¶172; EX2052, ¶¶52, 87. Because Bodor's

bioavailability is at least comparable to Stelmasiak's and Bodor's maximum dose is close to Stelmasiak's dose, as Dr. Lublin agrees (EX2051, ¶172), a POSA would have expected Bodor's dosing regimen to reduce or maintain patients' EDSS scores, which is a metric of efficacy, in light of Stelmasiak. *See* ¶23.

2. A POSA would have reasonably expected to successfully re-treat patients with cladribine after Bodor's induction/cladribine-free period.

95. For the same reasons explained above in Section VIII.E.1, a POSA would have reasonably expected that continuing treatment with cladribine would result in efficacy in treating MS. Indeed, Stelmasiak demonstrates a "very marked" reduction in relapse rate after cyclically administering cladribine to maintain lymphocyte count suppression, which Dr. Lublin disregards when he contends that Stelmasiak's cyclical dosing regimen only resulted in "maintenance" of EDSS scores. EX1013, 7; EX2051, ¶183. In any event, as I've explained, the fact that the average EDSS scores did not increase by the end of Stelmasiak's study compared to baseline indicates a lack of disability progression. *See* ¶23; *see also* EX1002, ¶26. Indeed, as I explained in my first declaration, one of the goals of DMT therapy is to "slow further progression of the disease," and Dr. Lublin agrees. EX1002, ¶87; EX2051, ¶¶63, 105. As such, Dr. Lublin's conclusion that Stelmasiak's dosing regimen "lack[ed] … efficacy in improving disability" is wrong. EX2051, ¶176. A POSA would have known that "improving

disability" was not a goal of DMT therapy before 2004. Dr. Lublin also admits that Stelmasiak's cyclical dosing regimen maintained a reduction in lymphocyte counts, as well. EX2051, ¶183. As such, a POSA would have reasonably expected that re-treating with cladribine after Bodor's induction dose and cladribine-free period would have maintained lymphocyte count.

96. As I explained above, a POSA would have reasonably expected Bodor's induction dose to sufficiently lower lymphocyte counts and reduce relapse rates and/or brain lesions. *See* ¶¶89–94. A POSA would have reasonably expected those treatment responses to be maintained when re-treating with cladribine, as demonstrated by Stelmasiak. EX1013, 7. Further, a POSA would have known that not *all* patients in a clinical study need to demonstrate improvement in *all* outcome measures to determine the efficacy of a drug. In fact, while Dr. Lublin points to the reduced lymphocyte counts of two "non-responders" as evidence that "a reduction in lymphocyte count does ***not*** correlate with cladribine efficacy," Dr. Lublin admitted during his deposition that 100% of the patients in a clinical study do not need to see improvement in any one metric for cladribine's efficacy to be determined. EX2051, ¶140 (emphasis is Dr. Lublin's); EX1061, 51:9–14.

F. Claims 38, 39, and 41–46 would have been obvious over the combination of Bodor and Stelmasiak.

97. Claims 38, 39, and 41–46, which depend from claim 36, would have also been obvious to a POSA over Bodor and Stelmasiak, as I explained in my first declaration. EX1002, ¶¶120–136. My additional explanations regarding Bodor and Stelmasiak above also apply to claims 38, 39, and 41–46. Dr. Lublin provides no additional arguments regarding claims 38 and 41–46. I offer further comments below in response to Dr. Lublin's arguments to claim 39.

98. **Claim 39.** I maintain my opinion that a POSA would have administered Bodor's dosing regimen to a patient of average weight (e.g., 70 kg), resulting in the patient receiving 1.4 mg/kg to 2 mg/kg of cladribine, which encompasses the dose of "about 1.7 mg/kg." Claims 36 and 39 both recite "about" 1.7 mg/kg. As I explained above in Section VI.C, a POSA would have understood "about 1.7 mg/kg" to mean a range of doses both higher and lower than 1.7 mg/kg. *See* ¶¶33–35. As such, claim 39 encompasses an induction dose that may be higher than the maintenance dose. Both doses are encompassed by Bodor's dosing regimen when administered to an average weight patient (1.4 mg/kg to 2 mg/kg). *See* ¶62. Accordingly, a POSA would have been motivated to arrive at the method of claim 39 in light of Bodor and Stelmasiak, with a reasonable expectation of success.

IX. DR. LUBLIN'S OBJECTIVE EVIDENCE DO NOT SUPPORT NONOBVIOUSNESS OF THE CLAIMED METHODS.

99. As I explained in my first declaration, in reaching my opinions regarding obviousness, I considered whether there were any objective evidence (i.e., objective indicia, also referred to as "secondary considerations") of nonobviousness. EX1002, ¶140. I concluded that there is no objective evidence that supports nonobviousness of the methods claimed in the '947 patent. EX1002, ¶140. I maintain this view.

100. Dr. Lublin presented additional evidence that, as he argues, acknowledges skepticism by others and a long-felt but unmet need and establishes unexpected superiority of the claimed method over the prior art. But, even in view of such evidence, the methods claimed in the '947 patent would have been obvious to a POSA, as I explain in detail below.

A. Dr. Lublin does not demonstrate skepticism.

101. My understanding of the requirements to demonstrate skepticism in support of nonobviousness are explained in paragraph 43 above.

102. None of the references Dr. Lublin cites to express skepticism about cladribine's efficacy in treating RRMS—a type of MS that falls within the claimed methods, as Dr. Lublin himself conceded. EX2051, ¶222. Dr. Lublin only cites to generic comments made in the art regarding cladribine's effect in

progressive MS patients to assert that the art was skeptical that cladribine could be used to treat MS.

103. For example, in 2000, I commented that cladribine was "found not to be of benefit" "in progressive disease." EX2005, 45, 67. I expressed no skepticism about cladribine's efficacy in treating RRMS. My comment was only related to a study limited to patients with progressive disease and was not based on the full scope of the prior art (e.g., Bodor, Stelmasiak, and Romine) that a POSA would have considered when assessing the obviousness of treating other forms of MS, such as RRMS. As I explained above, a POSA would have understood cladribine to have efficacy in treating RRMS, as demonstrated by Stelmasiak and Romine. *See* ¶¶51–52.

104. Also, as Dr. Lublin admitted, Exhibit 2005 does not express skepticism about using an *oral* cladribine formulation, as required by the challenged claims. EX1061, 119:12–20; EX1001, 19:13–30, 20:3–7, 20:11–25. Dr. Lublin also admitted that Exhibit 2005 expresses no skepticism regarding a particular dosing regimen. Thus, a POSA would not have understood my comments in Exhibit 2005 to express skepticism regarding oral administration of a cladribine formulation or a cladribine dosing regimen comprising (i) an induction period lasting from about 2–4 months, (ii) an 8- to 10-month cladribine-free

period, (iii) a maintenance period lasting from about 2–4 months, and (iv) a second cladribine-free period, as required by the challenged claims.

105. Dr. Lublin also contends that a book chapter I wrote in 2008 (EX2004), in which I discuss Sipe (EX2030) and Rice (EX1018), provides evidence of skepticism. EX2051, ¶195. Dr. Lublin contends that I "expressed skepticism that cladribine would be useful to treat MS given that previous studies showed 'unconvincing clinical benefit.'" EX2051, ¶196. However, my comments were not made from the standpoint of a POSA who was considering all the pertinent art in the field (e.g., Stelmasiak and Romine studies), but rather from the standpoint of a practicing clinical expert.

106. Further, Sipe and Rice described treating patients with progressive MS, which is harder to treat than RRMS, as Dr. Lublin conceded. EX1061, 61:7–10. Thus, my comments in Exhibit 2004 were limited to two studies in patients with progressive disease and were not based on the full scope of the prior art (e.g., Bodor, Stelmasiak, and Romine) that a POSA would have considered when assessing the obviousness of treating other forms of MS, such as RRMS. And, as I explained above, a POSA would have understood cladribine to have efficacy in treating RRMS, as demonstrated by at least Stelmasiak and Romine. *See* ¶¶51–52. Thus, a POSA would not have understood my post-filing comments to provide skepticism regarding treating RRMS with cladribine.

107. In any event, my statement in Exhibit 2004 that "it seems prudent to await the results of a prospective, randomized, blinded trial of oral cladribine" suggests that the trial *should* be conducted. EX2004, 341. And Dr. Lublin did not provide any other reading of the quoted statement. EX2051, ¶¶70, 143,144.

108. Also, as Dr. Lublin conceded during his deposition, Exhibit 2004 makes no mention of an *oral* cladribine formulation. EX1061, 123:14–17. Thus, a POSA would not have understood my comments in Exhibit 2004 to express skepticism about using an *oral* cladribine formulation, as required by the challenged claims. EX1061, 119:12–20; EX1001, 19:13–30, 20:3–7, 20:11–25.

109. Dr. Lublin also cites a 2006 book chapter by Dr. Noseworthy (not a POSA who is presumably aware of all pertinent prior art) (EX2031), which briefly reviewed several pre-2004 cladribine clinical studies. EX2051, ¶197. Of the four clinical studies reviewed, only one—Romine (EX1031)—treated RRMS patients, which, as Dr. Lublin conceded, is easier to treat than progressive MS. EX1061, 61:7–10; EX2031, 753. Importantly, Dr. Noseworthy did not criticize Romine's study. In fact, according to Noseworthy 2005, Romine reported that "[r]elapse rate fell dramatically during the first 6 months of the trial" and "treated patients continued to show fewer episodes." EX2031, 753. Romine's patients also had "fewer gadolinium enhancing MRI lesions." EX2031, 753. A POSA would have known that both of these outcomes indicate efficacy of the therapy, as Dr. Lublin

conceded. *See* ¶¶22, 24; EX2051, ¶¶60–61; EX1061, 61:11–18, 62:3–5. Further, as Dr. Lublin admitted, Noseworthy 2005 did not discuss Stelmasiak's study, or provide any indication that Noseworthy was aware of Stelmasiak's data, which also demonstrated cladribine's efficacy in treating RRMS. EX1061, 127:1–4; EX2031, 753; EX1013, 7. A POSA also would have recognized that Noseworthy 2005 did not discuss Bodor or provide any indication that Noseworthy was aware of Bodor. EX2031, 753.

110. In addition, as Dr. Lublin conceded during his deposition, Noseworthy 2005 makes no mention of an *oral* cladribine dosage form, nor does it express skepticism about a particular dosing regimen. EX1061, 127:5–13. Thus, a POSA would not have understood Noseworthy 2005 to express skepticism about using an *oral* cladribine formulation or a dosing regimen comprising (i) an induction period lasting from about 2–4 months, (ii) an 8- to 10-month cladribine-free period, (iii) a maintenance period lasting from about 2–4 months, and (iv) a second cladribine-free period, as required by the challenged claims. EX1061, 119:12–20; EX1001, 19:13–30, 20:3–7, 20:11–25.

111. Dr. Lublin also claims that he personally (not a POSA who is presumably aware of all pertinent prior art), was skeptical in 2005 of cladribine's utility for treating MS. EX2051, ¶198. While Lublin 2005 (EX2011) states in the Abstract that "treatment with oral myelin, cladribine, sulfasalazine and inhibitors

of tumour necrosis factor" "proved unsuccessful," this comment seems to only be based on the review of one cladribine reference: Rice (EX1018). EX2011, Abstract, 7. In discussing Rice, Lublin 2005 states that "[s]tudies with cladribine in primary progressive MS and SPMS, for example, showed evidence for a good response in terms of gadolinium-enhancing lesions in the absence of any benefit on clinical parameters, suggesting a dissociation between inflammatory changes and ***relapses*** in progressive MS." EX2011, 7 (emphasis added). However, Rice did not measure or report relapses or relapse rates, so a POSA would not have given much regard to Lublin 2005's "skepticism" of Rice's study vis-à-vis relapses because such skepticism was not based on actual data disclosed in Rice. EX1018. Further, a POSA would have known that a "good response in terms of gadolinium-enhancing lesions" is evidence of cladribine's efficacy as disclosed in the '947 patent. EX1001, 5:52–63. Dr. Lublin agrees that MRI assessment provides a "strong evidence of treatment effects." EX2011, 4. Further, patients do not need to show improvement in every metric, with which Dr. Lublin also agrees. *See* ¶29; EX1061, 52:10–15.

112. In addition, Lublin 2005 expresses no skepticism—or even commentary—regarding cladribine's efficacy in treating RRMS. Nor does Lublin 2005 provide skepticism about using an *oral* cladribine dosage form or a dosing regimen comprising (i) an induction period lasting from about 2–4 months, (ii) an

8- to 10-month cladribine-free period, (iii) a maintenance period lasting from about 2–4 months, and (iv) a second cladribine-free period, as required by the challenged claims. EX1061, 119:12–20; EX1001, 19:13–30, 20:3–7, 20:11–25.

113. Dr. Lublin argues that the "unique characteristic of the claimed invention is the four-step method of treating MS using orally-administered cladribine, comprising (i) an induction period lasting from about 2–4 months, wherein the total dose of cladribine administered is from about 1.7–3.5 mg/kg; (ii) an 8- to 10-month cladribine-free period; (iii) a maintenance period lasting from about 2–4 months, wherein the total dose of cladribine administered is about 1.7 mg/kg; and (iv) a second cladribine-free period." EX2051, ¶218. However, Dr. Lublin provides no explanation that the alleged skepticism expressed in any of Exhibit 2004, Exhibit 2005, and Exhibit 2031 are connected to the two year dosing regimen.

114. Lastly, Dr. Lublin provides no evidence to support his argument that "there was skepticism of the safety of the cladribine dosing regimen." EX2051, ¶199. Dr. Lublin claims that the "FDA's complete response letter cited concerns over higher cancer risks associated with MAVENCLAD®," citing to a press release by Serono. EX2051, ¶199; EX2038, 1. However, the press release makes no mention of higher cancer risks associated with MAVENCLAD®, nor does it cite any other specific safety concern, a fact that Dr. Lublin admitted to during his

deposition. EX1061, 131:3–7. The FDA simply "requested that the Company provide an improved understanding of safety risks and the overall benefit-risk profile either through additional analyses or by additional studies." EX2038, 1. Merck responded to the FDA by saying they "intend[] to request an end-of-review meeting with the FDA to clarify next steps and to identify whether data from completed and ongoing clinical studies can address the Agency's questions." EX2038, 1. Nothing in this press release would have led a POSA to think that the FDA's concerns about safety were so great as to leave the FDA skeptical about whether the claimed cladribine dosing regimen could be used in treating MS. Further, Dr. Lublin provided no evidence to suggest that Merck had modified their dosing regimen to address FDA's request, and admitted he was unaware of such in his deposition. EX1061, 134:1–4.

115. Further, Merck's press release makes no mention of skepticism regarding the claimed dosing regimen. In fact, the press release states that "the FDA concluded that substantial evidence of Cladribine Tablets' effectiveness was provided by the CLARITY1 study," which, according to Dr. Lublin, is an embodiment of the claimed dosing regimen. EX2038, 1; EX2051, ¶220. Thus, a POSA would not have understood the FDA to be skeptical of the efficacy of the claimed oral cladribine dosing regimen. As such, a POSA would not have

understood this press release to undermine the obviousness of the claims as I've discussed above.

116. Finally, references EX2004, EX2011, EX2031, and EX2038 were published after 2004. EX2051, ¶¶195–198. As such, these post-2004 papers would not have informed a POSA prior to the filing date of the '947 patent, nor do they reflect the art prior to 2004.

117. Accordingly, Dr. Lublin's evidence of alleged skepticism does not provide additional objective evidence of nonobviousness of claims 36, 38, 39, and 41–46.

B. Dr. Lublin does not demonstrate unexpected results.

118. My understanding of the requirements to demonstrate unexpectedly superior results in support of nonobviousness are explained in paragraph 41 above.

119. According to Dr. Lublin, the claimed methods exhibit unexpected results because MAVENCLAD® demonstrated "unexpected durable efficacy and safety in treating MS." EX2051, ¶200. I disagree with Dr. Lublin's opinion because Dr. Lublin does not to compare MAVENCLAD® to the closest prior art, provide evidence that was in line with the full scope of the claims, or establish that the evidence is attributable to any unique characteristics of the claimed invention.

120. *First*, neither Dr. Lublin[4] nor Merck's attorneys compared the evidence of unexpected results to the closest prior art. The only prior art Dr. Lublin mentions in his analysis of unexpected results is Stelmasiak: "[t]he optimal cladribine dosing length of two years is also surprising in view of Stelmasiak." EX2051, ¶207. And I understand that Merck's attorneys have also argued that the two-year dosing length was surprising because of Romine's disclosure that cladribine's "beneficial effect should eventually decline and would not be expected to last much beyond 2 years" for chronic progressive MS. EX1031, 43. But neither Stelmasiak nor Romine are the closest prior art to the claimed methods; Bodor is. As I've shown in the table below, Bodor has more elements in common with the claimed invention than Stelmasiak and Romine:

Claim 36	**Bodor**	**Stelmasiak**	**Romine**
A method of treating multiple sclerosis	**Yes**	**Yes**	**Yes**
comprising the oral administration of a formulation comprising cladribine following the sequential steps below:	**Yes**	**Yes**	**No**

[4] Dr. Lublin conceded during his deposition that he was not aware of the meaning of the term "closest prior art," and that he did not consider what the closest prior art may have been before forming an opinion in this case. EX1061, 113:4–115:20.

Claim 36	Bodor	Stelmasiak	Romine
(i) an induction period lasting from about 2 to about 4 months	Yes	No	No
total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg	Yes	No	No
(ii) a cladribine-free period lasting from about 8 months to about 10 months	Yes	No	No
(iii) a maintenance period	Yes	Yes	Yes
lasting from about 2 months to about 4 months	No	No	Yes
total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg	No	No	No
(iv) a cladribine-free period wherein no cladribine is administered.	No	Yes	No

Bodor discloses treating MS by orally administering cladribine tablets with an induction dose of 100–140 mg (resulting in a mg/kg dose of 1.4 mg/kg to 2 mg/kg when administered to an average-weight patient) over a 2-month period, followed by a 10-month cladribine-free period. EX1022, 23:15–20. A POSA would have

understood Bodor to teach re-treatment, as I explained above. *See* ¶¶69–70. Stelmasiak teaches orally administering a cladribine solution to treat MS, however, Stelmasiak does not teach an induction dose of about 1.7 mg/kg to about 3.5 mg/kg or an induction period of 2 to 4 months. EX1013, 5. While Stelmasiak does disclose re-treatment with cladribine, they disclose a 3-month cladribine-free period after the induction dose. EX1013, 5. Also, Stelmasiak does not disclose administering about 1.7 mg/kg over a 2–4 month maintenance period, but does disclose a 9-month cladribine-free period after the maintenance period. EX1013, 5. Romine discloses administering cladribine subcutaneously to treat MS for 6 months for a total dose of 2.1 mg/kg. EX1031, Abstract. Romine does not disclose the claimed induction period, 8–10 month cladribine-free period, or a maintenance period dose of about 1.7 mg/kg, as recited in the claims. Neither Stelmasiak nor Romine is the closest prior art because Bodor has more elements in common with the claims – an overlapping induction period dose, the induction period length, and a 10-month cladribine-free period – which are lacking in Stelmasiak and Romine.

121. Therefore, it is my opinion that Bodor is the closest prior art to the claimed methods, and neither Dr. Lublin nor Merck's attorneys compared MAVENCLAD®'s results with the closest prior art.

122. Even if Stelmasiak was the closet prior art (which it isn't), CLARITY's results are not superior to Stelmasiak's. Dr. Lublin states that a

dosing length of 2 years is "surprising in view of Stelmasiak, which showed that EDSS scores of the RRMS patients treated with cladribine *returned to baseline* by the end of the 24-month study." EX2051, ¶207 (emphasis added). But in CLARITY, many of the patients experienced *an increase* in the EDSS scores, as evidenced by the time to 3-month EDSS progression data. *See, e.g.*, EX2033, 423, FIG. 1. Thus, Dr. Lublin's evidence does not demonstrate that CLARITY was superior to Stelmasiak.

123. And even if Romine was the closest prior art (which it isn't), CLARITY's results are not superior to Romine's. I understand that Merck's attorneys argued that the two-year dosing length was surprising because of Romine's disclosure that cladribine's "beneficial effect should eventually decline and would not be expected to last much beyond 2 years" for chronic progressive MS. EX1031, 43. However, Romine's disclosure only relates to chronic progressive MS, not RRMS. The CLARITY study only treated patients with RRMS. EX2033, Abstract. Dr. Lublin provides no evidence that the CLARITY results are superior compared to Romine's study or any other study that treated patients with progressive MS.

124. *Second,* the evidence Dr. Lublin relies on to form his opinions is not in line with the full scope of the claims. The challenged claims of the '947 patent encompass treating any course of MS with any type of oral cladribine formulation.

However, the CLARITY clinical trials only administered one oral cladribine dosage form (tablets) and only one formulation of that dosage form to patients with only one type of MS: RRMS. EX2033, 417. Dr. Lublin provides no evidence that other types of oral cladribine formulations (e.g., solutions, capsules, mucoadhesive tablets) would have also provided unexpectedly superior results. Dr. Lublin also provides no evidence that the claimed dosing regimen was effective in treating patients with progressive disease.

125. The claims also encompass administering cladribine for two ***or more*** years, as Dr. Lublin admitted. EX1061, 146:17–21. But according to Dr. Lublin, the two-year dosing length of the CLARITY study is "optimal" and additional courses of treatment provided no additional benefit. EX2051, ¶207. However, the claims are not limited to only administering two courses of treatment. EX1001, 19:13–30, 20:26–27. As such, the evidence Dr. Lublin relies on to form his opinions about unexpected results are not in line with the full scope of the challenged claims.

126. *Third,* Dr. Lublin does not demonstrate that the evidence he relies on is attributable to the unique features of the claimed invention. Dr. Lublin contends that the "unique characteristic of the claimed invention is the four-step method of treating MS using orally-administered cladribine, comprising (i) an induction period lasting from about 2–4 months, wherein the total dose of cladribine

administered is from about 1.7–3.5 mg/kg; (ii) an 8- to 10-month cladribine-free period; (iii) a maintenance period lasting from about 2–4 months, wherein the total dose of cladribine administered is about 1.7 mg/kg; and (iv) a second cladribine-free period." EX2051, ¶218. However, Dr. Lublin attributes MAVENCLAD®'s "unexpected durability" to cladribine's "unique mechanism of action" "as an immune reconstitution therapy." EX2051, ¶¶212–213. Thus, Dr. Lublin provides no explanation that his evidence of alleged unexpected results are a result of the claimed dosing regimen rather than a prior art cladribine formulation and dosing regimen, such as Bodor and Stelmasiak.

127. Accordingly, Dr. Lublin's argument of unexpected results does not provide additional objective evidence of nonobviousness of claims 36, 38, 39, and 41–46.

C. Dr. Lublin does not establish a long-felt, but unmet need.

128. My understanding of the requirements to demonstrate long-felt but unmet need in support of nonobviousness are explained in paragraph 42 above.

129. Dr. Lublin provides no evidence that at the time the '947 patent was filed, the art recognized a need for "safe, effective, and convenient oral therapy for MS." EX2051, ¶¶209–216. Nor did Dr. Lublin provide any evidence that this alleged need was unmet at the time of filing.

130. Dr. Lublin cites to the fact that as of 2004, all FDA-approved MS drugs on the market were injectables. EX2051, ¶210. Dr. Lublin also contends that FDA-approved drugs prior to 2004 "were also dosed continuously 'without an intended interruption in dosing.'" EX2051, ¶211. However, the only reference Dr. Lublin relies on for his argument is a review paper published in 2020, well after the filing date of the '947 patent. EX2051, ¶211.

131. Dr. Lublin further suggests that MAVENCLAD®'s approval fulfilled the alleged long-felt need ("MAVENCLAD® is given in two short courses of tablets in the first and second year for two years."). EX2051, ¶212. However, Bodor and Stelmasiak, alone or in combination, would have met any long-felt need prior to the 2004 filing date of the patent because a POSA would have understood Bodor and Stelmasiak to both disclose "safe, effective, and convenient oral therapy for MS." *See* ¶¶51–52, 58–61. For example, Stelmasiak discloses its study "indicates that in this clinical setting a two- to three-fold reduction of blood lymphocyte count can be achieved by the drug given subcutaneously without clinically significant hematological side effects." EX1013, 7. As such, Bodor and Stelmasiak would have satisfied any alleged long-felt need for an oral MS drug.

132. Dr. Lublin also admits that the effects of drugs are "closely related to their short half-lives and pharmacokinetic and pharmacodynamic profiles." EX2051, ¶211. Dr. Lublin attributes MAVENCLAD®'s "unexpected durability"

to cladribine's "unique mechanism of action" "as an immune reconstitution therapy." EX2051, ¶¶212–213. Dr. Lublin does not attribute MAVENCLAD®'s "unexpected durability" to the claimed dosing regimen.

133. Accordingly, Dr. Lublin's argument of long-felt but unmet need does not provide additional objective evidence of nonobviousness of claims 36, 38, 39, and 41–46.

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 Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Aaron Miller, MD

Date: 04/04/2024

Aaron E. Miller, MD