

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.
Petitioner,

v.

MERCK SERONO S.A.
Patent Owner.

Case IPR2023-00481
U.S. Patent No. 8,377,903

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 8,377,903**

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TABLE OF CONTENTS

I.	STATEMENT OF PRECISE RELIEF REQUESTED AND REASONS THEREFOR (37 C.F.R. § 42.22(A)).....	1
II.	INTRODUCTION	1
III.	THE '903 PATENT AND ITS PROSECUTION HISTORY	7
	A. Specification of the '903 Patent	8
	B. Challenged Claims	8
	C. The prosecution history	9
IV.	STATE OF THE ART BEFORE DECEMBER 22, 2004.....	13
	A. MS is a chronic disease with no known cure	13
	B. Immunosuppression was a common treatment strategy; lymphocyte count was a common measure for assessing response to treatment.....	15
	C. Treatment of MS required cyclical drug therapies.....	16
	D. Cladribine, a known immunosuppressant, was used to treat MS, including RRMS	18
	E. Oral cladribine compositions and dosages for treating MS, including RRMS, were known in the art.....	20
	F. Petitioner's ground relies specifically on the following publications	22
	1. Bodor (EX1022).....	22
	2. Stelmasiak (EX1013).....	24
V.	PERSON OF ORDINARY SKILL IN ART	28
VI.	CLAIM CONSTRUCTION	29
	A. "total dose of cladribine".....	29
	B. "an induction period"	29
	C. "a maintenance period"	30
VII.	IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 42.104(B))	33
VIII.	GROUND 1: THE CLAIMS WOULD HAVE BEEN OBVIOUS OVER BODOR AND STELMASIAK	33
	A. Claim 17	33
	1. A POSA would have had a reason to combine Bodor and Stelmasiak	33

2.	A POSA would have had a reasonable expectation of success.....	44
3.	Each limitation of claim 17 is disclosed in the art.....	46
B.	Claim 19	57
C.	Claim 20	57
D.	Claim 22	58
E.	Claim 23	59
F.	Claim 24	60
G.	Claims 25 and 26.....	61
H.	Claim 27	62
IX.	NO OBJECTIVE INDICIA WEIGH AGAINST THE STRONG OBVIOUSNESS SHOWING HERE	62
X.	THE FACTS AND LAW WEIGH AGAINST DISCRETIONARY DENIAL UNDER § 325(D).....	63
XI.	<i>FINTIV</i> DOES NOT SUPPORT DISCRETIONARY DENIAL.	66
XII.	<i>GENERAL PLASTIC</i> DOES NOT SUPPORT DISCRETIONARY DENIAL	68
XIII.	CERTIFICATION AND STANDING (37 C.F.R. § 42.104(A)).....	69
XIV.	MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1)).....	69

EXHIBIT LIST

<i>Exhibit #</i>	<i>Description</i>
1001	De Luca, G., et al., “Cladribine Regimen for Treating Multiple Sclerosis,” U.S. Patent No. 8,377,903 B2 (filed April 23, 2010; issued February 19, 2013)
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Exhibit #	Description
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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)
1027	Docket Report, <i>Merck KGaA et al. v. Hopewell Pharma Ventures, Inc.</i> , Case No. 1:22-cv-01365-GBW (D.Del.)
1028	Docket Report, <i>Merck KGaA et al. v. Accord Healthcare, Inc.</i> , Case No. 1:22-cv-00974-GBW (D.Del.)
1029	United States District Courts - National Judicial Caseload Profile, June 2022

Exhibit #	Description
1030	<i>Curriculum Vitae</i> for Nancy E. Adams, Ed.D.
1031	Romine, J. S., et al., “A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis,” <i>Proceedings of the Association of American Physicians</i> , 111(1):35-44 (1999)
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1035	Stipulation and [Proposed] Order Staying Litigation with Respect to Accord Healthcare, Inc., <i>Merck KGaA et al. v. Accord Healthcare, Inc. et al.</i> , Case No. 1:22-cv-00974 (D. Del.), December 14, 2022
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<i>Exhibit #</i>	<i>Description</i>
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TABLE OF ABBREVIATIONS

Abbreviation	Definition
MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
ESPMS	Early secondary progressive multiple sclerosis
CNS	Central nervous system
EDSS	Expanded disability status scale
SNRS	Scripps neurologic scoring scale
IVMP	Intravenous methylprednisolone

TABLE OF AUTHORITIES

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<i>Abbott Labs. v. Andrx Pharm., Inc.</i> , 452 F.3d 1331 (Fed. Cir. 2006).....	22
<i>ACCO Brands Corp. v. Fellowes, Inc.</i> , 813 F.3d 1361 (Fed. Cir. 2016).....	38
<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH</i> , IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020).....	63
<i>Agrofresh Solutions, Inc. v. Lytone Enterprise, Inc.</i> , IPR2021-00451, Paper 11 (P.T.A.B. July 27, 2021)	64
<i>Amgen Inc, v. Hoechst Marion Roussel, Inc.</i> , 314 F.3d 1313 (Fed. Cir. 2003).....	11
<i>Amneal Pharms. v. Supernus Pharms.</i> , IPR2013-00368, Paper 8 (P.T.A.B. Dec. 17, 2013)	63
<i>Apple Inc. v. Fintiv, Inc.</i> , IPR2020-0019, Paper 11 (P.T.A.B. Mar. 20, 2020)	66, 67
<i>Becton, Dickinson & Co. v. Baxter Corp. Englewood</i> , 998 F.3d 1337 (Fed. Cir. 2021).....	54
<i>Biogen Idec, Inc. v. GlaxoSmithKline LLC</i> , 713 F.3d 1090 (Fed. Cir. 2013).....	31
<i>Code200 UAB v. Bright Data Ltd.</i> , IPR2022-00861, IPR2022-00862, Paper 18 (P.T.A.B. Aug. 23, 2022)	68, 69
<i>Duramed Pharm., Inc. v. Watson Labs., Inc.</i> , 413 F. App'x 289 (Fed. Cir. 2011)	34
<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013).....	40
<i>Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha</i> , IPR2016-01357, Paper 19 (P.T.A.B., Mar. 20, 2020)	68, 69
<i>In re Aller</i> , 220 F.2d 454 (C.C.P.A. 1955)	41, 43
<i>In re Applied Materials</i> , 692 F.3d 1289 (Fed. Cir. 2012).....	41

<i>In re Geisler</i> , 116 F.3d 1465 (Fed. Cir. 1997).....	41
<i>In re Peterson</i> , 315 F.3d 1325 (Fed. Cir. 2003).....	40
<i>In re Woodruff</i> , 919 F.2d 1575 (Fed. Cir. 1990).....	41
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	53
<i>Medichem, S.A. v. Rolabo, S.L.</i> , 437 F.3d 1157 (Fed. Cir. 2006).....	12, 44
<i>Micron Tech., Inc. v. Godo Kaisha IP Bridge 1</i> , IPR2020-01007, Paper 15 (P.T.A.B. Dec. 7, 2020)	67
<i>Microsoft Corp. v. Multi-Tech Systems, Inc.</i> , 357 F.3d 1340 (Fed. Cir. 2004).....	31
<i>Newell Cos., Inc. v. Kenney Mfg. Co.</i> , 864 F.2d 757 (Fed. Cir. 1988).....	62
<i>NOF Corp. v. Nektar Therapeutics</i> , IPR2019-01394, Paper 68 (P.T.A.B. July 30, 2021)	41
<i>Opensky Indus., LLC v. VLSI Tech. LLC</i> , IPR2021-01064, Paper 17 (P.T.A.B. Dec. 23, 2021)	68
<i>Randall Mfg. v. Rea</i> , 733 F.3d 1355 (Fed. Cir. 2013).....	22
<i>Sand Revolution II, LLC v. Continental Intermodal Group – Trucking LLC</i> , IPR2019-01393, Paper 24 (P.T.A.B. June 16, 2020).....	67
<i>Santarus, Inc. v. Par Pharm., Inc.</i> , 694 F.3d 1344 (Fed. Cir. 2012).....	12
<i>Shenzhen Silver Star Intelligent Tech. Col., Ltd. v. iRobot Corp.</i> , IPR2018-00761, Paper 15 (P.T.A.B. Sept. 5, 2018).....	69
<i>Sotera Wireless, Inc. v. Masimo Corporation</i> , IPR2020-01019, Paper 12 (P.T.A.B. Dec. 1, 2020)	66
<i>Vudu, Inc. v. Ideahub, Inc.</i> , IPR2020-01689, Paper 16 (P.T.A.B. Apr. 19, 2021).....	65

Statutes

35 U.S.C. § 102	66
35 U.S.C. § 102(a)	22
35 U.S.C. § 102(e)	22
35 U.S.C. § 103	66

Other Authorities

U.S. Patent and Trademark Office, Memorandum, Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022).....	66, 67
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Regulations

37 C.F.R. § 42.10(b)	71
37 C.F.R. § 42.104(a).....	69
37 C.F.R. § 42.106(a).....	71
37 C.F.R. § 42.22(a).....	1
37 C.F.R. § 42.63(e).....	71
37 C.F.R. § 42.8(a)(1)	69
37 C.F.R. § 42.8(b)(1).....	69
37 C.F.R. § 42.8(b)(2).....	70
37 C.F.R. § 42.8(b)(3).....	71
37 C.F.R. § 42.8(b)(4).....	71

I. STATEMENT OF PRECISE RELIEF REQUESTED AND REASONS THEREFOR (37 C.F.R. § 42.22(A))

Hopewell Pharma Ventures, Inc. (“Hopewell”) petitions for *inter partes* Review, seeking cancellation of claims 17, 19, 20, and 22-27 of U.S. Patent No. 8,377,903 (“the ’903 patent”; EX1001), assigned to Merck Serono S.A. (“Merck”). The challenged claims are unpatentable under 35 U.S.C. § 103. This Petition is supported by the Declaration of Dr. Aaron Miller, M.D. (EX1002), an expert in multiple sclerosis.

II. INTRODUCTION

The claims encompass methods of treating relapsing-remitting multiple sclerosis (“RRMS”) or early secondary progressive multiple sclerosis (“early SPMS” or “ESPMS”) comprising “oral administration of a formulation comprising cladribine” following “the sequential steps” of “an induction period,” “a cladribine-free period,” “a maintenance period,” and another “cladribine-free period.” EX1001, 18:7-26. Properly construed, the claims require that a total dose of cladribine administered in the maintenance period is lower than the total dose of cladribine administered in an induction period in the claimed method. The prior art would have rendered such methods obvious.

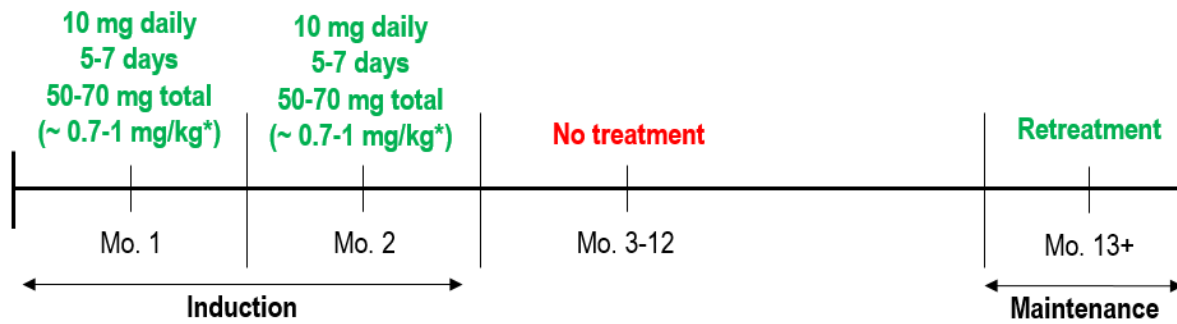
MS is a chronic autoimmune disease with no known cure. EX1009, 263; EX1002, ¶15. Most patients experience a relapsing-remitting form of MS (“RRMS”), in which neurological symptoms and signs develop over several days,

plateau, and then usually improve—events known as “relapses.” EX1009, 263; EX1002, ¶15. Many RRMS patients go on to develop secondary progressive multiple sclerosis (“SPMS”), characterized by emerging “progressive neurological dysfunction.” EX1009, 263; EX1002, ¶15. The period of transition from RRMS to SPMS was sometimes labeled ESPMS. EX1038, 63; EX1042, 278; EX1002, ¶¶15, 25. Therefore, a person of ordinary skill in the art (“POSA”) would have known before December 2004 that as a rule, an MS patient typically needs ongoing care. EX1013, 6; EX1009, 263; EX1002, ¶¶15, 57.

Given the autoimmune nature of MS, “the most common therapeutic approach” to MS, including RRMS, before December 2004 was by immunosuppression. EX1013, 4; EX1007, 131; EX1031, 35; EX1002, ¶¶16, 30. Before 2004, cladribine emerged as a useful drug “in modulating autoimmune processes involving lymphocyte abnormalities.” EX1018, 1146; EX1002, ¶34. Scientists originally developed cladribine for treatment of leukemia, but quickly repurposed it for treatment of MS due to its demonstrated ability to, e.g., “impressively decrease[]” relapse rate in patients with RRMS. EX1013, 5, 7; EX1002, ¶¶16, 42. A POSA treating MS would have used the common strategy of immunosuppression and chosen cladribine because it was known to “selectively damage lymphocytes” while being “not harmful to normal bone marrow cells and other cell types,” unlike other immunosuppressants (e.g., cyclophosphamide,

cyclosporine A, and chlorambucil). EX1015, 1752; EX1013, 6-7; EX1002, ¶30, 34. In treating MS with cladribine, neurologists commonly assessed cladribine's effect by measuring a patient's lymphocyte count, with a sustained decrease in count being characteristic of a treatment response. EX1018, 1146; EX1013, 5; EX1014, 1717; EX1002, ¶31.

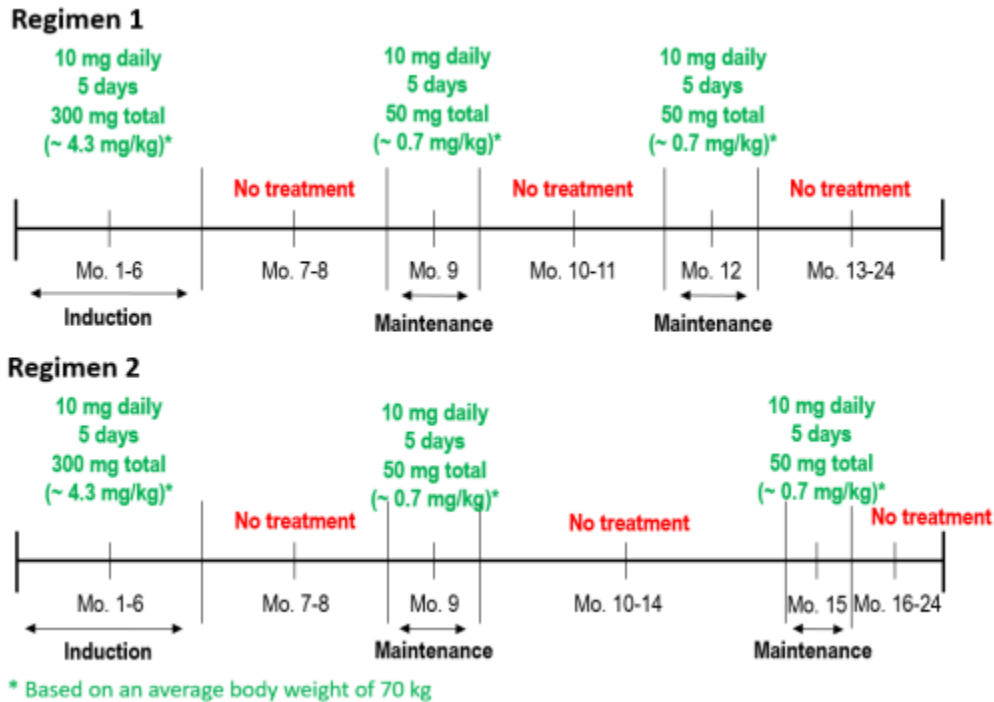
Before December 2004, Bodor, noting a preference of “[o]ral delivery of [cladribine] ... to parental delivery,” described an oral formulation of cladribine that exhibited “improved cladribine absorption, as reflected by higher bioavailability.” EX1022, 2, 11-12; EX1002, ¶97. Bodor taught the following cyclical regimen for treating MS: “10 mg of cladribine ... administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 2, 11-12; EX1002, ¶79. Because MS is an incurable disease, a POSA reading Bodor in light of general knowledge in the art, would have understood that there would have been MS patients who would need to be retreated after the “no-treatment” (cladribine-free) period. EX1002, ¶17. Dr. Miller prepared a graphic to demonstrate how a POSA would have understood Bodor's regimen (EX1002, ¶84):



* Based on an average body weight of 70 kg

In following Bodor's express teachings, a POSA would have orally administered cladribine for two months (an induction period), followed by a ten-month cladribine-free period. EX1022, 23; EX1002, ¶17. And because a POSA would have understood that an MS patient typically needs ongoing care, a POSA would have retreated a relapsing patient after the initial induction/cladribine-free cycle, as Stelmasiak expressly taught, thus arriving at the claimed methods. EX1013, 6; EX1002, ¶17.

Indeed, before December 2004, Stelmasiak described a trial of oral cladribine in RRMS, where cladribine was administered according to one of two regimens. EX1013, Abstract; EX1002, ¶17. Dr. Miller prepared the following graphic to illustrate how a POSA would have understood Stelmasiak's regimens (EX1002, ¶89):



A POSA would have recognized that both regimens were cyclical¹: they included an induction, a cladribine-free, and a maintenance period. EX1013, Abstract; EX1002, ¶¶17, 88. Further, a POSA would have appreciated that Stelmasiak’s maintenance period in both regimens included a lower dose of cladribine compared to the induction period (compare 50 mg (maintenance) to 300 mg (induction)). EX1013, Abstract. According to Stelmasiak, the induction period was characterized by a drop in lymphocyte count from 2336±595 per µl to 968±229 per µl.” EX1013, 5; EX1002, ¶90. Notably, the lower dose of cladribine

¹ In a “cyclical” treatment regimen, cycles (or courses) of cladribine administration are repeated at a given interval. EX1026, 11:5-7; EX1002, ¶ 63.

in the maintenance period, compared to the induction period, was sufficient to maintain the decreased lymphocyte count. EX1013, FIG. 1; EX1002, ¶91.

Stelmasiak concluded that “cladribine favourably compare[d] with other immunosuppressants” vis-à-vis side-effects. EX1013, 7; EX1002, ¶102. And it caused “a very marked” reduction in the relapse rate. EX1013, 5; EX1002, ¶102. Given Stelmasiak’s success, a POSA would have been motivated to use Stelmasiak’s approach involving a lower maintenance cladribine dose, compared to the induction dose, after the induction/cladribine-free periods of Bodor’s cycle, arriving at the claimed regimen. EX1002, ¶¶18, 110.

The claims also require that the total dose of cladribine reached at the end of the induction period is “about 1.7 mg/kg to about 3.5 mg/kg.” EX1001, 18:21-23. The claimed range overlaps with Bodor’s range of about 1.4 mg/kg to about 2 mg/kg, and therefore would have been *prima facie* obvious. EX1022, 23; EX1002, ¶ 88. And the claimed length of the maintenance period (“about 2 months to about 4 months”) and total dose of cladribine reached at the end of the maintenance period (“about 1.7 mg/kg”) are merely workable ranges that a POSA would have arrived at by routine experimentation. EX1002, ¶¶92-94. Cladribine’s dose and duration of administration are result-effective variables: the art taught 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, 5:22-25²; EX1018, FIG. 4; EX1022, 22:17-19; EX1002, ¶118. Thus, the claimed total doses of cladribine and the length of administration are not inventive.

A POSA further would have reasonably expected that cladribine’s immunosuppressive effect could be maintained with a lower dose of cladribine during retreatment because the induction period would have decreased the patient’s lymphocyte count. EX1013, FIG. 1; EX1002, ¶¶18, 91. Thus, a lower cladribine dose would have been expected to be enough for maintaining the suppressed lymphocyte count, and a POSA would have used the lowest effective dose to minimize toxicity associated with cladribine. EX1013, FIG. 1, 7; EX1002, ¶¶90-91.

Thus, the claimed method would have been obvious to a POSA, and there are no secondary considerations that weigh against the strong obviousness showing here. EX1002, ¶141.

III. THE ’903 PATENT AND ITS PROSECUTION HISTORY

The ’903 patent issued on February 19, 2013, from U.S. Appl. No. 12/766,173, which is a continuation of U.S. Application No. 11/722,018, now U.S.

² Emphasis is added throughout.

Patent No. 7,713,947, filed as PCT Appl. No. PCT/EP2005/056954 on December 20, 2005, and claims a priority date of December 22, 2004.³

A. Specification of the '903 Patent

The patent provides a dosing regimen for using cladribine to treat multiple sclerosis. *Id.*, 3:42-44; EX1002, ¶64. The regimen includes orally administering cladribine following the sequential steps of “an induction treatment,” “a cladribine-free period,” “a maintenance treatment,” and another “cladribine-free period.” *Id.*, 4:3-13; EX1002, ¶64. According to the specification, “the total dose of [c]ladribine reached at the end of the maintenance period is lower than the total dose of [c]ladribine reached at the end of the induction period.” *Id.*, 3:50-4:13.

B. Challenged Claims

Independent claim 17 recites:

17. A method of treating relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis comprising the oral administration of a formulation comprising cladribine to an individual having relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis following the sequential steps below:

- (i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and

³ Petitioner does not concede that the '903 patent is entitled to this date.

wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

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

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

EX1001, 18:7-26; EX1002, ¶¶65, 77.

Claims 19, 20, and 22-27 depend from claim 17 and add limitations such as the length of the induction, cladribine-free, and maintenance periods, as well as cladribine doses. EX1002, ¶66.

C. The prosecution history

In the first Office Action, the Examiner rejected then-pending claims 1-29 under 35 U.S.C. 103(a) as obvious over Bodor and Grieb (*Arch. Immunol. Therap. Exp.* 1995; 43:323-327), in view of USPN 4,964,848 (“Bloom”). EX1004, 100.

The Examiner found that Bodor and Grieb teach every limitation of the claims except that “the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase.” *Id.*, 103.

But, the Examiner, relying in part on Bloom, found that “the artisan would have been motivated to use a lower dose in subsequent treatment periods (i.e., the maintenance phase) that is still sufficient to sustain a therapeutically-effective immunosuppressive state” (*id.*, 105), and that “the treatment durations, frequency of treatment (i.e., time between active therapy periods), and administered dosages are clearly recognized result-effective variables that a person of ordinary skill in the art would routinely optimize.” *Id.*, 105-06.

In response, Merck did not, and could not, dispute that Bodor taught a cyclical treatment of MS using cladribine, with a two-month induction period followed by a ten-month cladribine-free period. Nor did Merck dispute the Examiner’s finding that a POSA would have “routinely optimized” the recited doses, treatment durations, and frequencies.

Instead, Merck ignored Bodor’s undisputed and express teaching of an “induction period of about two to four months,” and faulted Grieb for failing to teach this limitation. *Id.*, 123. Merck argued that Grieb taught the use of an initial “administration of cladribine for at least six months” as “lymphocyte counts are not maximally suppressed until the individuals have been treated for at least six months.” EX1004, 125. Relatedly, Merck also argued that Greib “teaches away from the use of a two to four month induction period as recited in the claims of this

application” because it teaches that “maximal reduction in lymphocyte numbers is observed after six months of treatment with cladribine.” EX1004, 126.

However, Merck’s assertions that Bodor’s two- to four-month induction period should be disregarded in favor of Grieb’s six-month induction period (and thus Grieb taught away from a two-to-four month induction period as claimed) are simply wrong. A POSA would have understood that Bodor had created an improved oral cladribine tablet that had higher bioavailability compared to earlier cladribine dosage forms, such as Grieb’s. EX1002, ¶110. Thus, the length of time it took for *Grieb*’s dosage form to adequately suppress lymphocyte counts is not informative of the length of an induction period to use with *Bodor*’s improved dosage form. EX1002, ¶110. Indeed, a POSA would have reasonably expected that Bodor’s two-month induction period, using its improved tablet, would have had a sufficient immunosuppressive effect.⁴ EX1022, 23; EX1015, 1752; EX1002, ¶104. For similar reasons, it also cannot be said that Grieb provides any sort of teaching away, as Grieb does not “suggest that the line of development flowing from

⁴ Because Bodor eventually issued as U.S. Patent No. 7,888,328, it is presumed that a POSA could make and use all disclosure in Bodor, and Bodor’s regimen would be expected to be operational. *Amgen Inc, v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

[Bodor's] disclosure is unlikely to be productive of the result sought by the applicant," and instead is simply uninformative to the length of the induction period using Bodor's tablet. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("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"))

Merck also argued that "nowhere in the teachings of [Bodor] is there any discussion about repeating a treatment course at any point in time at either the original dosage or at a lower dosage in a manner that could be construed as a 'maintenance period'." *Id.*, 121. And Merck argued that none of the cited art taught "lowering treatment dosages" in such a maintenance phase. *Id.*, 125. But, as this Petition shows, and Dr. Miller confirms, Bodor *does* suggest to a POSA repeating the treatment course, and the prior art, e.g., the Stelmasiak reference, *does* expressly teach administering a lower total dose of cladribine in such a maintenance period compared to that in an induction period. EX1013, Abstract; EX1002, ¶94.

The Examiner did not find Merck's arguments persuasive and issued a second Office Action, maintaining the obviousness rejection over "the combination of" Bodor, Grieb, and Bloom. EX1004, 130-42.

Merck responded by repeating its previous arguments, and again highlighted the alleged fact that Grieb “teaches ‘**an initial treatment period of up to 6 months.**’” *Id.*, 150 (emphasis in original). But Merck’s argument is inapplicable for the same reasons as discussed above: Grieb used a different dosage form than the improved cladribine tablet used in Bodor, rendering its teachings uninformative regarding the length of the induction period to use with Bodor’s tablet. Thus, Grieb’s teachings cannot overcome Bodor’s express teachings regarding the claimed length and the total dose of cladribine in the induction period.

The Examiner allowed the claims without providing a specific reason for allowance. EX1004, 0157-63, 0164-73, 0174-82.

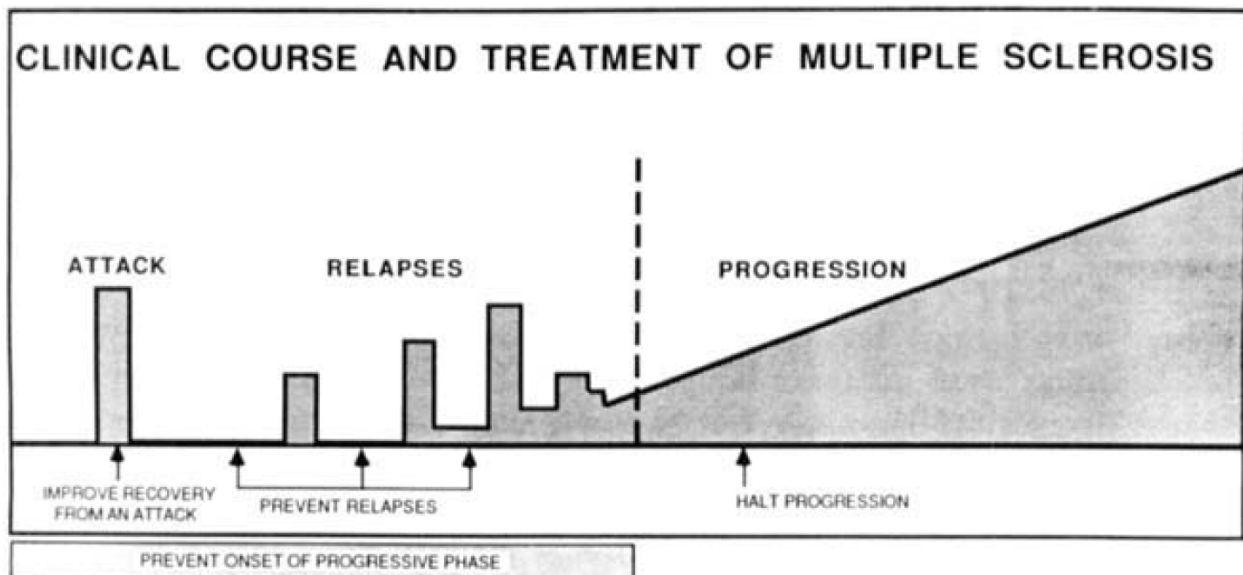
IV. STATE OF THE ART BEFORE DECEMBER 22, 2004⁵

A. MS is a chronic disease with no known cure

MS is an autoimmune disease with no known cure. EX1009, 263; EX1002, ¶22. MS is also typically a progressive disease. EX1008, 212-213. Most patients experience RRMS, in which “neurological symptoms and signs develop over several days, plateau, and then usually improve over days to weeks.” EX1009, 263; EX1002, ¶15. Many RRMS patients will go on to develop SPMS, characterized by

⁵ As Dr. Miller confirms, references cited herein reflect general knowledge in the art. EX1002, ¶ 14.

emerging “progressive neurological dysfunction” “as relapse frequency lessens over time.” *Id.* The transitional period between RRMS and SPMS was referred to by some in the field as a distinct form of MS called “early SPMS” or “ESPMS.” EX1038, 63; EX1042, 278, FIG.1; EX1002, ¶25. A small number of patients have the primary progressive form (“PPMS”) from clinical onset, in which their disease gradually worsens over time without periods of remission. EX1009, 263; EX1002, ¶15. In sum, studies of large numbers of patients suggest that clear disease patterns emerge over time, as illustrated in the following graphic (EX1008, FIG. 1; EX1002, ¶57):



Monitoring of patients for signs and symptoms of MS involves MRI examination for assessment of brain lesion formation (which may be associated with clinical relapses depending on where the lesion(s) occur) and progression, as well as measures of clinical disability with a physical exam, defined clinical scales,

such as the Expanded Disability Status Scale (EDSS), and relapse frequency.

EX1010, generally; EX1037, 910; EX1002, ¶¶26-27. Despite the disease form, “[a]ll actively demyelinating lesions were associated with an inflammatory process.” EX1036, 118; EX1002, ¶24. It is also common to measure lymphocyte count during treatment to assess a patient’s response to an immunosuppressive therapy. EX1013, 5; EX1014, 1717; EX1018, 1146; EX1002, ¶52.

B. Immunosuppression was a common treatment strategy; lymphocyte count was a common measure for assessing response to treatment

Given the autoimmune nature of MS, a common strategy for treating MS, including RRMS, before December 2004 involved suppression of autoantigen-specific T lymphocytes (i.e., cells that react directly with proteins in the CNS) using immunosuppressive therapies. EX1007, 131; EX1002, ¶30. Indeed, by December 2004, a number of clinical trials “designed to suppress the immune system or to restore immune balance in multiple sclerosis” had been conducted. EX1008, Abstract; EX1012, S104. The immunosuppressive agents used to treat MS before December 2004 included general immunosuppressants, such as mitoxantrone, azathioprine, cyclosporine A, methotrexate, and cyclophosphamide, as well as more lymphocyte-selective agents, such as cladribine. EX1007, 133; EX1013, Abstract; EX1018, Abstract; EX1014, Abstract; EX1006, 947; EX1002, ¶34. And because “[c]linical trials of general immunosuppressants in multiple sclerosis produced disappointing results” due to “systemic side-effects,”

researchers focused on cladribine over general immunosuppressants before

December of 2004. EX1013, 6; EX1002, ¶34.

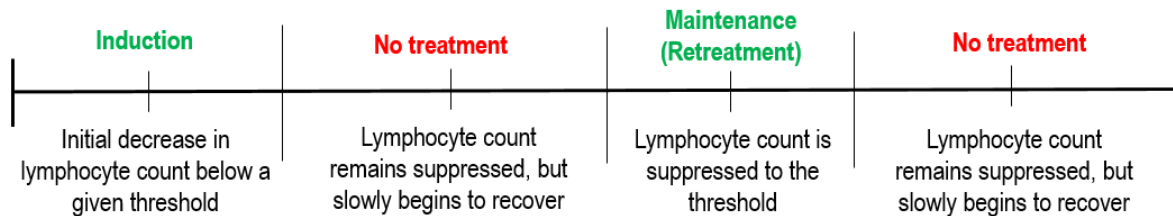
Before 2004, a POSA would have known that it was common to measure lymphocyte counts during treatment to assess a patient's response to an immunosuppressive therapy.⁶ EX1013, 5; EX1014, 1717; EX1018, 1146; EX1002, ¶31. For example, to measure cladribine-induced immunosuppression on patients with RRMS, Stelmasiak monitored patients' lymphocyte count every 3 months during a 24-month clinical trial. EX1013, 5; EX1002, ¶31. In Beutler's cladribine trial, a "[l]ymphocyte subset evaluation was done monthly during the course of drug administration and less frequently thereafter." EX1014, 1717; EX1002, ¶31. And, during a phase III clinical trial, Rice monitored patients' "total lymphocyte count and lymphocyte subset counts" to assess the efficacy of cladribine in patients with progressive MS. EX1018, 1146; EX1002, ¶32.

C. Treatment of MS required cyclical drug therapies

Given the chronic and incurable nature of MS, the primary goal of treatment is to reduce signs or symptoms of MS, for example, decrease lymphocyte count,

⁶ A positive response to the therapy was achieved when lymphocyte count dropped below about 1,000 lymphocytes per microliter (µl) of blood. EX1018, Figure 4; EX1013, 5; EX1014, 1717; EX1002, ¶¶ 32-39.

reduce relapse rate, and postpone disease progression. EX1008, 212-213; EX1013, 5; EX1014, 1717; EX1018, 1146; EX1002, ¶63. Because of the cyclical nature of many forms of MS (e.g., the relapse-and-recovery cycle seen in RRMS), patients were often treated in cycles—patients received a drug for a period of time, stopped taking the drug for a period of time, and then began treatment again. EX1008, 211-213; EX1019, 384; EX1002, ¶57-63. Dr. Miller prepared the following schematic to illustrate how a POSA would have understood this concept (EX1002, ¶105):



Clinicians applied this type of general regimen frequently because MS is a chronic autoimmune disease, and clinical care of an MS patient generally requires that the patient undergo periodic immunosuppressive retreatments to prevent relapses and progression of the disease. *See, e.g.*, EX1013; EX1019; EX1020; EX1021; EX1002, ¶57.

For example, Stelmasiak described “[t]reatment [of RRMS patients] with repeated doses of [oral] cladribine:” “six courses of [cladribine] given once a month, followed by two additional courses at three month intervals” (“9 and 12 or 15 months”). EX1013, Abstract, 5, 6; EX1002, ¶39. As another example, Barkof

taught treating MS patients, wherein initial treatment is administered, and “[w]hen new clinical relapses occurred, treatment was repeated.” EX1019, Abstract, 382; EX1002, ¶59.

Pirko described treating progressive MS patients with intravenous methylprednisolone (IVMP), concluding that “there may be a treatment effect of *pulsed* IVMP in a subset of patients with progressive MS.” EX1020, 1148; EX1002, ¶¶60-61. And Weiner 1993 discussed a study in which patients with progressive MS were given induction doses of cyclophosphamide plus adrenocorticotrophic hormone, followed by “boosting” with cyclophosphamide every 2 months for 2-years. EX1021, 911; EX1002, ¶62.

Thus, a POSA would have understood that a common strategy for treating MS, including RRMS, involved a cyclical drug administration. EX1002, ¶62.

D. Cladribine, a known immunosuppressant, was used to treat MS, including RRMS

Cladribine, an adenosine deaminase inhibitor, was first launched in the US in 1993 for treatment of various neoplasms. EX1015, Abstract; EX1002, ¶33. Before 2004, it was known that “cladribine causes prolonged, profound suppression of lymphocyte counts,” which “suggests that a cladribine-induced reduction in the number of lymphocytes may help to slow progression of the disease [MS].” EX1016, 421; EX1002, ¶34. As such, in the mid-1990s, researchers began using cladribine to treat MS. EX1016, 421; EX1002, ¶35.

In 1996, **Beutler** reported the results of a 2-year clinical study of cladribine in patients with chronic progressive MS. EX1014, Abstract; EX1002, ¶¶35-38. According to Beutler, “average EDSS and SNRS scores of patients receiving cladribine improved modestly during the first year of the study.” EX1014, 1717; EX1002, ¶36. Beutler also reported that a “highly significant difference” in brain lesions was seen on MRI and noted a “marked depletion” of lymphocytes. EX1014, 1718-19; EX1002, ¶37. Beutler concluded that “[o]ur studies clearly show that cladribine retards the progression of neurologic impairment of patients with chronic progressive MS.” EX1014, 1719-1720; EX1002, ¶38.

In 1998, **Stelmasiak** reported the results of a clinical study of cladribine in RRMS patients. EX1013, Abstract; EX1002, ¶¶39-42. Like Beutler, Stelmasiak observed a drop in lymphocytes count in response to cladribine, noting that a “tendency toward normalization of lymphocyte counts became evident only at the end of the 2-year observation period.” EX1013, 5-6; EX1002, ¶41. Stelmasiak also reported that “EDSS scores were significantly reduced during the treatment compared to the initial values,” and that the decreases were “significant.” EX1013, 6; EX1002, ¶97.

In 1999, **Romine** reported the results of a clinical study of cladribine also involving RRMS patients. EX1031, Abstract; EX1002, ¶45-46. Romine reported that cladribine “appears to be safe and effective in reducing the rate and severity of

clinical exacerbations” during the study, with “relative freedom from exacerbations [] an effect that continued into the second year of the study. EX1031, 42; EX1002, ¶44. Romine further noted an “almost complete suppression of MRI-enhancing lesions with cladribine.” EX1031, 42; EX1002, ¶45. Further, like Beutler and Stelmasiak, Romine observed that “[a]verage lymphocyte counts in the cladribine group declined.” EX1031, 41; EX1002, ¶44.

In 2000, **Rice** evaluated “the safety and efficacy of two doses of cladribine in patients with progressive MS.” EX1018, Abstract; EX1002, ¶¶47-49. Rice observed “a suppression in lymphocyte count” in response to both doses of cladribine. EX1018, 1152, Figure 4; EX1002, ¶48. Rice also reported that gadolinium-enhancing brain lesions (lesions that reflect active disease) “were virtually eliminated by treatment with cladribine.” EX1018, 1153; EX1002, ¶49. And although “no significant treatment effects were found” using “EDSS scores as an outcome measure,” Rice explained that the severe disability of the majority of the patients enrolled in the study made it difficult to assess overall treatment difference by EDSS. EX1018, 1153; EX1002, ¶63.

E. Oral cladribine compositions and dosages for treating MS, including RRMS, were known in the art

Because “[o]ral delivery of drugs is often preferred to parenteral delivery” (EX1022, 2:9-11), multiple groups developed oral cladribine compositions and regimens for treating MS, including for RRMS and progressive forms of MS.

EX1002, ¶53. Stelmasiak's oral cladribine composition and regimens for treating RRMS are discussed above. EX1013, 5. Schultz disclosed "oral solid pharmaceutical dosage forms containing a mixture of cladribine (2-chloro-2'-deoxyadenosine; 2-CdA) and cyclodextrin." EX1024, Abstract; EX1002, ¶54. According to Schultz, for treatment of MS the dosage can range from "about 0.04 to about 1.0 mg/kg of body weight per day, preferably from about 0.05 to about 0.15 mg/kg/day." EX1024, 6:45-49, 6:53-56.

Bodor disclosed oral "compositions of cladribine and cyclodextrin" EX1022, Abstract; EX1002, ¶¶56, 78. Bodor further cited and incorporated by reference "the literature" regarding cladribine's use in treating MS, including the Romine reference regarding RRMS and the Rice reference regarding progressive MS, discussed above, and disclosed that "for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment." EX1022, 22:27-2320. Bodor further taught that the amount of cladribine "may be lowered or increased by fine tuning and/or by administering cladribine according to the invention with another active ingredient." *Id.*, 24:2-4; EX1002, ¶¶78-79, 93.

Thus, multiple publications described oral cladribine compositions and suggested doses for treating MS, recognizing that POSAs could fine-tune the total dose of cladribine.

F. Petitioner’s ground relies specifically on the following publications

While this IPR relies on Bodor and Stelmasiak, the background art discussed above and in Dr. Miller’s declaration reflect the general knowledge of a POSA before December 22, 2004, which must be taken into account when evaluating obviousness. *See Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1336 (Fed. Cir. 2006); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013).

1. Bodor (EX1022)

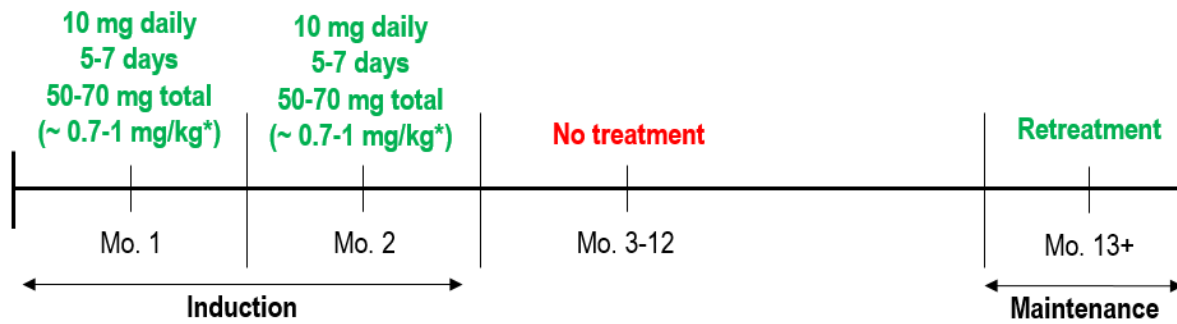
Bodor is a PCT application filed on March 26, 2004, which designated the United States and published on October 14, 2004, in the English language. Bodor, therefore, is prior art under 35 U.S.C. 102(a) and (e).

Bodor is directed to oral formulations of cladribine. EX1022, Abstract. Bodor explains that cladribine has been used to treat autoimmune conditions, including “multiple sclerosis.” EX1022, 1:18-2:5; EX1002, ¶78. Bodor teaches that “[o]ral delivery of drugs is often preferred to parenteral delivery” for several reasons, including “patient compliance, or for cost or therapeutic considerations.” EX1022, 2:9-11; EX1002, ¶79. To this end, Bodor teaches improved solid oral

dosage forms of cladribine. EX1022, 2:22-27 (internal citations omitted); EX1002, ¶79.

Bodor teaches oral dosage forms containing “a complex cladribine-cyclodextrin complex” containing amorphous cyclodextrine and cladribine. EX1022, 6:3-4, 26:25-33:9; EX1002, ¶79. According to Bodor, cladribine formulated into the described solid oral dosage forms is in “a high thermodynamic state,” which results in “improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.” EX1022, 11:27-12:3, 33:10-36:8; EX1048, 122; EX1002, ¶79.

Bodor further teaches that the described compositions “optimize the bioavailability of cladribine following oral administration,” and that it can be used to treat MS. EX1022, 23:9-20, EX1002, ¶¶78, 97. Bodor teaches the following cyclical regimen for treating MS: “10 mg of cladribine ... administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 23:9-20, EX1002, ¶79. Dr. Miller prepared the following schematic to illustrate how a POSA would have understood Bodor’s regimen (EX1002, ¶84):



* Based on an average body weight of 70 kg

Bodor teaches that the amount of cladribine “may be lowered or increased by fine-tuning and/or by administering cladribine according to the invention with another active ingredient.” EX1022, 24:1-4; EX1002, ¶117. Bodor also describes clinical studies that measure cladribine’s “relative bioavailability” (Example 4, 3 mg tablets) and “dose response and absolute bioavailability” (Example 5, 3 mg and 10 mg tablets) in MS patients. EX1022, Examples; EX1002, ¶79.

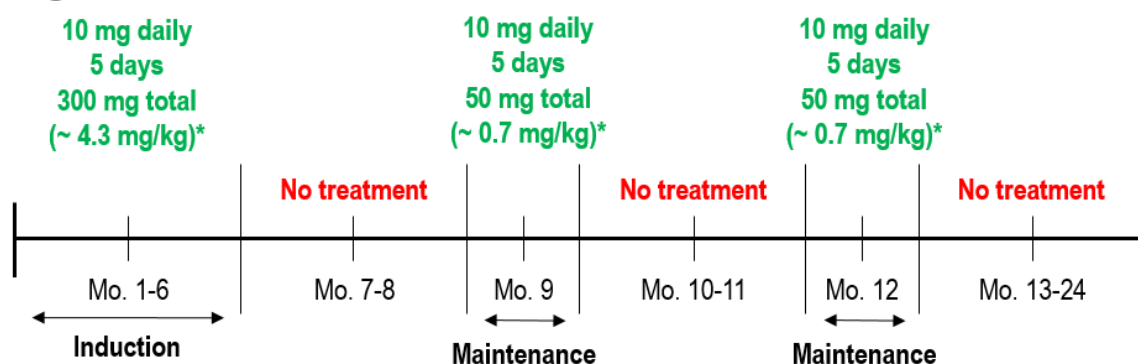
2. Stelmasiak (EX1013)

Stelmasiak, published in 1998 and prior art under 35 U.S.C. 102(b) (EX1040, ¶¶11-15), describes a trial of cladribine in RRMS. Stelmasiak explains that because MS is “an autoimmune disease” characterized by “abnormalities in immune regulation,” “the most common” therapeutic approach to MS is based “on the use of drugs producing general immunosuppression.” EX1013, 4. However, according to Stelmasiak, “available immunosuppressants (such as cyclophosphamide, methotrexate, or cyclosporin A) evidenced at most a modest

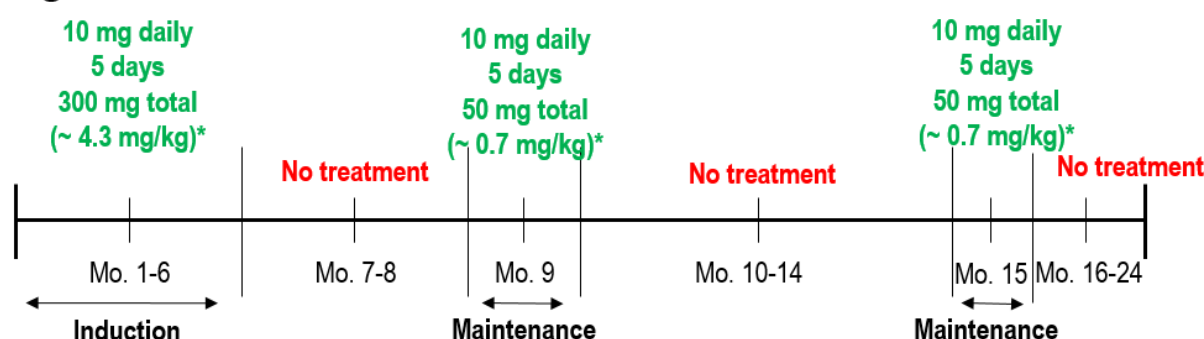
and transient benefit to MS patients.” *Id.* Stelmasiak, therefore, proposes and demonstrates oral cladribine for treating MS. EX1013, 4-5; EX1002, ¶80.

Stelmasiak suggests that because normal lymphocytes are subject to the cytotoxic effect of cladribine, “immunosuppressive activity of the drug may be useful in the treatment of diseases of autoimmune etiology.” EX1013, 4-5; EX1002, ¶80. Accordingly, Stelmasiak “tested clinical efficacy of cladribine” in RRMS patients “in a two-year open-label pilot clinical trial.” EX1013, 5; EX1002, ¶80. Stelmasiak treated patients with “six courses of [cladribine] given once a month [i.e., one course of cladribine (10 mg orally, once daily) per month for six months], followed by two additional courses at three month intervals” (“9 and 12 or 15 months”). EX1013, Abstract, 5. Stelmasiak stated, “[c]ladribine was given either subcutaneously (dose 5 mg per day, six patients) or orally (dose 10 mg per day, four patients).” EX1013, 5; EX1002, ¶80. Stelmasiak’s study then observed patients “for two years after the initiation of the therapy.” EX1013, Abstract; EX1002, ¶94. Dr. Miller prepared the following graphic to illustrate how a POSA would understand Stelmasiak’s administration of oral cladribine (EX1002, ¶89):

Regimen 1



Regimen 2



* Based on an average body weight of 70 kg

The study showed that “lymphocyte counts dropped from the initial count of 2336 ± 595 per μl (mean $\pm$ S.D.) to 968 ± 229 per μl at 6 months, and remained at approximately 1000 per μl for the next 15 months.” *Id.*, 5; EX1002, ¶90. A reduction in lymphocyte count is an indication of effective immunosuppression—a desired result in the treatment of MS. EX1013, 5; EX1014, 1717; EX1018, 1146; EX1002, ¶90. Stelmasiak observed, “[a] tendency toward normalization of lymphocyte counts became evident only at the end of the 2-year observation period”—about 9 to 12 months after the last treatment. EX1013, 5-6; EX1002, ¶41. Stelmasiak summarized average lymphocyte count during and after the treatment

as shown in the following graph, which Dr. Miller annotated in red and green to show what a POSA would have understood from Stelmasiak's results:

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

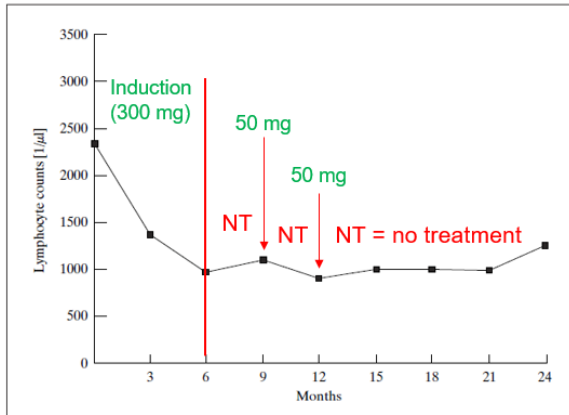
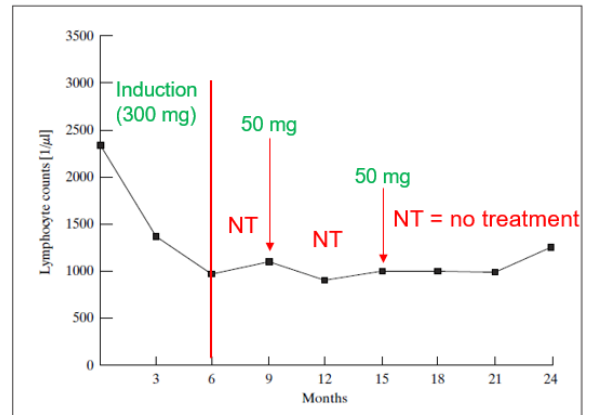


Figure 1. Average lymphocyte counts during and after treatment with cladribine.



EX1013, 5; EX1002, ¶108.

Stelmasiak observed that EDSS scores were “significantly reduced during the treatment compared to the initial values.” EX1013, 6. Stelmasiak states, “the decreases observed [in the EDSS scores] at the third to fifteenth month were significant.” EX1013, 6; EX1002, ¶90.

Stelmasiak also reported that “[c]ompliance of patients and tolerance of therapy was good,” and that “cladribine favourably compares with other immunosuppressants” vis-à-vis side-effects. EX1013, 5, 7; EX1002, ¶101. Furthermore, “[t]he therapy appeared to be effective in seven patients”: these patients reported “a very marked” reduction in the relapse rate during the 2 years after the initiation of the treatment. EX1013, 7; EX1002, ¶101. And, while three patients did not respond to the therapy, in seven “responders” the total number of

relapses during the two preceding years dropped from 29 to six—an “impressive” decrease. EX1013, 6-7.

Stelmasiak attributed cladribine’s beneficial activity to its pharmacokinetics and pharmacodynamics (e.g., ability to cross blood brain barrier, to inhibit T and B cell activation, and to restore natural killer (NK) cells’ impaired activity *in vivo*). EX1013, 6-7; EX1002, ¶101. Stelmasiak concluded, “[a]long with clinical evaluation in MS, the detailed pattern of cladribine-induced immunosuppression in clinical conditions deserves further study.” EX1013, 7.

V. PERSON OF ORDINARY SKILL IN ART

Because the ’903 patent relates to methods of human therapeutic treatments, the level of skill required in this field is high. EX1002, ¶¶20-21. A POSA here would have drawn upon the knowledge and experience of related disciplines of a multi-disciplinary team that might lie outside the POSA’s primary training. *Id.*, ¶20. For example, a physician might rely upon the knowledge and experience of a pharmacologist on a multi-disciplinary team to determine the appropriate dose for a particular patient.

A POSA for the ’903 patent would have the knowledge of multiple disciplines, such as immunology, biochemistry, and human physiology and anatomy, and also typically be a clinician with experience and/or training in neurology. *Id.*, ¶¶20-21. The POSA typically would be a medical doctor with a

specialty in neurology, specifically in treating autoimmune disorders of the nervous system, such as multiple sclerosis, and typically at least 2 years of experience with administering treatments to patients and evaluating results of such treatments, as well as experience or knowledge in related research and development. *Id.*, ¶20.

VI. CLAIM CONSTRUCTION

The following definitions are found in the '903 patent's specification:

A. “total dose of cladribine”

Claim 17 requires administration of a “total dose of cladribine.” The '903 patent defines “total dose” as “the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses.” EX1001, 4:19-22; EX1002, ¶68. Petitioner adopts this definition.

B. “an induction period”

Claim 17 recites a method comprising “an induction period.” The '903 explains induction as follows:

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

EX1001, 4:55-58. The '903 patent further specifies that “[a]n induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month,” (EX1001, 4:61-64) and “lasts up to about 4 months or up to about 3 months or up to about 2 months” (*id.*, 4:58-60). “An induction period,” therefore, means a treatment period of a defined length that is followed by a treatment-free period. EX1002, ¶69. Further, as discussed immediately below, the term “induction period” should be construed as a period during which a total dose of cladribine is higher than the total dose of cladribine administered in maintenance period. EX1002, ¶69.

C. “a maintenance period”

Claim 17 recites a method comprising “a maintenance period.” The '903 explains maintenance as follows:

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

EX1001, 5:6-11; *see also* EX1001, 3:60-63, 4:8-11, 8:31-34, 9:40-43, 9:66-10:4, 10:19-22, 10:45-49, 12:17-21, 12:36-41, 12:56-59, 15:62-67, 16:1-6. Thus, the specification supports a construction of the term “maintenance period” as a period

during which a total dose of cladribine is lower than the total dose of cladribine administered in an induction period. EX1002, ¶70.

Merck's arguments during prosecution of the '903 and '947 patents⁷, are consistent with the proposed construction. During prosecution of the '903 patent, Merck accepted⁸ the Examiner's statement that "neither [Bodor nor Grieb] teach that the total dose of cladribine reached at the end of the maintenance phase is *lower* than the total dose reached at the end of the induction phase." *Id.*, 248; *see*

⁷ Merck's arguments during prosecution of the '947 patent should be considered for construction of the claims of the '903 patent. *Microsoft Corp. v. Multi-Tech Systems, Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004) ("Any statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction [of the patent at issue].").

⁸ Merck is bound by accepting the Examiner's statement, which reflects Merck's own understanding of the claimed invention. *See Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1097 n.6, 1099-100 (Fed. Cir. 2013) (while "it is the applicant, not the examiner, who must give up or disclaim subject matter" for estoppel to apply, this "case deal[t] not only with [an] applicant[] letting stand an examiner's narrow characterization ... but also their adoption of that characterization to overcome the examiner's enablement rejection.").

Section III.C. Merck argued that none of the cited art taught “*lowering* treatment dosages with each successive use of the drug.” EX1025, 251.

Similarly, while prosecuting 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 (even for the pending claims that did not expressly require a lower dose, e.g., claim 17 and 20):

Specifically, one skilled in the art **would not have had any reason to reduce the dosage of cladribine administered during the “maintenance period” as recited in the claims** such that the total dosage of cladribine administered to the patient is less than the total dose of cladribine the patient received during the induction period. Rather, the teachings of the reference would suggest that the same dosing regimen be applied to the patient (10 mg of cladribine administered for 5-7 days each month for two consecutive months followed by another 10 month period of time in which the patient receives no treatment). This would have resulted in the same total dose of cladribine being administered to the patient in both the induction phase and the maintenance phase. Thus, the combined teachings of the references would not have led one skilled in the art to a dosing regimen and/or total dosages recited in claims 1, 4, 5, 9, 10, 17, 20 or 21.

EX1004, 151.

Similarly, while prosecuting the '947 patent, Merck distinguished the prior art cited by the Examiner by emphasizing that none of the cited art taught “*lowering* treatment dosages with each successive use of the drug.” EX1025, 125.

The term “maintenance period,” therefore, should be construed as a retreatment period of a defined length during which the total dose of cladribine is *lower* than the total dose in the induction period, and that is followed by a treatment-free period. EX1002, ¶70.

Any terms not defined here should be given their plain and ordinary meaning.

VII. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 42.104(B))

Hopewell requests IPR based on the ground summarized below.

Ground	35 U.S.C. Section (pre-AIA)	Claims	References
1	§ 103(a)	17, 19, 20, 22-27	Bodor and Stelmasiak

VIII. GROUND 1: THE CLAIMS WOULD HAVE BEEN OBVIOUS OVER BODOR AND STELMASIAK

A. Claim 17

1. A POSA would have had a reason to combine Bodor and Stelmasiak

As discussed above, RRMS is a form of MS; that is, RRMS is also a type of autoimmune disease where certain cells, like T lymphocytes, attack the neurons in

the CNS. EX1002, ¶¶23, 28-29. Moreover, RRMS exhibits characteristics that may also be seen in the other forms of MS, such as clinical relapses or active lesions detected on MRI. § X. EX1002, ¶¶23-24. Thus, a POSA would have expected that an efficacious therapy that targets lymphocytes and further treats shared characteristics of the various forms of MS – such as inflammation caused by such lymphocytes, lesions detected on MRI, and clinical relapses – would also be efficacious in treating RRMS. EX1002, ¶¶24, 78-79, 100.

A POSA would have been motivated to use Bodor’s oral cladribine dosage forms to treat RRMS because of their “improved cladribine absorption,” compared to the previously known oral cladribine dosage forms. EX1022, 12, Example 4; EX1002, ¶79. In following Bodor’s express teachings, a POSA would have orally administered cladribine for two months (an induction period), followed by a ten-month cladribine-free period.⁹ EX1022, 23; EX1002, ¶81.

⁹ Were Merck to attempt to diminish Bodor’s relevance simply because Bodor did not test its regimen, the Board should soundly reject such an attempt. “[T]here is no requirement that a teaching in the prior art be scientifically tested or even guarantee success before providing a reason to combine.” *Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 F. App’x 289, 294 (Fed. Cir. 2011) (internal

Further, because a POSA would have understood that RRMS patients, typically need ongoing care, a POSA would have retreated an RRMS patient after the initial induction/cladribine-free cycle, using a lower (maintenance) cladribine dose, as Stelmasiak reported for RRMS patients. EX1013, 6; EX1002, ¶¶87, 99. And as explained further below, a POSA also would have used the Bodor's total doses of cladribine, thus arriving at the claimed methods. EX1022, 23; EX1002, ¶¶107-110.

a) A POSA would have retreated a RRMS patient with cladribine following Bodor's 2-month induction/10-month cladribine-free treatment cycle

Preference for oral drug delivery over parenteral and increased bioavailability and lowered interpatient variation with Bodor's cladribine oral dosage form would have given a POSA a reason to use Bodor's form to treat MS. EX1022, 2, 11-12, 23; EX1002, ¶79.

Dr. Miller further explains that after Bodor's "two months on/two months off" cycle (EX1022, 23), POSAs would have expected some or all patients to exhibit a breakthrough disease (a relapse) that would require further treatment. EX1013, 7; EX1002, ¶100. This is particularly the case for RRMS patients.

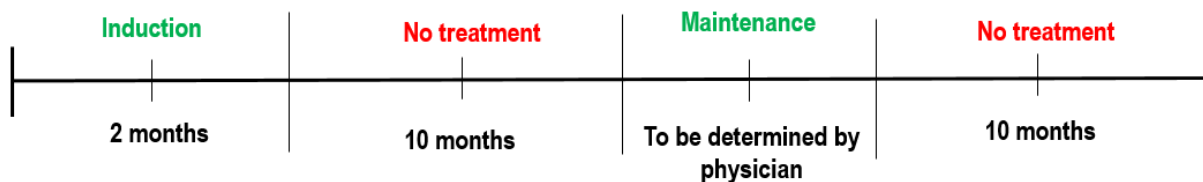
citations omitted).

EX1002, ¶100. Such patients would be showing worsening signs and/or symptoms of MS, characterized by, *e.g.*, new brain lesion formation, increased lymphocyte count, appearance of new symptoms or worsening of old symptoms, disability progression (as described by a patient or determined by a physical examination), etc. EX1013, 6; EX1002, ¶100. Cladribine's effects in RRMS patients are best described as "disease-modifying": cladribine does not cure MS (no drug does), but can reduce the number of relapses by causing "prolonged, profound suppression of lymphocyte counts." EX1016, 420; EX1013, 6; EX1002, ¶100. Thus, a POSA treating RRMS would have expected eventual relapse in a cladribine-treated patient. EX1002, ¶100. Indeed, Stelmasiak reports such relapses. EX1013, 6; EX1002, ¶100.

Because a POSA would have expected relapse, and to decrease the relapse rate, a POSA would have retreated the patient with cladribine, as Stelmasiak taught. EX1013, 5-7; EX1002, ¶¶100-101. Stelmasiak reported "a very marked (almost five-fold on average)" reduction in the relapse rate and "more pronounced improvement in [patients'] neurological status as measured by EDSS scores" after the retreatment with cladribine (i.e., the maintenance period, as POSA would have understood it). EX1013, 5-7; EX1002, ¶101. Thus, a POSA would have had a reason to continue treating the patients with cladribine after the induction/cladribine-free cycle of Bodor. EX1002, ¶101. In doing so, a POSA

would have done nothing more than followed the general immunosuppression framework common with MS therapies: an induction period, followed by a drug-free period, and followed by a further retreatment (maintenance) period. EX1002, ¶113; EX1026, 11:5-7; EX1022, 23; EX1013, Abstract; EX1018, Abstract;.

Dr. Miller also explains that a POSA would have followed the maintenance period with another cladribine-free period, just as Stelmasiak reported, because, as Stelmasiak taught, “hematological toxicity of the drug (bone marrow depression) raised some concern,” and a POSA would have been motivated to control the toxicity by giving the patient drug-free periods. EX1013, 5; EX1002, ¶103. Accordingly, a POSA would have arrived at the following general treatment framework:



EX1002, ¶105

Thus, a POSA would have orally administered Bodor’s cladribine dosage form for two months, followed by a ten-month cladribine-free period. EX1002, ¶105. A POSA would have further retreated any patient exhibiting worsening signs or symptoms of MS, as Stelmasiak did, followed by another cladribine-free period to control cladribine’s toxicity. EX1013, Abstract, 5; EX1002, ¶¶105-106.

b) A POSA would have lowered¹⁰ the total dose of cladribine in the maintenance period compared to the total dose in the induction period

Stelmasiak's clinical data supports lowering cladribine's total dose in the maintenance period compared to the dose in the induction period, when retreating the patients following the 2-month induction/10-month cladribine-free treatment cycle. EX1002, ¶89. According to Stelmasiak, the induction treatment with oral cladribine was characterized by a drop in lymphocyte count from "2336±595 per µl (mean±S.D.) to 968±229 per µl." EX1013, 5; EX1002, ¶89. This is also illustrated in the following figure (EX1013, FIG. 1 (annotated)), which Dr. Miller annotated (EX1002, ¶108) in red and green to illustrate how POSAs would have understood it:

¹⁰ According to Dr. Miller, POSAs may also have considered administering cladribine in the maintenance period at the same total dose as in the induction period. EX1002, ¶ 57; see *ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) (explaining that where an "ordinary artisan would ... be left with two design choices ... [e]ach of these two design choices is an obvious combination.").

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

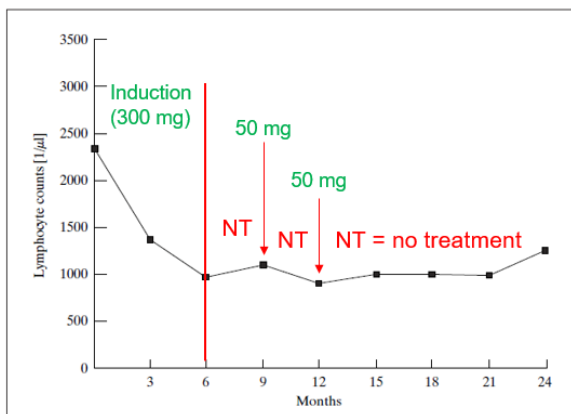
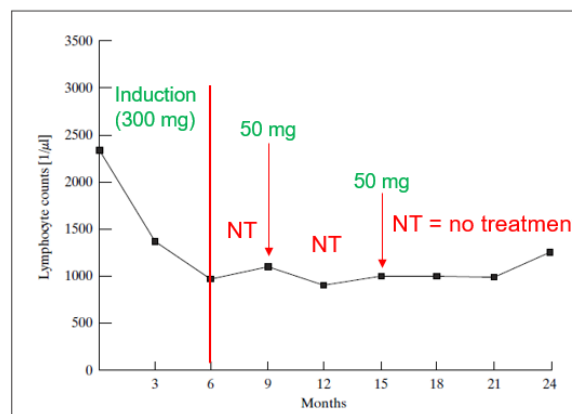


Figure 1. Average lymphocyte counts during and after treatment with cladribine.



EX1013, Figure 1 (annotated); EX1002, ¶ 108.

These data would have indicated to a POSA that to maintain an immunosuppressive effect after the induction, a lower dose of cladribine would suffice. EX1002, ¶109. This is because the higher dose in the induction period would have decreased the patient's lymphocyte count, and a lower dose of cladribine would have been expected to be enough for maintaining the lowered count. EX1013, Figure 1; EX1002, ¶109. Further, the lower cladribine dose would have been desirable to keep the toxicity effects of cladribine as low as possible. EX1013, 7; EX1002, ¶102. Indeed, lowering the total dose of cladribine in the maintenance period compared to the induction period is precisely what Stelmasiak did (compare 50 mg/kg in Stelmasiak's maintenance period versus 300 mg/kg at the end of the induction period). EX1013, Abstract; EX1002, ¶89.

Thus, in retreating a patient following the 2-month induction/10-month cladribine-free treatment cycle, a POSA would have had a reason to lower the total

dose of cladribine administered during the maintenance period, compared to the total dose administered during the induction period. EX1002, ¶¶108-109.

c) The claimed total dose of cladribine reached at the end of the induction period would have been *prima facie* obvious

The total dose of cladribine reached at the end of the induction period of “about 1.7 mg/kg to about 3.5 mg/kg” overlaps with Bodor’s range in the induction period of about 1.4 mg/kg to about 2 mg/kg, and is therefore *prima facie* obvious over Bodor’s range. EX1002, ¶¶83. 107. It is settled law that “even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003). And, “where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results or criticality, or other pertinent objective indicia indicating that the overlapping range would not have been obvious in light of that prior art.” *E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)). During prosecution, Merck pointed to no evidence that the dose range was not obvious in light of the prior art. EX1002, ¶107. Therefore, the claimed method where the total dose of cladribine (from “about 1.7 mg/kg to about 3.5 mg/kg”) administered to an MS patient during the induction period of the 2-month

induction/10-month cladribine-free treatment cycle would have been *prima facie* obvious. See, e.g., *NOF Corp. v. Nektar Therapeutics*, IPR2019-01394, Paper 68, at 36-37 (P.T.A.B. July 30, 2021).

d) The claimed length of the maintenance period and total cladribine dose in the maintenance period are merely routinely optimized workable ranges

The claimed methods requiring a length of the maintenance period (“about 2 months to about 4 months”) and total dose of cladribine reached at the end of the maintenance period (“about 1.7 mg/kg”) would have been *prima facie* obvious over the prior art’s ranges. EX1022, 23; EX1002, ¶110. When a variable is “result-effective” and “the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)); see also, e.g., *In re Geisler*, 116 F.3d 1465, 1469–70 (Fed. Cir. 1997); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Bodor discloses the general conditions of the claim: a two-month-long treatment period followed by a 10-month-long cladribine-free period, and further suggests a retreatment. EX1022, 2, 11-12, 23; EX1013, Abstract; EX1002, ¶¶84-87. Any modifications to such readily optimized parameters as a total dose of cladribine or length of administration, which are disclosed in the prior art, such as Bodor and Stelmasiak, are not inventive. EX1002, ¶110.

Dr. Miller confirms that a POSA would have deemed cladribine's total dose and length of administration to be result-effective. EX1002, ¶¶91-92. Bodor teaches, "one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be *lowered or increased* by fine tuning." EX1022, 24:1-3; EX1002, ¶93. By "therapeutically effective amount," Bodor means "treatments at dosages effective to achieve the therapeutic result sought," which a POSA would have recognized as effecting a particular result. EX1022, 22:17-19; EX1002, ¶117. Similarly, Beutler teaches "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; EX1002, ¶117. And Rice uses two different cladribine doses, 0.7 mg/kg and 2.1 mg/kg, with the higher dose having a higher suppression of lymphocyte counts. EX1018, Figure 4; EX1002, ¶91; *see also* EX1047, 297. The prior art, therefore, teaches that cladribine's dose and length of administration are result-effective variables because they achieve a recognizable result—"the therapeutic effect," which can be measured by, e.g., the change in a patient's lymphocyte count. *E.I. DuPont de Nemours*, 904 F.3d at 1009 ("A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective.").

It would have been well within the purview of POSAs to "fine tune" cladribine total dose and length of administration during the maintenance period.

EX1002, ¶93. Bodor even teaches a general strategy for doing so:

“[t]herapeutically effective amounts may be easily determined [] empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.” EX1022, 24:6-9, EX1002, ¶93. And a POSA would have easily done so by adjusting the daily dose administered. EX1002, ¶117. Furthermore, because Bodor teaches an initial treatment period that lasts two months (EX1022, 23), it would have been logical and well within the POSA’s skill to take Bodor’s two-month treatment period as a starting point for optimization. EX1002, ¶102. A POSA would have arrived at a suitable dose and length of administration, for example, by regularly measuring the patient’s lymphocyte counts and evaluating the efficacy of a given dose based on the changed in the count. *Id.*, ¶102. This was a standard practice in the field, as demonstrated by at least Stelmasiak, Rice, and Beutler. EX1013, 5; EX1014, 1717; EX1018, 1146; EX1002, ¶¶31-32. Thus, the claimed cladribine’s length of administration and total dose achieved in the maintenance period are not inventive. *See E.I. DuPont de Nemours*, 904 F.3d at 1009.

Petitioner is not aware of any evidence of criticality associated with the claimed “about 2 months to about 4 months” length of the maintenance period and “about 1.7 mg/kg” dose. And it is Merck’s burden to rebut the presumption of obviousness that Petitioner established here. *In re Aller*, 220 F.2d at 456 (“the

applicant has the burden of proving ... criticality” of the claimed parameter in order to rebut the presumption of obviousness); *E.I. DuPont de Nemours*, 904 F.3d 996 (applying the same burden-shifting framework in an *inter partes* review context).

In sum, a POSA would have combined Bodor and Stelmasiak by administering Bodor’s “improved” oral dosage form to RRMS patients following the steps of an induction period, cladribine-free period, a maintenance period, and a cladribine-free period, at the dosages and durations taught by the art, thus arriving at the claimed methods. EX1002, ¶¶96-110.

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

Given Bodor’s and Stelmasiak’s teachings of all claimed elements, coupled with the high level of skill in the art, a POSA would have had a reasonable expectation of success that the claimed regimen would be effective in treating RRMS. EX1002, ¶¶111-119. “Obviousness does not require absolute predictability of success,” only “a reasonable expectation of success.” *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d at 1165.

Indeed, Bodor provided a detailed description of cladribine oral dosage forms for use in the treatment method: excipients, cladribine dosages, method of manufacturing, and *in vitro* testing. EX1022, Examples 1-3; EX1002, ¶¶111-112. A POSA would have readily followed the instructions in Bodor to orally

administer the dosage forms following the disclosed regimen, because of the high level of skill and experience in treating MS patients. EX1002, ¶111.

Similarly, a POSA would have incorporated maintenance and cladribine-free periods into the regimen because it was standard practice in the field to retreat MS patients over the course of the disease. EX1013, Abstract; EX1002, ¶¶113-114. And it would have been well within the POSA's purview to optimize cladribine's total dose and length of administration in the maintenance period because patient-specific dose optimization is a common practice. EX1022, 23; EX1002, ¶114.

A POSA would have also had a reasonable expectation of success that the claimed cladribine regimen would be effective. EX1002, ¶¶115-116. As described, well before 2004, cladribine was known to cause "prolonged, profound suppression of lymphocyte counts." EX1016, 420; EX1013, 4; EX1022, 1-2; EX1002, ¶¶52, 114. Further, before 2004, at least Stelmasiak and Romine published clinical studies reporting cladribine's efficacy in RRMS patients. EX1013, 7; EX1023, Abstract; EX1031, Abstract; EX1002, ¶¶35-50. Stelmasiak reported that cladribine "impressively" decreases the relapse rate in RRMS patients. EX1013, 7; EX1002, ¶115. Similarly, according to Romine, cladribine had a "statistically significant favorable effect" on "frequency and severity of relapses," as well on MRI findings. EX1031, Abstract; EX1002, ¶115. Notably, Bodor itself took, e.g., Romine's report into account when determining its

disclosed cyclical dosing regimen. EX1022, 23:7-20. Thus, because cyclical treatment with oral cladribine has been previously shown to have clinical efficacy in RRMS (EX1013, 7; EX1031, Abstract), as explicitly recognized by Bodor (EX1022, 22), a POSA would have reasonably expected to treat MS by orally administering Bodor's oral cladribine following the claimed steps of an induction, cladribine-free, maintenance, and cladribine-free periods. EX1002, ¶¶35-50.

3. Each limitation of claim 17 is disclosed in the art

Claim 17	Bodor (EX1022) and Stelmasiak (EX1013)
17. A method of treating relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis comprising the oral administration of a formulation comprising cladribine	“At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 23:15-20. “Lymphocytotoxic nucleoside analog cladribine (2-chlorodeoxyadenosine) has recently been reported to favourably alter the clinical course of chronic progressive multiple sclerosis (MS). In the present study 10 patients with the remitting-relapsing form of MS were treated with six courses of this drug (5 mg subcutaneously or 10 mg orally, once daily, repeated on five consecutive days) given once a month, followed by two additional courses at three month intervals.” EX1013, Abstract. “In patients with remitting-relapsing multiple sclerosis treatment with cladribine decreases lymphocyte counts in peripheral blood, to 1/3 of the

Claim 17	Bodor (EX1022) and Stelmasiak (EX1013)
	initial values on average. The relapse rate in some (but not all) patients is impressively decreased.” EX1013, 7.
to an individual having relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis following the sequential steps below:	“Participation in the experimental trial of cladribine was offered to a limited group of multiple sclerosis patients with a definitive remitting-relapsing course of the disease[.]” EX1013, 5.
(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and	“At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 23:15-20. “Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months. Each course consisted of five doses of the drug taken once daily on consecutive days.” EX1013, 5.
wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;	“At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month , followed by ten months of no treatment.” EX1022, 23:15-20.
(ii) a cladribine-free period lasting from about 8 months to about	“At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex

Claim 17	Bodor (EX1022) and Stelmasiak (EX1013)
10 months, wherein no cladribine is administered;	in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. EX1022, 23:15-20.
(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and	“At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 23:15-20. “Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months. Each course consisted of five doses of the drug taken once daily on consecutive days.” EX1013, 5.
wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg; and	“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.” EX1022, 24:1-9.
(iv) a cladribine-free period wherein no cladribine is administered.	“In the present study 10 patients with the remitting-relapsing form of MS were treated with six courses of this drug (5 mg subcutaneously or 10 mg orally, once daily, repeated on five consecutive days) given once a month, followed by two additional courses at three month intervals. The patients were observed for two years after the initiation of the therapy. ” EX1013, Abstract.

a) Bodor and Stelmasiak teach treating RRMS by orally administering cladribine

Bodor and Stelmasiak both teach “[a] method of treating relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis comprising the oral administration of a formulation comprising cladribine to an individual having relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.” EX1001, 14-16; EX1002, ¶¶78-80. Bodor teaches “compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine.” EX1022, Abstract. According to Bodor, cladribine is a known “immunosuppressive agent” used “for the treatment of a variety of autoimmune conditions,” such as MS. *Id.*, 1:18-2:5. EX1002, ¶78. Bodor also incorporates by reference Romine’s cladribine’s trial in RRMS, thus expressly teaching treatment of RRMS with Bodor’ oral dosage form. EX1022, 22; EX1002, ¶78; *Cook Biotech v. Acell*, 460 F.3d 1365, 1376 (Fed. Cir. 2006) (quoting *Advanced Display Systems v. Kent State University*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)).

Stelmasiak similarly teaches treating RRMS with oral cladribine. Specifically, Stelmasiak describes a study where ten patients having RRMS were treated with oral cladribine and observed for two years after the initiation of the therapy. EX1013, Abstract. EX1013, Abstract; EX1002, ¶80. Stelmasiak reports that in these RRMS patients, “lymphocyte counts in peripheral blood” decreased

“to 1/3 of the initial values on average” and for some patients in the study the relapse rate “impressively decreased.” EX1013, 7; EX1002, ¶80.

b) Bodor and Stelmasiak’s regimens include “an induction period”

Both Bodor and Stelmasiak teach regimens that include “an induction period.” EX1002, ¶¶81-82. According to Bodor, cladribine should be administered to MS patients “once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.” EX1022, 23:15-20; EX1002, ¶81. A POSA would have understood the first two months of Bodor’s treatment regimen to be “an induction period,” as construed above. EX1002, ¶81.

Stelmasiak treated patients “with six courses of [cladribine] given once a month, followed by two additional courses at three month intervals” (“9 and 12 or 15 months”). EX1013, Abstract, 5. The study then observed patients “for two years after the initiation of the therapy.” *Id.* Therefore, a POSA would have understood Stelmasiak’s 6 months of treatment to constitute “an induction period.” EX1002, ¶82.

c) Bodor teaches the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg to about 3.5 mg/kg

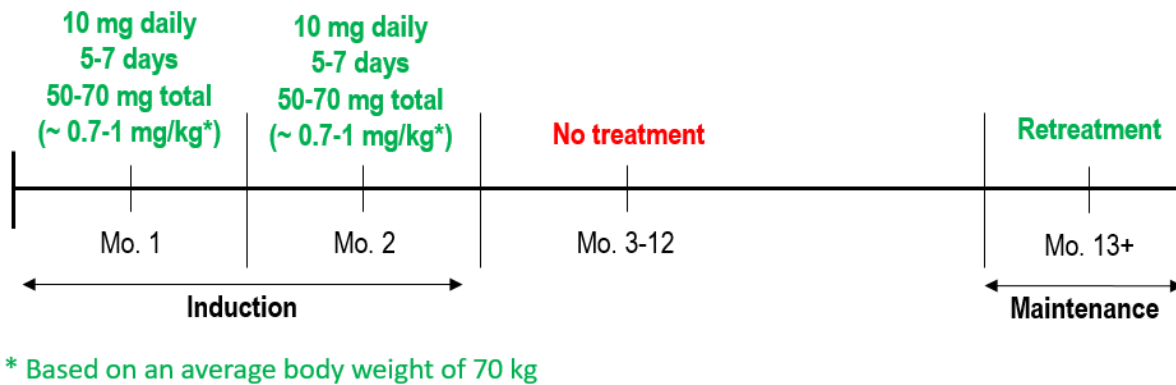
Bodor expressly teaches the claimed cladribine dose reached at the end of the induction period. Bodor’s induction period includes “10 mg of cladribine”

administered “once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month.” EX1022, 23:15-20. This equals a total amount of 100 mg to 140 mg of cladribine by the end of the induction period. EX1002, ¶83. With the average weight of a patient being about 70 kg, the total dose of cladribine reached at the end of the induction period in Bodor is about 1.4 mg/kg to about 2 mg/kg,¹¹ which overlaps with the claimed “about 1.7 mg/kg to about 3.5 mg/kg” range. EX1002, ¶83.

d) Bodor teaches “a cladribine-free period lasting from about 8 months to about 10 months”

Bodor expressly teaches the claimed cladribine-free period: administer cladribine to MS patients “once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment”:

¹¹ Dr. Miller explains that a POSA would have calculated the total mg/kg dose by dividing 100 mg or 140 mg by 70 kg. EX1002, ¶ 83.



EX1002, ¶84.

A POSA would have understood that no cladribine is administered during Bodor’s “no treatment” period of ten months. EX1002, ¶105.

e) Bodor and Stelmasiak teach a retreatment period after the cladribine-free period

Dr. Miller confirms that a POSA would have understood that Bodor teaches a retreatment period after the cladribine-free period. EX1002, ¶¶84-86. As described, Bodor teaches administering cladribine “once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by *ten months of no treatment.*” EX1022, 23:15-24. Bodor also teaches that, “[a]lternatively the patient would be treated with 10 mg of cladribine ... once per day for a period of five to seven days per month for a total of six months, followed by *eighteen months of no treatment.*” *Id.* A POSA would have understood that the only thing that distinguishes the “ten months” and the “eighteen months” treatment-free periods is the time when a

treatment is re-imitated again: after ten months or, alternatively, after eighteen months. EX1002, ¶86.

In any event, Bodor would have suggested to POSAs that patients would have needed retreatment after the no-treatment period. EX1002, ¶87. This is because MS is a progressive and incurable disease, and POSAs reading Bodor in light of general knowledge in the art would have understood that many, if not all, MS patients would need subsequent retreatment. EX1013, 6; EX1009, 263; EX1002, ¶87. Thus, POSAs would have understood that Bodor’s “induction period/cladribine-free period” regimen suggests retreatment after the cladribine-free period. EX1002, ¶86.

To the extent that Merck argued during prosecution of the ’903 patent that “nowhere in the teachings of [Bodor] is there any discussion about repeating a treatment course at any point in time,” and therefore the Examiner’s “obviousness rejection fails,” Merck misapprehended the legal requirement for obviousness. EX1004, 121. “A person of ordinary skill is also a person of ordinary creativity, not an automaton.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Bodor is not the only source POSAs would have considered for what “additional information might be relevant” because POSAs would have been aware of general knowledge in the art establishing that MS patients typically require retreatment, and thus Merck’s argument, if repeated, must be rejected. EX1002, ¶¶17,57-

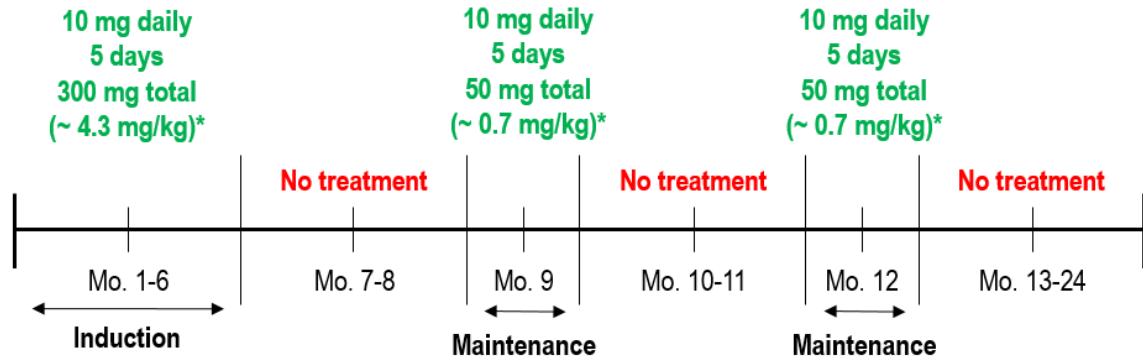
63,100-102; *Becton, Dickinson & Co. v. Baxter Corp. Englewood*, 998 F.3d 1337, 1344 (Fed. Cir. 2021).

Moreover, as explained, Stelmasiak teaches a cyclical regimen that includes monthly administration of cladribine for six months (an induction period), followed by three months of no treatment (cladribine-free treatment), and further followed by two retreatment periods (at 9 months and 12 or 15 months). EX1013, Abstract, 5; EX1002, ¶88. Therefore, a POSA would have understood Stelmasiak's regimen to include retreatment with cladribine, which a POSA would have combined with Bodor for the reasons discussed above. EX1002, ¶88.

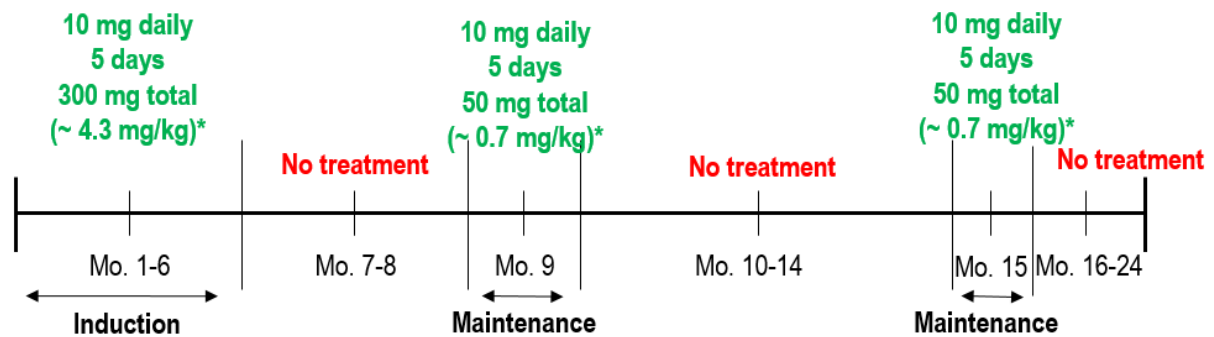
f) Stelmasiak teaches “a maintenance period”

Stelmasiak teaches “a maintenance period,” as construed: a period during which a total dose of cladribine is lower than the total dose of cladribine administered in an induction period:

Regimen 1



Regimen 2



* Based on an average body weight of 70 kg

EX1013, Abstract; EX1002, ¶¶88-89. Thus, because Stelmasiak teaches administering a lower total dose of cladribine (50 mg) after the initial induction dose (300 mg), Stelmasiak teaches the “maintenance period” limitation of claim 36. EX1002, ¶88.

g) Optimizing cladribine’s total dose and length of administration during the maintenance period would have been routine

As explained in Section VIII.A.1.b, a POSA would have found it routine to optimize the length of administration and total dose of cladribine in the maintenance period, arriving at the claimed method. EX1002, ¶¶89-93.

h) Stelmasiak teaches a cladribine-free period after the maintenance period

Stelmasiak teaches a cladribine-free period following a maintenance period. EX1002, ¶¶94-95. As described, Stelmasiak teaches a regimen that included monthly administration of cladribine for six months (an induction period), followed by two additional courses at three month intervals (maintenance periods). EX1013, Abstract, 5. After the maintenance periods, patients were “observed” for 9 to 12 months. *Id.*, Abstract. Dr. Miller confirms that POSAs would have understood the observation period in Stelmasiak to be cladribine-free. EX1002, ¶¶94-95.

In sum, as explained in Sections VIII.A.1 and VIII.A.2, because of the cyclical and incurable nature of RRMS, a POSA would have been motivated to administer Bodor’s oral cladribine dosage form to an RRMS patient for two months, followed by a ten-month cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1002, ¶¶96-110, 119. And a POSA would have had a reasonable expectation of success at arriving at the claimed methods, given the teachings of Bodor and Stelmasiak, coupled with the high level of skill in the art. EX1002, ¶¶111-119. There are no objective indicia that weigh against the strong obviousness showing here. *See* Section IX.

B. Claim 19

Claim 19 depends from Claim 17, and requires that “the induction period lasts about 2 months.” EX1001, 18:29-30; EX1002, ¶120. As discussed in Section VIII.A.3.b, Bodor discloses an induction period of two months. EX1022, 23. And because of the cyclical and incurable nature of RRMS, a POSA would have been motivated to administer Bodor’s oral cladribine dosage form to a RRMS patient for two months, followed by a ten-month cladribine-free period, and then to retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23; EX1013, Abstract; EX1002, ¶121. A POSA would have had a reasonable expectation of success that the claimed regimen would be effective in treating RRMS, given Bodor’s successful regimen comprising an induction period of two months and the high level of skill in the art. EX1022, 23; EX1002, ¶¶121.

Thus, in addition to the reasons discussed for Claim 17, Claim 19 would have been *prima facie* obvious. EX1002, ¶122.

C. Claim 20

Claim 20 depends from Claim 17, and requires that “the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.” EX1001, 18:31-33; EX1002, ¶123. As discussed in Section VIII.A.3.c, Bodor teaches that the total dose of cladribine reached at the end of the induction period is about 1.4

mg/kg to about 2 mg/kg, which encompasses the claimed “about 1.7 mg/kg” dose.

EX1022, 23; EX1002, ¶124. As also discussed, a POSA would have arrived at a method comprising administer Bodor’s oral cladribine dosage form to an RRMS patient for two months, followed by a ten-month cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, with a reasonable expectation of success. EX1022, 23; EX1013, Abstract; EX1002, ¶124. Merck pointed to no evidence that the claimed total dose of cladribine reached at the end of the induction period is critical in light of the prior art. EX1002, ¶124. Therefore, the claimed method comprising administering a total dose of cladribine reached at the end of the induction period of “about 1.7 mg/kg” would have been obvious. EX1002, ¶124.

Thus, in addition to the reasons discussed for Claim 17, Claim 20 would have been *prima facie* obvious. EX1002, ¶125.

D. Claim 22

Claim 22 depends from Claim 17, and requires that “the cladribine-free period (ii) lasts about 10 months.” EX1001, 18:37-38; EX1002, ¶126. As discussed in Section VIII.A.3.d, Bodor discloses a cladribine-free period of 10 months. EX1022, 23; EX1002, ¶127. And because of the cyclical and incurable nature of RRMS, POSAs would have been motivated to administer Bodor’s oral cladribine dosage form to a RRMS patient for two months, followed by a ten-month

cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23; EX1013, Abstract; EX1002, ¶¶99-106, 128. POSAs would have had a reasonable expectation of success that the claimed regimen would be effective in treating RRMS, given Bodor's successful regimen comprising a ten-month cladribine-free period and the high level of skill in the art. EX1022, 23; EX1002, ¶¶113-119, 128.

Thus, in addition to the reasons discussed for Claim 17, Claim 22 would have been *prima facie* obvious. EX1002, ¶129.

E. Claim 23

Claim 23 depends from Claim 17, and requires that “the cladribine-free (iv) period lasts 10 months.” EX1001, 18:39-40; EX1002, ¶126. As discussed in Section VIII.A.3.d, Bodor discloses a cladribine-free period of 10 months. EX1022, 23; EX1002, ¶127. And because of the cyclical and incurable nature of RRMS, POSAs would have been motivated to administer Bodor's oral cladribine dosage form to an RRMS patient for two months, followed by a ten-month cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23; EX1013, Abstract; EX1002, ¶¶99-106, 128. Dr. Miller confirms that the length of a cladribine-free period is a result-effective variable because it effects a particular result—mitigation of hematological toxicity caused by administration of

cladribine. EX1013, 5; EX1002, ¶95. It would have been well within the purview of a POSA to optimize the length of the cladribine-free period. EX1002, ¶¶95, 118. And because Bodor teaches an initial cladribine-free period that lasts ten months (EX1022, 23), it would have been logical and well within the POSA's skill to take Bodor's ten-month cladribine-free period as a starting point for optimization. EX1002, ¶104.

Thus, in addition to the reasons discussed for Claim 17, Claim 23 would have been obvious. EX1002, ¶129.

F. Claim 24

Claim 24 depends from Claim 17, and requires that "the maintenance period lasts about 2 months." EX1001, 18:41-42; EX1002, ¶130. As discussed above, because of the cyclical and incurable nature of RRMS, a POSA would have been motivated to administer Bodor's oral cladribine dosage form to an RRMS patient for two months, followed by a ten-month cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23; EX1013, Abstract; EX1002, ¶¶131-132. As explained above, POSAs would have deemed the length of administration of cladribine to be a result-effective variable, and thus would have optimized it. EX1002, ¶¶18, 91-93. And because Bodor teaches an initial treatment period that lasts two months (EX1022, 23), it would have been logical and well within the

POSA's skill to take Bodor's two-month treatment period as a starting point for optimization of the length of the maintenance period. EX1002, ¶102.

Thus, in addition to the reasons discussed for Claim 17, Claim 24 would have been *prima facie* obvious. EX1002, ¶133.

G. Claims 25 and 26

Claim 25 depends from Claim 17, and requires that "the formulation is orally administered at a daily dose of 3 to 30 mg cladribine." EX1001, 18:43-45.

Claim 26 depends from Claim 17, and requires that "the formulation is orally administered at a daily dose of 10 mg cladribine." *Id.*, 18:46-48; EX1002, ¶134.

And because of the cyclical and incurable nature of RRMS, a POSA would have been motivated to administer Bodor's daily dose of cladribine of 10 mg to an RRMS patient for two months, followed by a ten-month- cladribine-free period, and to then retreat the patient using a lower cladribine dose, followed by another cladribine-free period, as taught by Stelmasiak. EX1022, 23; EX1013, Abstract; EX1002, ¶135. A POSA would have had a reasonable expectation of success that the claimed regimen would be effective in treating RRMS, given Bodor's successful regimen comprising administering the daily dose of 10 mg cladribine and the high level of skill in the art. EX1022, 23; EX1002, ¶135.

Thus, in addition to the reasons discussed for claim 17, claims 25 and 26 would have been *prima facie* obvious to a POSA. EX1002, ¶136.

H. Claim 27

Claim 27 depends from claim 17, and requires that “the formulation is orally administered 1 to 7 days per month during the induction period.” EX1001, 18:49-51; EX1002, ¶137. As discussed above in Section IV.F.1, Bodor discloses administering a daily dose of cladribine “for a period of five to seven days in the first month” of the induction period (EX1022, 23; EX1002, ¶138), which overlaps with the claimed range and renders it *prima facie* obvious. Merck pointed to no evidence that the claimed administration schedule range was not obvious in light of the prior art. EX1002, ¶138. Therefore, the claimed method where “the formulation is orally administered 1 to 7 days per month during the induction period” would have been *prima facie* obvious.

Thus, in addition to the reasons discussed for Claim 17, Claim 27 would have been obvious. EX1002, ¶139.

IX. NO OBJECTIVE INDICIA WEIGH AGAINST THE STRONG OBVIOUSNESS SHOWING HERE

In addition to the strong *prima facie* obviousness case presented above, any objective indicia must also be considered, although they do not necessarily control the obviousness conclusion. See *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Merck did not present any objective evidence during prosecution, and Petitioner is not aware of any. EX1002, ¶140.

If Merck provides alleged objective evidence in its preliminary response, the Board should nonetheless institute trial, because “detailed consideration of [a patentee’s] secondary consideration evidence may not be undertaken until [the petitioner] has had an opportunity to test it.” *Amneal Pharms. v. Supernus Pharms.*, IPR2013-00368, Paper 8, at 12-13 (P.T.A.B. Dec. 17, 2013).

X. THE FACTS AND LAW WEIGH AGAINST DISCRETIONARY DENIAL UNDER § 325(D).

The *Advanced Bionics* test does not support discretionary denial of institution under § 325(d). *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) (precedential) (“*Advanced Bionics*”). The Examiner made two independent errors material to patentability: (i) disregarding Bodor’s express teachings of a 2- to 4-month induction period in favor of Merck’s argument that Grieb would have taught the use of a 6-month induction period instead; and (ii) failing to apply Stelmasiak and its teachings regarding lowering the total dose for the maintenance phase in a rejection. *Advanced Bionics* at 8 (the Board will not exercise discretionary denial under § 325(d) where the “petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims”).

First Material Error – Disregarding Bodor’s Express Teachings in Favor of Merck’s Incorrect Arguments Regarding Length of Induction Period

During prosecution, Merck repeatedly argued to the Examiner that Grieb taught the use of a 6-month induction period, ignoring Bodor's express disclosure of a 2- to 4-month induction period; the Examiner ultimately accepted this argument and allowed the claims. *See* § III.C, *supra*. This was material error and reveals that the Examiner misapprehended Bodor's express teaching that a 2- to 4-month induction period was suitable for Bodor's formulation that was "particularly advantageous" and "improve[d] oral bioavailability" compared to earlier dosage forms, such as Grieb's, that were "plagued by low bioavailability." EX1022, 2:22-23, 5:4-6 And because *Grieb's* induction period took six months to maximally reduce the lymphocyte count, it does not inform a POSA as to how long of an induction period to use with *Bodor's* improved tablet. Accordingly, it was material error for the Examiner to accept Merck's incorrect application of Grieb's uninformative teachings to dismiss Bodor's express teachings of a two-to-four month induction period, precisely as claimed. The Board should thus not deny trial under § 325(d). *Agrofresh Solutions, Inc. v. Lytone Enterprise, Inc.*, IPR2021-00451, Paper 11, at 13-14 (P.T.A.B. July 27, 2021) (declining to exercise discretion to deny institution under § 325(d) where petitioner provided additional evidence and information showing Examiner's conclusions were incorrect, and thus the Examiner materially erred in allowing the claims).

Second Material Error – Failing to Apply Stelmasiak in a Rejection

The Examiner also failed to apply Stelmasiak in a rejection, which was an independent, material error. Although Stelmasiak was cited in an IDS, (EX1004, 114), the Examiner did not issue a rejection in view of the reference even though Stelmasiak expressly teaches that the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase. EX1013, Abstract; EX1002, ¶89. This is the limitation the Examiner expressly found missing from Bodor and Grieb (EX1004, 103). And this is the alleged “deficiency” that Merck convinced the Examiner during prosecution of the parent U.S. Patent No. 7,713,947 was not “cured” by Bloom. EX1025, 253. Finally, during prosecution of the ’903 patent, in overcoming the Examiner’s previous rejections, Merck asserted that “one skilled in the art would not have had any reason to reduce the dosage of cladribine administered during the ‘maintenance period’ as recited in the claims.” EX1004, 151. Yet as discussed above, Stelmasiak expressly provides this purportedly missing reason to reduce the dosage of cladribine in the maintenance period as claimed. § VIII.A.1.a. Thus, the Examiner’s failure to issue a rejection in view of Stelmasiak was a material error. *Vudu, Inc. v. Ideahub, Inc.*, IPR2020-01689, Paper 16, at 18-20 (P.T.A.B. Apr. 19, 2021) (where prior art references were cited but not substantively discussed by the Examiner during prosecution, “Petitioner sufficiently demonstrate[d] that the Office erred in a manner material to the patentability of the challenged claims by

overlooking [the teachings of those references] and not applying [the references] in a rejection”).

Accordingly, any argument this Petition should be denied under § 325(d) is meritless.

XI. *FINTIV* DOES NOT SUPPORT DISCRETIONARY DENIAL.

Fintiv does not support discretionary denial. *Apple Inc. v. Fintiv, Inc.*, IPR2020-0019, Paper 11, at 6 (P.T.A.B. Mar. 20, 2020) (precedential).

Fintiv Factor 4 is **by itself** sufficient for the Board to decline to exercise its discretion to deny institution. Specifically, pursuant to *Sotera Wireless*, if the Board institutes trial, Hopewell will not pursue, in any further proceedings at the district court, the specific grounds asserted in the *inter partes* review, or on any other ground that was raised or could have been reasonably raised in an IPR (i.e., any ground that could be raised under §§ 102 or 103 on the basis of prior art patent or printed publications). See *Sotera Wireless, Inc. v. Masimo Corporation*, IPR2020-01019, Paper 12, at 18-19 (P.T.A.B. Dec. 1, 2020) (precedential as to § II.A). Under the Interim Procedure, “the PTAB will not discretionarily deny institution in view of parallel district court litigation where a petitioner presents a stipulation not to pursue in a parallel proceeding the same grounds or any ground that could have reasonably been raised before the PTAB.” EX1051, 3, 7.

The remaining factors also do not support discretionary denial. Hopewell diligently filed this Petition before any substantive proceedings have occurred or trial dates have been set in the parallel litigations. The Final Written Decision here is expected well before any trial in those cases, strongly favoring institution under factors 2 and 3. EX1027; EXX1028; EX1029, 14; EX1032; *Fintiv*, 9-10; *Micron Tech., Inc. v. Godo Kaisha IP Bridge 1*, IPR2020-01007, Paper 15, at 16 (P.T.A.B. Dec. 7, 2020).

Factor 6 also favors institution and is dispositive because Hopewell's Petition presents compelling evidence of unpatentability. EX1051, 2.

Factor 1 weighs in favor of institution or is at least neutral as the *Accord* litigation is stayed until final judgment or termination of any action involving the '903 patent, EX1034 and the parties in the *Hopewell* and *Aurobindo* litigations have not yet requested a stay. *Fintiv*, 8; *Sand Revolution II, LLC v. Continental Intermodal Group – Trucking LLC*, IPR2019-01393, Paper 24, at 7 (P.T.A.B. June 16, 2020) (informative).

Factor 5 weighs in favor of institution. Hopewell is not a party to the *Accord* or *Aurobindo* litigations, *Fintiv*, 13-14, and the *Hopewell* litigation, that case is still in the earliest stages and it is clear that the Board will evaluate the patentability of the '947 patent first. *Micron Tech.*, 18.

Accordingly, *Fintiv* weighs in favor of institution. *Fintiv*, 5-6.

XII. *GENERAL PLASTIC* DOES NOT SUPPORT DISCRETIONARY DENIAL

General Plastic does not support discretionary denial. *Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, at 16 (P.T.A.B., Mar. 20, 2020) (precedential).

General Plastic factor 1 weighs in favor of institution because Hopewell has not previously filed a petition. The other petition on the '903 patent was filed by an unrelated entity, TWi, and the ground for Hopewell's Petition here are distinct from the ground of TWi's petition. *Opensky Indus., LLC v. VLSI Tech. LLC*, IPR2021-01064, Paper 17, at 10 (P.T.A.B. Dec. 23, 2021) ("factor 1 weighs against discretionary denial for an independent petitioner").

General Plastic factors 2, 4, and 5 also weigh in favor of institution. These factors "assess and weigh whether a petitioner should have or could have raised the new challenges earlier." *Gen. Plastic*, 18; see also *Code200 UAB v. Bright Data Ltd.*, IPR2022-00861, IPR2022-00862, Paper 18, at 6 (P.T.A.B. Aug. 23, 2022) (precedential). Here, Hopewell independently filed the instant Petition before receiving the POPR in the TWi IPR and also only about a month after filing its answer in the *Hopewell* litigation, well before any invalidity contentions or discovery are due.

General Plastic factor 3 also weighs in favor of institution when evaluated in conjunction with factors 1 and 2. *Code200*, at 5 (factors 1-3 "must be read in

conjunction” with one another). Because Hopewell filed its Petition before both the POPR and the institution decision in the TWi IPR, there are no concerns that Hopewell used that case for “road-mapping.” *Id.*

Factors 6 and 7 also favor institution, consistent with the Board’s mission to “improve patent quality.” *Gen. Plastic*, 16; *Code200*, 6. This is especially so here, where Hopewell’s Petition is based on different grounds and claim constructions than TWi’s. Hopewell is unaware of any reasons the Board would be unduly taxed or could not meet its statutory requirements. *See Shenzhen Silver Star Intelligent Tech. Col., Ltd. v. iRobot Corp.*, IPR2018-00761, Paper 15, at 14 (P.T.A.B. Sept. 5, 2018).

XIII. CERTIFICATION AND STANDING (37 C.F.R. § 42.104(A))

Hopewell certifies that the ’903 patent is available for IPR and Hopewell is not barred or estopped from requesting IPR.

XIV. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

Real party-in-interest (37 C.F.R. § 42.8(b)(1)): Petitioner certifies the following information: Hopewell Pharma Ventures, Inc., Hopewell Pharma Ventures LLC, Levy SPV, LLC, GLS Capital Partners Fund I, LP, GLS Capital Partners GP, LLC and GLS Capital, LLC are the real parties in interest (collectively, “RPI”). Levy SPV, LLC, a Delaware limited liability company, is owned by GLS Capital Partners Fund I, LP, a Delaware limited partnership. GLS

Capital Partners GP, LLC, a Delaware limited liability company, is the general partner of GLS Capital Partners Fund I, LP, and GLS Capital, LLC, a Delaware limited liability company, is the investment manager to GLS Capital Partners Fund I, LP and Levy SPV, LLC. No other person (including any investor, limited partner, or member or any other person in any of Levy SPV, LLC, GLS Capital Partners Fund I, LP, GLS Capital Partners GP, LLC, or GLS Capital, LLC) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition are expected to be borne by Hopewell Pharma Ventures, Inc., Hopewell Pharma Ventures LLC, Levy SPV, LLC, GLS Capital Partners Fund I, GLS Capital Partners GP, LLC, or GLS Capital, LLC.

Related Matters (37 C.F.R. § 42.8(b)(2)): The '903 patent has been asserted in *Merck KGaA et al v. Accord Healthcare, Inc. et al.*, 1-22-cv-00974 (D. Del.), *Merck KGaA et al v. Hopewell Pharma Ventures, Inc.*, 1-22-cv-01365 (D. Del), and *Merck KGaA et al v. Aurobindo Pharma USA, Inc. et al*, 1-23-cv-00039 (D. Del.). The '903 patent is also subject to TWi Pharmaceuticals Inc.'s petition for *inter partes* review. *TwI Pharmaceuticals Inc. v. Merck Serono SA*, IPR2023-

00050. Concurrently herewith, Petitioner also files IPR2023-00480 against Patent No. 7,713,947, a parent of the '903 patent.

Lead and back-up counsel (37 C.F.R. § 42.8(b)(3)) for Hopewell Pharma Ventures, Inc. are

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Notice of Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence regarding this Petition to counsel at the above addresses and PTAB@sternekessler.com. Hopewell Pharma Ventures, Inc. consents to service by email at the addresses above.

Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith are a Power of Attorney and Exhibit List under 37 C.F.R. §§ 42.10(b) and 42.63(e), respectively. The required fee is paid

through Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is
authorized to charge any fee deficiency, or credit any overpayment, to Deposit
Acct. No. 19-0036 (Customer ID No. 45324).

Respectfully submitted,
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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

Petitioner certifies that this Petition is 13,956 words in length, as determined by the Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Respectfully submitted,
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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e)), § 42.105(a))

I certify that the above-captioned **PETITION FOR *INTER PARTES***
REVIEW FOR U.S. PATENT NO. 8,377,903, and associated Exhibits 1001-
1004, 1006-1010, 1012-1040, 1042-1048, AND 1051 were served in their
entireties upon the Patent Owner on January 23, 2023, via U.S.P.S. Priority Mail
Express at the following address:

23557 - SALIWANCHIK, LLOYD & EISENSCHENK
P.O. BOX 142950
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Patent Owner's Correspondence Address of Record for U.S. Patent No. 8,377,903

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