

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

MERCK SERONO SA,
Patent Owner.

Case IPR2023-00481
Patent 8,377,903

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Background.....	4
III.	Person Of Ordinary Skill In The Art	6
IV.	Claim Construction.....	6
V.	Petitioner Is Not Reasonably Likely To Prevail On Ground I	16
A.	Petitioner Fails To Establish That Bodor And Stelmasiak Disclose Or Suggest All Claim Limitations.....	17
1.	Neither Bodor Nor Stelmasiak Discloses Or Suggests The Claimed Weight-Based Oral, Induction Or Maintenance Dosing	17
2.	Neither Bodor Nor Stelmasiak Discloses Or Suggests A Maintenance Period As Claimed	21
B.	Petitioner Has Not Established Any Motivation To Combine Bodor With Stelmasiak To Arrive At The Challenged Claims	29
1.	A POSA Would Not Have Been Motivated To Adopt Weight-Based Dosing	29
2.	A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed Induction Doses.....	30

3.	A POSA Would Not Have Been Motivated To Re-Treat Patients After Bodor's 10-Month Cladribine-Free Period.....	37
4.	A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed 1.7 Mg/Kg Maintenance Dose	38
5.	Petitioner's Routine Optimization Arguments Fail To Explain How A POSA Would Have Been Motivated To Arrive At Claimed Dosing Methods.....	40
C.	Petitioner Has Not Established Any Reasonable Expectation Of Success In Combining Bodor's Method With Stelmasiak To Arrive At The Challenged Claims	45
1.	A POSA Would Not Have Reasonably Expected To Arrive At The Claimed Weight-Based Dosing.....	46
2.	A POSA Would Not Have Reasonably Expected To Arrive At The Claimed 1.7-3.5 Mg/Kg Total Induction Dose By Modifying Bodor's Method In View Of Stelmasiak	46
3.	A POSA Would Not Have Reasonably Expected To Treat RRMS Or Early SPMS Using The Claimed About	

8-10- Or 10-Month Cladribine-Free Period By Modifying Bodor’s Method In View Of Stelmasiak	47
4. A POSA Would Not Have Reasonably Expected To Arrive At The Claimed About 1.7 Mg/Kg Maintenance Dose By Modifying Bodor’s Method In View Of Stelmasiak	49
5. A POSA Would Not Have Reasonably Expected To Arrive At A Safe And Effective Method Of Treating RRMS Or Early SPMS As Claimed By Modifying Bodor’s Method In View Of Stelmasiak	50
VI. Objective Indicia Support Non-Obviousness	52
VII. The Petition Should Be Denied Under 35 U.S.C. § 325(d).....	53
A. The Office Already Considered Petitioner’s Alleged Prior Art And Arguments	53
1. Becton Dickinson Factors (a) And (b): Asserted Art Was Considered During Examination	54
2. Becton Dickinson Factor (d): Petitioner’s And The Examiner’s Arguments Are Not Materially Different.....	55
B. Petitioner Has Not Identified A Material Error By The Examiner	58

1.	Becton Dickinson Factor (c): Asserted Art Was Evaluated During Examination.....	59
2.	Becton Dickinson Factor (e): Petitioner Has Not Identified Material Examiner Error	60
3.	Becton Dickinson Factor (f): Additional Evidence Does Not Warrant Reconsideration	63
VIII.	Conclusion	64

TABLE OF AUTHORITIES

Page(s)

CASES

<i>Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH,</i> IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020).....	<i>passim</i>
<i>Agrofresh Solutions, Inc. v. Lytone Enterprise, Inc.,</i> IPR2021-00451, Paper 11 (P.T.A.B. Jul. 27, 2021)	62
<i>ATD Corp. v. Lydall, Inc.,</i> 159 F.3d 534 (Fed. Cir. 1998)	26
<i>Becton, Dickinson & Co. v. B. Braun Melsungen AG,</i> IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017)	<i>passim</i>
<i>Belden Inc. v. Berk-Tek LLC,</i> 805 F.3d 1064 (Fed. Cir. 2015)	41
<i>Biogen Idec, Inc. v. GlaxoSmithKline LLC,</i> 713 F.3d 1090 (Fed. Cir. 2013)	11
<i>Dafron Elecs. Corp. v. Shipman,</i> IPR2022-01008, Paper 11 (P.T.A.B. Dec. 2, 2022)	57, 63
<i>Epistar Corp. v. Int’l Trade Comm’n,</i> 566 F.3d 1321 (Fed. Cir. 2009)	10
<i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat.</i> <i>Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012).....	43
<i>In re Enhanced Sec. Research, LLC,</i> 739 F.3d 1347 (Fed. Cir. 2014)	26
<i>In re Gurley,</i> 27 F.3d 551 (Fed. Cir. 1994)	30
<i>In re Peterson,</i> 315 F.3d 1325 (Fed. Cir. 2003)	40

<i>Invitrogen Corp. v. Biocrest Mfg., L.P.</i> , 327 F.3d 1364 (Fed. Cir. 2003)	11
<i>Omega Eng'g, Inc. v. Raytek Corp.</i> , 334 F.3d 1314 (Fed. Cir. 2003)	11
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (en banc)	6, 15
<i>R.J. Reynolds Vapor Co. v. Fontem Holdings I B.V.</i> , IPR2017-01642, Paper 10 (P.T.A.B. Jan. 16, 2018)	59
<i>Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.</i> , 492 F.3d 1350 (Fed. Cir. 2007)	43
<i>TWi Pharms. Inc. v. Merck Serono SA</i> , IPR2023-00050, Paper 8 (P.T.A.B. Mar. 28, 2023)	<i>passim</i>
<i>Unigene Lab'ys, Inc. v. Apotex, Inc.</i> , 655 F.3d 1352 (Fed. Cir. 2011)	52
<i>Vudu Inc. v. Ideahub, Inc.</i> , IPR2020-01689, Paper 16 (P.T.A.B. Apr. 19, 2021)	63
<i>Ziegmann v. Stephens</i> , IPR2015-01860, Paper 13 (P.T.A.B. Sept. 6, 2017)	59

STATUTES, RULES, AND REGULATIONS

35 U.S.C. § 314(a)	16
35 U.S.C. § 325(d)	3, 64

I. INTRODUCTION

The Board should deny institution of *inter partes* review of claims 17, 19-20, and 22-27 of U.S. Patent No. 8,377,903 (“challenged claims”) because Petitioner fails to show any reasonable likelihood of prevailing.

Before the ’903 patent’s invention, numerous multiple sclerosis (“MS”) clinical trials concluded that high doses equivalent to at least 4.1 mg/kg oral cladribine (i.e., intravenous or subcutaneous doses of 2.1, 2.8, or 3.65 mg/kg, based on highest reported bioavailability) were “***not found to be effective against MS*** clinical deterioration[.]” *See* Ex. 1015, 1754¹; Ex. 1016, 425 (Table III). Further, there were significant long-term safety concerns about using cladribine to treat MS, and the art provided no guidance on which specific combination of doses and dosing periods would be safe and effective. Ex. 1001, 2:59-3:2, 3:22-30; Ex. 1031, 43-44; Ex. 1014, 1720; Ex. 1016, 430-431. The ’903 patent claims a dosing regimen for treating relapsing-remitting MS (“RRMS”) or early secondary progressive MS (“SPMS”) based on the inventors’ surprising discovery of a specific combination of (a) cladribine dosing periods, (b) low oral cladribine weight-based doses, and (c) cladribine-free periods. The claimed method

¹ Hereinafter, all emphasis is added unless otherwise noted.

overcame the challenges of the cladribine clinical studies and provides a safe and effective method for treating MS, now approved by the FDA in MAVENCLAD®.

Petitioner's one ground is based solely on art teaching *flat* dosing—neither Bodor (Ex. 1022) nor Stelmasiak (Ex. 1013) teaches or suggests weight-based dosing—and thus it is even more deficient than the ground asserted against the '903 patent in *TWi Pharmaceuticals Inc. v. Merck Serono SA*, in which the Board denied institution. *See* IPR2023-00050, Paper 8 at 21-27 (P.T.A.B. Mar. 28, 2023). In that proceeding, the ground relied on Bodor and a different secondary reference, Rice, that taught subcutaneous weight-based dosing. *Id.* at 6, 17. Nonetheless, the Board found that “Bodor already considered Rice prior to envisioning its orally administered flat dosage” and concluded “the motivation to modify Bodor's method of dosing to a weight-based dosage or to achieve a total dose based on weight remains missing.” *Id.* at 26. Petitioner here cannot establish that Bodor or Stelmasiak discloses or suggests *any* weight-based dosing, let alone the claimed weight-based induction or maintenance period dosing, and thus the Petition must fail.

Petitioner's Ground also fails because Petitioner does not establish why a person of ordinary skill in the art (“POSA”) would have been motivated to shift from Bodor or Stelmasiak's flat dosing method to a weight-based one, or to modify Bodor's method in view of Stelmasiak to arrive at the claimed about 1.7-3.5 mg/kg

or 1.7 mg/kg induction period dose, or the claimed about 1.7 mg/kg maintenance period dose. Particularly in view of Petitioner's argument that cladribine causes "suppression of lymphocyte counts" (Pet. 36 (citations omitted)), where a decrease in lymphocyte levels to ≤ 1000 cells/ μ L constitutes "suppression" and a "positive response" (Ex. 1002, ¶32; Pet. 16, n.6), and its declarant's opinion that "a *direct correlation* exists between the dose and length of administration of cladribine and level of lymphocyte suppression" (Ex. 1002, ¶91), a POSA considering Bodor and Stelmasiak would not have been motivated to modify Bodor's method in view of Stelmasiak to arrive at the claimed induction or maintenance period, or have any reasonable expectation of success in doing so.

Further, Petitioner's routine-optimization argument fails to explain why a POSA would have been motivated to select the claimed specific dosing method from the infinite number of potential combinations of doses, dosing period length and number, and drug-free period length and number, or have any reasonable expectation of success in doing so, when the prior art provides no guidance regarding which combination would result in a safe and effective method to treat RRMS or early SPMS.

The Petition also should be denied under § 325(d). Petitioner does not dispute that it presents the same art and arguments already evaluated and overcome during prosecution. But rather than demonstrating any material error, Petitioner

merely disagrees with the Examiner's evaluation of the art and allowance of the challenged claims so institution should be denied under *Advanced Bionics*.

For at least the foregoing reasons, institution of *inter partes* review should be denied.

II. BACKGROUND

MS is a chronic inflammatory demyelination disease of the central nervous system. Ex. 1001, 1:26-28. Clinically defined MS types include RRMS and SPMS. *Id.*, 1:48-50.

The '903 patent specification describes five FDA-approved disease modifying treatments ("DMTs") for MS: three beta interferons (Betaseron[®]; Avonex[®]; Rebif[®]), glatiramer acetate (Copaxone[®]), and mitoxantrone (Novantrone[®]). *Id.*, 2:14-21. Other than mitoxantrone, these drugs are administered parenterally in a continuous, single-dosing phase at flat (i.e., not weight-based), fixed doses without any extended drug-free period. Ex. 1006, 947 (Table 2). Mitoxantrone is administered intravenously based on body surface area every 3 months. *Id.* Thus, a POSA would have understood that as of December 2004, most FDA-approved MS drugs used a continuous, single-dosing phase without any extended drug-free period and that none of these drugs used oral or weight-based dosing.

By December 2004, several clinical trials had investigated the use of cladribine for treating MS. Most of these trials used a single, high intravenous- or subcutaneous-dose dosing phase (e.g., total doses of 2.1, 2.8, or 3.65 mg/kg per dosing period); achieving the same cladribine exposure would be expected to require even higher doses when administered orally. *See* Ex. 1016, 425 (Table III); Ex. 1001, 2:37-42; Ex. 1047, 295; Ex. 1031, 36. A limited number of cladribine trials used more than one dosing phase. *See* Ex. 1013, 5; Ex. 1014, 1716; Ex. 1018, 1146-47.

Despite the numerous clinical trials, “cladribine was not found to be effective against MS clinical deterioration[.]” Ex. 1015, 1754. Further, there were significant long-term safety concerns about using cladribine to treat MS, including increased cancer risk, hematologic toxicity, and bone marrow suppression. Ex. 1001, 2:59-3:2, 3:22-30; Ex. 1031, 40-41; Ex. 1014, 1720; Ex. 1016, 430. And while these clinical trials used varying dosing periods and doses, nothing in the prior art taught a POSA how the combination of the different dosing variables—dose, length and number of dosing period or length of drug-free periods—would impact the treatment of MS or what specific combination (if any) would result in a safe and effective MS treatment method. Indeed, the art taught “[t]here is still more to be learned about optimal cladribine dosages, ideal timing for retreatment and how cladribine compares with other agents used to treat MS.” Ex. 1016, 431.

III. PERSON OF ORDINARY SKILL IN THE ART

Patent Owner (“PO”) reserves the right to challenge Petitioner’s definition at a later stage in this proceeding, should the Board institute trial.

IV. CLAIM CONSTRUCTION

Petitioner contends the claim term “a maintenance period” should be construed as “a period during which a total dose of cladribine is *lower* than the total dose of cladribine administered in an induction period.” Pet. 30-31.

Petitioner argues that “the specification supports [such] a construction” (*id.*) even though Petitioner’s declarant states, “[t]he ’903 patent does not explicitly define ‘maintenance period[.]’” Ex. 1002, ¶70. The Board should reject Petitioner’s construction because (1) it disregards the plain and ordinary meaning of the term “maintenance period,” as informed by the ’903 patent claims and specification; and (2) Petitioner fails to show that PO disclaimed subject matter directed to using the same dose for the maintenance and induction periods.

It has long been held that the “words of a [patent] claim are generally given their ordinary and customary meaning” “in the context of the entire patent, including the specification.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (internal citations and quotations omitted).

First, a POSA considering the plain language of the ’903 patent claims and specification would have understood a “maintenance period” means “a treatment

period that follows an induction period and a cladribine-free period.” For example, claim 17 recites a “method of treating [RRMS] ... following the *sequential steps* ... [of] (i) an induction period ..., (ii) a cladribine-free period ..., (iii) a maintenance period ..., (iv) a cladribine-free period[.]” Ex. 1001, 18:7-26; *see also id.*, 16:52-17:5 (claim 1). Similarly, Example 1 of the ’903 patent discloses a study in which the “maintenance period” occurs “at month 13,” *after* an “induction period” and a cladribine-free period. *Id.*, 15:47-67. Thus, a POSA considering the claims and specification would have understood that a maintenance period is a treatment period that follows an induction period and a cladribine-free period.

Contrary to Petitioner’s assertion, a POSA would not understand the term “maintenance period” itself to require administration of any particular dose of cladribine. Instead, other language in the claims specifies the exact dose to be administered during the maintenance period. *See, e.g., id.*, 18:7-26 (claim 17, reciting “the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg”). Thus, Petitioner’s attempt to read a dosing amount into the construction of “maintenance period” is improper.

Indeed, Petitioner’s argument that a maintenance period requires a lower total dose than the induction period dose is directly contradicted by the claim language, which makes clear that the total cladribine dose administered during a maintenance period can be *either* the same as *or* lower than that administered

during the induction period. For example, independent claim 1 expressly recites “wherein the total dose of cladribine reached at the end of the maintenance period is **lower than** the total dose of cladribine reached at the end of the induction period” (i.e., the “lower than” limitation). *Id.*, 16:52-17:5. On the other hand, independent claim 17 recites “the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg” and “the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg[.]” *Id.*, 18:7-26. That is, if the total dose administered during the induction period were about 1.7 mg/kg (the low end of the claimed range), then the total dose administered during the maintenance period would be the **same as** the total dose administered during the induction period. In fact, claim 20, which depends from claim 17, expressly recites that “the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.” *Id.*, 18:30-32. A POSA would thus have understood that claim 20 requires the total cladribine dose during the induction period to be the same as the total cladribine dose during the maintenance period, i.e., “about 1.7 mg/kg” in each case. Thus, reading the claims as a whole, a POSA would have understood that the total dose of cladribine administered during the maintenance period could be **either the same as or lower than** the total dose administered during the induction period.

Consistent with the claims, the specification describes embodiments wherein the total cladribine dose administered during a maintenance period is ***the same as or lower than*** the total dose of cladribine administered during the induction period. Example 1 discloses a study in which patients in Groups 2 and 3 receive a total induction period dose of 1.75 and 3.5 mg/kg cladribine, respectively. *Id.*, 14:6-15:61. After a cladribine-free period, Groups 2 and 3 both “receive re-treatment with Cladribine ... for 2 months (***maintenance period***) with the lower dose,” i.e., the lower of the two induction period doses—1.75 mg/kg. *Id.*, 15:62-67; *see also id.*, 14:49-15:19 (“[A]dministration schemes for the induction period ... are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable,” which discloses a target dose of “1.75 mg/kg”); 16:1-6. Thus, for Group 3, the total cladribine dose during the maintenance period is lower than that administered during the induction period, whereas for Group 2, the total doses administered for each of the induction and maintenance periods are ***the same***, i.e., 1.75 mg/kg.

The '903 patent further describes embodiments wherein the total cladribine dose administered during a maintenance period is the ***same as*** that administered during the induction period. For example, “[i]n a further preferred embodiment,” “the total dose of Cladribine reached at the end of the induction period is about 1.7

mg/kg” and “the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.” *Id.*, 12:65-67, 13:13-15.

Thus, a POSA reading the claim term “maintenance period” in the context of the claims and the specification would have understood that its plain and ordinary meaning is “a treatment period that follows an induction period and a cladribine-free period,” without requiring administration of a particular dose. Instead, the total doses for the maintenance period are clearly recited in the claims, e.g., “lower than the total dose of cladribine reached at the end of the induction period” in claim 1; or “about 1.7 mg/kg” in claim 17. The claims and specification clearly describe and support that the total cladribine dosing during a maintenance period can be either the *same as or lower than* the total dose of cladribine administered during the induction period.

Second, Petitioner fails to show that PO disclaimed a maintenance period dosing that was the same as the induction period dosing and thus cannot overcome the plain and ordinary meaning of a “maintenance period” as claimed.

Courts have declined to apply the doctrine of prosecution disclaimer where an alleged infringer’s arguments fail to “show the patentee expressly relinquished claim scope,” and thus are insufficient to “overcome [the] heavy presumption that claim terms carry their full ordinary and customary meaning[.]” *Epistar Corp. v. Int’l Trade Comm’n*, 566 F.3d 1321, 1334 (Fed. Cir. 2009). “[F]or prosecution

disclaimer to attach, [Federal Circuit] precedent requires that the alleged disavowing actions or statements made during prosecution be both *clear and unmistakable*.” *Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325-26 (Fed. Cir. 2003); *see also Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1369 (Fed. Cir. 2003) (same).

Here, Petitioner’s estoppel arguments are not supported by the prosecution history. *See* Pet. 31, n.8.

Petitioner first argues that “Merck is bound by accepting the Examiner’s statement” that neither Bodor nor Grieb teaches that the total maintenance period dose is *lower* than the total induction period dose, citing *Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090 (Fed. Cir. 2013). *Id.* But the present situation is far different than in *Biogen*, where the Court found the patentees had disclaimed subject matter when patentees “did not directly challenge the examiner’s characterization” of the disputed term but also “adopted that characterization when applicants limited their claims.” 713 F.3d at 1096-97& n.6. Here, PO did not “accept” an alleged characterization that *all* claims required a lower maintenance period dose, and instead argued that “nowhere” in 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.’” Ex. 1004, 121, 151 (same); *see also* Pet. 12

(Petitioner acknowledging PO argued that Bodor did not teach a “maintenance period” dose that was the same or lower than the original dose). Further, in contrast to the patentees in *Biogen*, who limited their claims to match the examiner’s characterization and therefore “adopted” that characterization, PO here made no amendments with either of its Responses, which addressed **some** claims reciting the “lower than” limitation and others allowing the total maintenance period dose to be the same or lower. Ex. 1004, 117-127, 147-153. This directly contradicts Petitioner’s purported acquiescence. Under these circumstances, there can be no “clear and unmistakable disavowal.”

Petitioner’s additional arguments concerning the prosecution history are similarly misplaced. After rebutting the Examiner’s rejection of all claims (claims 1-29) by arguing that Bodor did not teach a maintenance period at all—either the **same** dosage as or **lower than** the total induction period dosage—PO further argued that “[e]ven if one were to accept [the] ‘implied’ teaching in Bodor et al.,” i.e., “that following these 10 months, treatment with cladribine is resumed,” “the teachings of the reference would not lead [a POSA] to the claimed invention” and “[s]pecifically, a [POSA] would not have had any reason to reduce the dosage of cladribine administered during the ‘maintenance period’[.]” *Id.*, 151. PO concluded that “the **combined teachings** of the references would not have led [a POSA] to a dosing regimen and/or total dosages recited in claims 1, 4, 5, 9, 10, 17,

20 or 21.” *Id.* Thus, PO never argued the maintenance period must always use a total dose lower than the induction period dose.

To the contrary, PO repeatedly distinguished Bodor on the grounds that it failed to teach a maintenance period dosage that was *either* the *same* as *or lower* than the total induction period dosage. *See* Ex. 1004, 121 (“nowhere in ... [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”), 151 (same). As such, PO made clear that the then-pending claims included claims directed to not just a lower maintenance period dosage relative to the induction period dosage, but also claims allowing the *same* total dosages for both periods (e.g., claims 17 and 20).

Likewise, the prosecution history shows the Examiner recognized the application included claims directed to a method having the same total cladribine dosage for the maintenance and induction periods. During prosecution, the Examiner stated:

[A] woman weighing approximately 58 kg and treated for 2 months with 10 mg cladribine daily for 5 days per month would reach a *total dose of 1.72 mg/kg*, which would be *on point* to claims 4 and 20 (i.e., the *total dose* of cladribine reached at the *end of the induction period is about 1.7 mg/kg*).

Id., 101. Then claim 20, through dependency from claim 17, recites “the total dose of cladribine reached at the end of the ***maintenance*** period is about 1.7 mg/kg[,]” thus reciting the ***same dose*** of about 1.7 mg/kg for ***both the induction and maintenance periods***. Ex. 1001, 18:7-26, 18:30-33. The Examiner’s specific reference to claim 20 and discussion of the recited doses show her appreciation of certain claims directed to a method having the same total cladribine dosage for the maintenance and induction periods.

Petitioner also asserts that the prosecution history of the parent patent (U.S. Patent No. 7,713,947) supports Petitioner’s proposed construction. Pet. 31-33. But the only evidence identified by Petitioner is PO’s argument that ***Bloom*** did not teach “lowering treatment dosages with each successive use of the drug.” *Id.*, 32 (quoting Ex. 1025, 251). Regardless, during prosecution of the ’947 patent, PO’s arguments regarding the art reflected the scope of then-pending claims 18-37, which contained an express limitation that the total dose during the maintenance period was “lower than” the total induction period dose. Ex. 1025, 3-6, 237-255. PO then added claims specifying that the maintenance period dosing may be the same as the induction period dosing. *Id.*, 243-245. These circumstances do not “show the patentee expressly relinquished claim scope” regarding the maintenance period dosing.

Accordingly, nowhere in the file histories of the '947 or '903 patents is there a “clear and unmistakable” disavowal of a total maintenance period dose that is the same as the total induction period dose. Instead, PO’s statements during prosecution of both patents show the maintenance and induction period doses can be the same in the challenged claims.

Thus, Petitioner fails to show that PO disclaimed a maintenance period dosing that was the same as the induction period dosing and cannot overcome the plain and ordinary meaning of a “maintenance period,” as a POSA reading the claim term in the context of the challenged claims, the specification, and the file histories would have understood it. *See Phillips*, 415 F.3d at 1312-13. The Board should thus reject Petitioner’s proposed construction of “maintenance period.”

Petitioner similarly asserts that “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.” Pet. 30. For the same reasons discussed above with respect to “maintenance period,” a POSA would have understood that the plain meaning of “induction period” does not require a particular dose, and the total cladribine induction period dose can be either the **same as** or **higher than** the total cladribine maintenance period dose. The Board should reject Petitioner’s construction of “induction period” as requiring a higher dose than the “maintenance period.” PO reserves the right to

further address construction of “induction period” and “maintenance period” should the Board institute trial.

Lastly, regardless of how “maintenance period”/“induction period” is construed, Petitioner is not reasonably likely to prevail on its sole Ground. *See* Section V, *infra*.

V. PETITIONER IS NOT REASONABLY LIKELY TO PREVAIL ON GROUND I

The Petition should not be instituted because Petitioner has not established a reasonable likelihood that it will prevail on Ground I, its only ground asserted. *See* 35 U.S.C. § 314(a).

The Petition challenges claims 17, 19-20, and 22-27 of the '903 patent as unpatentable over Bodor and Stelmasiak. Pet. 33. The Petition fails at least because Petitioner fails to show that the references, even in combination, teach or suggest all limitations of the challenged claims. Neither reference teaches or suggests either an induction period as claimed or a maintenance period as claimed. In particular, neither reference teaches or suggests weight-based dosing as claimed. Furthermore, Petitioner fails to establish any motivation to modify Bodor's flat-dosing regimen in view of Stelmasiak's high-dose, flat-dosing method to arrive at the claimed weight-based dosing method, or any reasonable expectation of success in doing so. The Petition should not be instituted.

A. Petitioner Fails To Establish That Bodor And Stelmasiak Disclose Or Suggest All Claim Limitations

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

Petitioner's ground is solely based on art teaching *flat* dosing—neither Bodor nor Stelmasiak teaches or suggests weight-based dosing—and thus is even more deficient than the ground put forward in *TWi*, in which the Board denied institution. In that proceeding, the petitioner challenged the '903 patent based on Bodor and a different secondary reference, Rice, which taught subcutaneous weight-based dosing. *TWi*, IPR2023-00050, Paper 8 at 6, 22. The Board denied institution, finding that “Bodor already considered Rice prior to envisioning its orally administered flat dosage” and concluded “the motivation to modify Bodor's method of dosing to a weight-based dosage or to achieve a total dose based on weight remains missing.” *Id.* at 26. Here, Petitioner cannot establish that Bodor or Stelmasiak discloses or suggests any weight-based dosing, let alone the claimed weight-based induction dosing of about 1.7 or 1.7-3.5 mg/kg or maintenance dosing of about 1.7 mg/kg. Thus, the Petition must fail.

Petitioner asserts that “Bodor *expressly* teaches the claimed cladribine dose reached at the end of the induction period” but fails to cite *any* passage in Bodor as support. Pet. 50. Petitioner later cites the declaration of Dr. Miller, who opines

that “a POSA would have been able to determine that Bodor teaches administering a total [induction period dose] of 100 to 140 mg of cladribine ... [and] that, for an average adult weighing about 70 kg, Bodor’s dose is equivalent to approximately 1.4 to 2 mg/kg[.]” Ex. 1002, ¶83. But there is no teaching or suggestion in Bodor regarding weight-based dosing. As the *TWi* Board explained, “Bodor’s disclosure regarding a treatment dose does not include any consideration of a patient’s weight” and “Bodor ... does not teach or suggest switching to a weight-based dosage.” *TWi*, IPR2023-00050, Paper 8 at 14, 20. There is nothing in Bodor that would have led a POSA to understand that Bodor’s flat dosing is “equivalent” to weight-based dosing at approximately 1.4-2 mg/kg. While Bodor mentions weight-based cladribine dosages for treating MS in the context of prior art subcutaneous dosing regimens (e.g., Rice), Bodor never teaches or suggests dosing its oral cladribine formulation based on body weight. Ex. 1022, 22:19-26.

Instead, as the *TWi* Board noted, even after recognizing certain prior art methods involving weight-based dosing approaches, Bodor expressly teaches a method using flat dosing, **not** weight-based dosing. *TWi*, IPR2023-00050, Paper 8 at 21. Bodor discloses that “[a]t the present time, it is envisioned that, for the treatment of [MS], 10 mg of cladribine ... would be administered once per day for ... five to seven days in the first month, repeated for ... five to seven days in the second month,” i.e., flat, “fixed oral doses” of cladribine. Ex. 1022, 23:15-20.

Whether administered for 10 or 14 days, the daily dosage remains flat. Because Bodor does not disclose any relationship between dosage and patient weight, the disclosed 100, 120, and 140 mg doses are *flat* for all patients and not weight-adapted.

Further, Bodor's examples confirm administration based on flat, fixed dosing. Example 4 discloses that "[MS] [p]atients received randomly three different *fixed oral doses* (3.0 mg)" and Example 5 discloses that "[MS] patients received randomly two different *fixed* oral doses (3.0 mg and 10.0 mg) and a fixed intravenous dose of 3.0 mg." *Id.*, 33:25-27; 36:18-20. Nowhere does Bodor suggest administering its oral formulation of cladribine based on patient weight. *See TWi*, IPR2023-00050, Paper 8 at 14, 20.

Petitioner's reading of Bodor is driven by hindsight and arbitrarily limits Bodor's disclosed method to a 70 kg adult. Petitioner arrived at the 1.4-2 mg/kg range based on hindsight reasoning—by selecting an exemplary patient weight, back-calculated from the claims—but there is nothing in Bodor teaching or suggesting dosing focused on a patient weighing 70 kg. *See id.* at 21 (where the "Petitioner[] conten[ds] that a skilled artisan would have modified Bodor's method of dosing ... to depend upon a patient's weight or to provide a total dosage that is about 1.7 mg/kg at the end of the induction period and at the end of the

maintenance period,” such a contention “is improperly guided by hindsight and not the teachings of Bodor, or in view of the knowledge in the art.”).

Thus, Petitioner fails to establish that Bodor teaches or suggests a method of treating MS with a total oral, weight-based dosage of about 1.7 or 1.7-3.5 mg/kg cladribine in an induction period, or weight-based dosage of about 1.7 mg/kg cladribine in a maintenance period. Only by rewriting Bodor with hindsight knowledge of the claimed dosing regimen, and ignoring Bodor’s express teaching of flat, fixed-dose dosing (Ex. 1022, 23, 33, 36), can Petitioner argue that Bodor discloses the claimed weight-based dosages.

Stelmasiak does not remedy the deficiencies of Bodor, because, like Bodor, it teaches flat cladribine dosing. Stelmasiak discloses that RRMS patients received 300 mg oral cladribine (i.e., 10 mg/day for 5 days/month for six months), followed by 50 mg at month nine and 50 mg at month twelve or fifteen. Ex. 1013, 5. Stelmasiak does not suggest weight-based dosing but instead reports that “[t]here was *no indication* that a ‘good response’ is related to the actual cladribine dose per body weight.” *Id.*, 7. Even if a POSA would have considered the reported “body weight [of] 52-75 kg” (*id.*, 5), the 300 mg initial dose would correspond to 4.0-5.8 mg/kg, well above the claimed weight-based induction dose. Thus, Stelmasiak does not teach or suggest weight-based dosing at all, let alone the claimed about 1.7 or 1.7-3.5 mg/kg total induction dosing.

Accordingly, neither Bodor nor Stelmasiak teaches or suggests a method of treating RRMS or early SPMS with a total oral, weight-based induction period dosage of about 1.7 or 1.7-3.5 mg/kg cladribine, or a total oral maintenance period dosage of about 1.7 mg/kg cladribine.

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

Bodor does not teach or suggest any maintenance period or maintenance dosing regimen, let alone a maintenance period of about 2-4 months with a total, weight-based dose of about 1.7 mg/kg after an about 8-10 or about 10-month cladribine-free period.

Petitioner relies on Dr. Miller to argue that “Bodor teaches a retreatment period after the cladribine-free period.” Pet. 52 (citing Ex. 1002, ¶¶84-86).

Petitioner is wrong for the following reasons.

First, Bodor does not teach or suggest a maintenance period or a “cyclical” cladribine regimen including “an induction, a cladribine-free, and a maintenance period.” Pet. 5. Bodor does not teach or suggest any maintenance period or maintenance dosing regimen, let alone a maintenance period after an 8-10- or 10-month cladribine-free period. While Dr. Miller opines that “Bodor does not teach administering a different drug therapy after the cladribine-free period, so a POSA would have understood Bodor to re-administer cladribine at the end of the ...

cladribine-free period,” (Ex. 1002, ¶86), Bodor discloses at least one other dosing regimen and there is nothing in Bodor to suggest that the *same* cladribine dosing regimen would be used again. *See* Ex. 1022, 23:20-24 (“Alternatively 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”). Further, Dr. Miller overlooks that Bodor discloses that other active ingredients may be used for treatment. *Id.*, 24:10-26 (“administration of cladribine ... may be accompanied by administration of one or more additional active ingredients,” such as interferon beta, glatiramer acetate, natalizumab, and alemtuzumab). Bodor does not specify what, if anything, is administered at the end of the cladribine-free period. As such, there is nothing in Bodor to suggest that cladribine—and not one of the other active ingredients disclosed therein, if anything—is re-administered at the end of the cladribine-free period.

Second, as of 2004, most MS treatments were not “cyclical,” i.e., they did not require re-treatment after an extended drug-free period. While Petitioner argues that “POSAs would have been aware of general knowledge in the art establishing that MS patients typically require retreatment” (Pet. 53), the art suggests otherwise.

As of December 2004, most FDA-approved MS drugs were not dosed cyclically, but in a continuous, single-dosing phase without any extended drug-free

period using subcutaneous or intravenous administration. Ex. 1006, 947 (Table 2); *see* Section II, *supra*.

Further, by 2004, most MS clinical trials studying cladribine used a single, high intravenous- or subcutaneous-dose dosing phase (e.g., total doses of 2.1, 2.8, or 3.65 mg/kg per dosing period²) without re-treatment. Ex. 1016, 425 (Table III, “Scripps pilot,” “Scripps 2-year CPMS,” “Scripps CPMS retreatment,” “Multicentre North American CPMS,” “Scripps 2-year RRMS”). And for the few trials that re-treated patients, the published trial protocols expressly stated as such. *See* Ex. 1013, 5 (“[T]wo additional courses were given at 9 and 12 or 15 months.”); Ex. 1018, 2 (re-treatment was permitted “provided at least 12 months had elapsed since the last dose of cladribine”); Ex. 1014, 1719 (“retreatment with cladribine under another protocol”). Thus, the art did not establish that MS patients typically required re-treatment, and expressly disclosed re-treatment when applicable.

Third, Bodor does not teach the claimed weight-based maintenance dose, or the specific dose of about 1.7 mg/kg. While Petitioner contends that a POSA

² Langtry discloses cladribine oral bioavailability of 37-51%. Ex. 1016, 423. A 2.1 mg/kg intravenous/subcutaneous dose would require at least 4.1 mg/kg oral cladribine, based on 51% bioavailability.

would have been able to “fine tune” the total maintenance dose because Bodor “teaches a general strategy for doing so” (Pet. 42-43), Petitioner fails to establish any maintenance dose actually taught by Bodor or any weight-based dose in Bodor that would even provide a starting point for such optimization. Nor does Petitioner explain why a POSA would have shifted from Bodor’s flat dosing method to a weight-based one. As discussed above (Section V.A.1), Bodor expressly teaches flat dosing, *not* weight-based dosing. Bodor’s disclosure regarding “fine tuning” a treatment dose does not change this—it does not include any consideration of patient weight, and thus does not support Petitioner’s assertion that a POSA would have arrived at the claimed weight-based maintenance dosing of about 1.7 mg/kg by routine optimization. As the *TWi* Board found:

[*TWi*] has not shown, nor do we find, that Bodor’s teaching of increasing or decreasing the daily dose means shifting to a weight-based dosing method or arriving at a total dosage based on a patient’s weight. Indeed, Bodor recognized methods involving weight-based dosing in the prior literature and expressly disclosed a different method of treating MS orally with a flat daily dosage of its cladribine complex, independent of a patient’s weight.

TWi, IPR2023-00050, Paper 8 at 21.

Thus, Bodor does not teach or suggest a total maintenance period dose of about 1.7 mg/kg as claimed, because Bodor teaches neither weight-based dosing nor a maintenance period. In view of the state of MS treatment in 2004, including cladribine clinical studies, a POSA considering Bodor would not have understood Bodor to teach readministering cladribine at the end of the 10-month cladribine-free period using the claimed maintenance dose.

Stelmasiak does not remedy the deficiencies of Bodor.

First, Stelmasiak does not teach or suggest a maintenance period occurring about 8-10 months after the induction period. Petitioner argues that Stelmasiak's "induction period" is "followed by *three months of no treatment*" (Pet. 54), i.e., re-treatment occurs three months after the first treatment period, not about 8-10 months, as claimed. While Stelmasiak teaches re-treatment after *two* months of no treatment (rather than three), the combination of Bodor and Stelmasiak does not teach or suggest a maintenance period that occurs about 8-10 or about 10 months after the induction period as claimed. *See* Ex. 1013, 5 ("Six cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months.").

Nevertheless, Petitioner argues that "a POSA would have retreated the patient with cladribine, as Stelmasiak taught," and that Stelmasiak and Bodor would have led a POSA to treat RRMS according to a "general treatment

framework” that provides for “maintenance” after a 2-month induction period and 10 months of no treatment. Pet. 36-37; Ex. 1002, ¶105. However, Petitioner cannot cherry pick in hindsight only the parts of Stelmasiak and Bodor that support its argument, while ignoring other relevant portions that teach or suggest otherwise. *See In re Enhanced Sec. Research, LLC*, 739 F.3d 1347, 1355 (Fed. Cir. 2014) (One cannot “stitch together an obviousness finding from discrete portions of prior art references without considering the references as a whole.”); *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998) (The “[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.”). Here, Stelmasiak requires re-treatment ***two months*** after the first treatment period, and thus does not teach or suggest a maintenance period about 8-10 or 10 months after the induction period as claimed.

Petitioner further argues that “[a] POSA would have further retreated any patient exhibiting worsening signs or symptoms of MS, as Stelmasiak did” because “a POSA would have expected relapse.” Pet. 36-37. Petitioner thus suggests that alleged re-treatment would occur based on disease activity, rather than a particular dosing timeframe. However, this individualized re-treatment theory undermines Petitioner’s suggestion that treatment for all patients would resume after 10 months.

Second, Stelmasiak does not teach or suggest a maintenance period lasting about 2-4 months with a total dose of about 1.7 mg/kg. Instead, Stelmasiak discloses a second dosing phase in which *one* 50 mg oral course of cladribine is administered at month nine, followed by a 2- or 5- month cladribine-free period. Ex. 1013, 5. Stelmasiak thus teaches re-administering cladribine over a one-month period, and not a 2–4-month maintenance period as claimed. Further, as discussed above (Section V.A.1), Stelmasiak teaches *flat* dosing. But even if the reported patient weight were considered, at 52-75 kg, Stelmasiak’s single re-treatment course of 50 mg after a two-month cladribine-free period would correspond to 0.67-0.96 mg/kg. Thus, Stelmasiak does not teach or suggest the claimed about 1.7 mg/kg total maintenance dosing.

Moreover, Stelmasiak and Bodor do not suggest extending Stelmasiak’s re-treatment period from one month to about 2-4 months as claimed. Stelmasiak reports that its single 50 mg course at month nine allowed lymphocyte levels to “remain[] at approximately 1000 per μL ” (Ex. 1013, 5 (Figure 1, showing maintenance of lymphocyte levels at $<1000/\mu\text{L}$)), which, according to Dr. Miller, is “characteristic of a treatment response.” Ex. 1002, ¶¶16, 38; Pet. 16, n.6. Dr. Miller further opines that “[a] POSA would also have followed the maintenance period with another drug-free period, similar to Stelmasiak’s dosing regimen, because cladribine toxicity was a concern.” Ex. 1002, ¶103. According

to Dr. Miller's opinions and Stelmasiak's reported data, Stelmasiak's 50 mg oral cladribine dose would have been sufficient to suppress lymphocytes and a POSA would have followed Stelmasiak's 50 mg re-treatment period with another drug-free period, but would not have seen any need to extend Stelmasiak's re-treatment period from one month to about 2-4 months as claimed.

Lastly, Petitioner fails to cite any specific teachings or doses in the prior art that would teach or suggest using a maintenance period of about 2-4 months with a total dose of about 1.7 mg/kg cladribine as claimed. Petitioner argues that the claimed maintenance period dosing and dosing length are "merely routinely optimized workable ranges." Pet. 40, 42. But as discussed in more detail below (Section V.B.5), Petitioner fails to establish that there would have been a finite number of identified and predictable solutions and provides no motivation as to *which* specific combination to pick.

Thus, Bodor and Stelmasiak, alone or in combination, fail to teach or suggest "a maintenance period" of about 2-4 or 2 months occurring about 8-10 or 10 months after an induction period and having a total dose of "about 1.7 mg/kg," as claimed at least because (1) Bodor and Stelmasiak only teach flat dosing; (2) Bodor and Stelmasiak, even in combination, do not teach or suggest a maintenance period of about 2-4 months after about 8-10 or 10 months of no treatment; and (3)

even if patient weight were considered, Stelmasiak's re-treatment dose still would not correspond to the claimed maintenance period dose.

B. Petitioner Has Not Established Any Motivation To Combine Bodor With Stelmasiak To Arrive At The Challenged Claims

Petitioner fails to establish why a POSA would have been motivated to modify Bodor's *flat*, oral cladribine dosing method in view of Stelmasiak's *flat* oral cladribine dosing method to arrive at the claimed weight-based dosing method. Particularly in view of Petitioner's praise of "Stelmasiak's success" (Pet. 6), Petitioner offers no rationale for why a POSA would have been motivated to modify Bodor's method to arrive at a method that effectively (1) reduces the initial treatment length and dose of Stelmasiak, which was reported to result in only "partial" patient response; (2) prolongs Stelmasiak's initial drug-free period; and (3) extends Stelmasiak's month-long re-treatment phase.

1. A POSA Would Not Have Been Motivated To Adopt Weight-Based Dosing

Petitioner fails to explain why a POSA would have shifted from Bodor and Stelmasiak's flat dosing method to a weight-based dosing method. *See TWi*, IPR2023-00050, Paper 8 at 26 ("In other words, the motivation to modify Bodor's method of dosing to a weight-based dosage or to achieve a total dose based on weight remains missing."). As discussed above (Section V.A.1), Bodor expressly teaches flat dosing, not weight-based dosing. And Stelmasiak not only teaches flat

dosing rather than weight-based dosing but also reinforces Bodor's flat dosing by reporting that "[t]here was *no indication* that a 'good response' is related to the actual cladribine dose *per body weight*." Ex. 1013, 7. For example, "there was *no correlation* between the depth of lymphocyte nadir, or the magnitude of lymphocyte count reduction from the initial value, and the *drug dose expressed per kg of body weight*["]” *Id.*, 6. A POSA would have understood that Stelmasiak teaches the effects of cladribine were not related to its dose per body weight, and thus would not have been motivated to adopt weight-based dosing as claimed because Stelmasiak teaches away from it. *See In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (“A reference may be said to teach away when a [POSA], upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path that was taken by the applicant.”).

2. A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed Induction Doses

As an initial matter, Petitioner fails to explain why a POSA would have started with Bodor's method, rather than Stelmasiak's, to treat RRMS or early SPMS. Petitioner identifies “oral drug delivery” and “increased bioavailability” as reasons for a POSA “to use Bodor's form to treat MS.” Pet. 35. However,

Stelmasiak's oral cladribine method was reported to provide higher bioavailability than Bodor's.

Stelmasiak reports 50% bioavailability for its oral cladribine method. Ex. 1013, 5; *see also* Ex. 1023 (Grieb), 325. Stelmasiak explains that cladribine administered "either subcutaneously (dose 5 mg per day...) or orally (dose 10 mg per day...)" "produce[s] *equivalent area under the concentration time curve* of the drug." Ex. 1013, 5. Grieb, which is co-authored by Stelmasiak, and has substantially the same disclosure, also discloses that the same saline-based cladribine formulation has 50% bioavailability. Ex. 1023, 324 ("The drug was prepared as isotonic saline solution ... for subcutaneous injections."), 325 (AUC "is practically of the same size when the dose is given ... subcutaneously, or when a doubled dose is given orally (oral bioavailability is approximately 50%)."). Thus, a POSA would have understood Stelmasiak and Grieb's saline-based oral cladribine formulation has 50% bioavailability, as determined from the AUC ratio of the administration forms.

In contrast, using the same relative AUC approach that Stelmasiak used to determine bioavailability (Ex. 1013, 5; Ex. 1023, 325), Bodor determined its tablets have 39.1-43.1% bioavailability. Bodor's Example 4 ("Clinical Study: Relative Bioavailability") shows the AUC ratio of Bodor's "Tablet 1" relative to the subcutaneous reference formulation ranged from 41.9-43.1%, and Example 5

(“Clinical Study: Dose Response and Absolute Bioavailability”) shows the AUC ratio of Bodor’s oral tablets relative to an intravenous reference formulation ranged from 39.1-39.4%. Ex. 1022, 36 (Table VI), 38 (Table VIII). Notably, Petitioner acknowledges that “Bodor also describes clinical studies that measure cladribine’s ‘relative bioavailability,’” and identifies Examples 4 and 5 of Bodor. Pet. 24 (quoting Ex. 1022).

Based on the bioavailability data reported by Bodor and Stelmasiak, a POSA would have understood Bodor’s oral cladribine has 39.1-43.1% bioavailability, which is *less* than the 50% bioavailability of Stelmasiak’s formulation. Given Bodor’s lower bioavailability, Petitioner’s argument that there is a “[p]reference for ... increased bioavailability” (Pet. 35), suggests, if anything, that a POSA would have been motivated to start with Stelmasiak’s 300 mg cladribine dose administered over six months, not Bodor’s 100-140 mg cladribine doses administered over two months. This is especially true given Petitioner’s praise of “Stelmasiak’s success,” (*id.*, 6), and Bodor’s lack of efficacy results.

While Petitioner contends that “a POSA also would have used [] Bodor’s total doses of cladribine” despite the fact that “Bodor did not test its regimen” (*id.*, 34-35, n.9), Petitioner offers no rationale as to why a POSA would not have started instead with Stelmasiak’s reportedly partially efficacious method using a formulation having a higher bioavailability (50%).

Further, a POSA would not have modified the teachings of Bodor and Stelmasiak to arrive at the claimed induction dose. Even if the reported patient weight (52-75 kg) were considered, Stelmasiak's 300 mg initial dose would correspond to 4.0-5.8 mg/kg, which is significantly higher than the claimed induction period doses of about 1.7-3.5 or 1.7 mg/kg. *See* Ex. 1013, 5. Given that even these dosages in Stelmasiak were reported to only result in a "partial" response, a POSA in view of Stelmasiak if anything would have been motivated to increase, not decrease, its dose to generate more response in treated patients. Indeed, Dr. Miller opines that "a ***direct correlation*** exists between the dose and length of administration of cladribine and level of lymphocyte suppression." Ex. 1002, ¶91. In other words, Dr. Miller suggests that a direct causal, dose-dependent relationship exists between cladribine dose and lymphocyte suppression level, such that a higher cladribine dose would lead to greater suppression of lymphocytes. *See id.* (Rice discloses "a higher dose of cladribine caused a more profound reduction of lymphocyte counts"). Conversely, Dr. Miller suggests that a lower cladribine dose or shorter dosing length would lead to decreased suppression of lymphocyte levels. For example, Dr. Miller references Selby's "dose-dependent decreases in lymphocyte counts" resulting from use of a lower treatment dose. *Id.*, ¶92 ("Selby reports that '[w]hen compared to the higher dose regimen [Beutler's

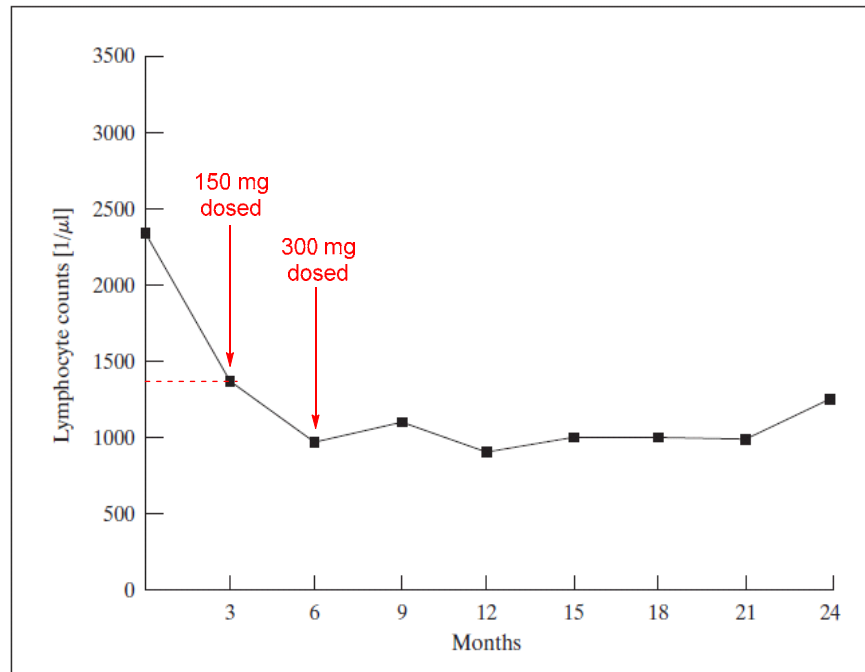
regimen], the rate of decline in the CD4 count using our [lower dose] regimen was less rapid.” (alterations in original) (quoting Ex. 1047, 297)).

In particular, Petitioner asserts that “the primary goal of [MS] treatment is to reduce signs or symptoms of MS, for example, *decrease lymphocyte count, reduce relapse rate*, and postpone disease progression.” Pet. 16-17. Petitioner further contends that cladribine “can reduce the number of relapses by causing prolonged, profound *suppression* of lymphocyte counts” (*id.*, 36 (internal quotations omitted)), where “a decrease in the lymphocyte count to $1 \times 10^9/\text{L}$ (or $1000/\mu\text{L}$) or below constitutes ‘suppression.’” Ex. 1002, ¶32. But based on Dr. Miller’s opinion of a “direct correlation” (*id.*, ¶91), between cladribine dose and lymphocyte suppression, a POSA would have been concerned that decreasing Stelmasiak’s dose (4.0-5.8 mg/kg if calculated by body weight) to the claimed induction dose would risk resulting in insufficient lymphocyte suppression and ineffective treatment of RRMS or early SPMS. As such, under Dr. Miller’s “direct correlation” theory, a POSA would not have been motivated to reduce Stelmasiak’s dose to arrive at the claimed about 1.7-3.5 or about 1.7 mg/kg for the induction period.

According to Petitioner and Dr. Miller, “a *sustained reduction* of lymphocytes, e.g. below $1000/\mu\text{L}$, [is] characteristic of a treatment response” (*id.*, ¶16), and “[a] positive response to the therapy was achieved when lymphocyte

count dropped below about 1,000 lymphocytes per microliter (μL) of blood.” Pet. 16, n.6. But Figure 1 of Stelmasiak shows that lymphocyte levels did not drop below 1000 cells/ μL until Stelmasiak’s full 300 mg dose of oral cladribine was given at month 6. Ex. 1013, 5. In comparison, Bodor uses a lower dose (100-140 mg) and shorter dosing period (two months). Based on Dr. Miller’s “direct correlation” theory (Ex. 1002, ¶91), a POSA would have expected Bodor’s lower dose and two-month dosing period to result in less lymphocyte suppression than Stelmasiak’s 300 mg dose over six months. Indeed, as shown in the annotated version of Stelmasiak’s Figure 1 below, after administration of 150 mg of oral cladribine at month three, lymphocyte levels remained at a level well above 1000 cells/ μL (~1350 cells/ μL). Ex. 1013, 5. Under Dr. Miller’s theory, a POSA would have expected that lowering the cladribine dose from 150 mg to Bodor’s maximum 140 mg dose would be even less likely to reduce lymphocyte levels below 1000 cells/ μL , especially in view of the lower bioavailability (39-43%) reported in Bodor, and thus would be insufficient to result in an effective MS treatment, according to Dr. Miller.

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



Therefore, based on Petitioner’s arguments and the “direct correlation” opinion of its declarant, a POSA considering Bodor and Stelmasiak would not have been motivated to start with Bodor’s oral cladribine dose of 100-140 mg administered over two months in an induction period or to reduce both Stelmasiak’s dose and dosing period to arrive at the claimed induction period dose of about 1.7-3.5 or 1.7 mg/kg, as Stelmasiak teaches that 300 mg oral cladribine (4.0-5.8 mg/kg if calculated by patient weight) with six-month dosing is required to suppress lymphocytes to the levels (≤ 1000 cells/ μ L) Petitioner associates with MS treatment efficacy.

3. A POSA Would Not Have Been Motivated To Re-Treat Patients After Bodor's 10-Month Cladribine-Free Period

Petitioner contends that following “Bodor’s ‘two months on/ten months off’ cycle, POSAs would have expected some or all patients to exhibit a breakthrough disease (a *relapse*) that would require further treatment.” Pet. 35. But based on Petitioner’s own theory that cladribine “can reduce the number of relapses by causing prolonged, profound *suppression* of lymphocyte counts,” (*id.*, 36 (internal quotations and citations omitted)), a POSA would not have been motivated to wait until after Bodor’s 10-month cladribine-free period to re-treat patients.

As discussed above, while Bodor does not teach or suggest re-treatment with cladribine after its 10-month cladribine-free period, Stelmasiak teaches cladribine re-treatment after *two months* of no cladribine (at month nine). Figure 1 of Stelmasiak indicates that lymphocyte count after the two-month cladribine-free period, i.e., at month nine, had already increased beyond 1000 cells/ μ L, even when 300 mg of cladribine, a dose significantly higher than Bodor’s 100-140 mg dose, was used in the initial treatment. Based on Dr. Miller’s argument that “a sustained reduction of lymphocytes, e.g. below 1000/ μ L, [is] characteristic of a treatment response,” a POSA would not have been motivated to prolong Stelmasiak’s cladribine-free period to 8-10 or 10 months as claimed. *See* Ex. 1002, ¶16; Pet. 16, n.6. Instead, under Petitioner’s theory, a POSA would have been motivated to

resume cladribine dosing after a two-month resting period (as was done in Stelmasiak), especially because Bodor's proposed oral cladribine dose and bioavailability (100-140 mg, 39.1-43.1%, respectively) are both lower than Stelmasiak's oral dose and bioavailability (300 mg, 50%, respectively).

Petitioner further argues that in administering re-treatment after Bodor's 10-month cladribine-free period, "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." Pet. 36-37. But as discussed above (Section V.A.2), this was not the "general immunosuppression framework common with MS therapies."

Even assuming a POSA would have considered readministering cladribine, under Petitioner's lymphocyte suppression theory, a POSA would not have been motivated to prolong Stelmasiak's cladribine-free period after the initial treatment period and thus would not have waited until after Bodor's 10-month cladribine-free period to re-treat patients.

4. A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed 1.7 Mg/Kg Maintenance Dose

As explained above (Section IV), the challenged claims do not require that the total maintenance dosing be lower than the total induction dosing.

Nevertheless, Petitioner argues that “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 [of Bodor, i.e., 100-140 mg].” *Id.*, 39-40. As support, Petitioner asserts that Stelmasiak’s data indicates “that to maintain an immunosuppressive effect after the induction, a lower dose of cladribine would suffice.” *Id.*, 39. But Stelmasiak’s “immunosuppressive effect” is based on a high initial dose (300 mg) that lowers lymphocyte levels to <1000 cells/ μ L. As discussed above (Section V.B.2), if one were to accept Dr. Miller’s “direct correlation” opinion, a POSA would not have expected Bodor’s lower oral dose of 100-140 mg to achieve sufficient lymphocyte reduction during the induction period, in particular because Stelmasiak’s Figure 1 indicates that an even higher dose (150 mg) did not do so (reaching ~1350 cells/ μ L) and because Bodor’s oral cladribine has a lower bioavailability. Nor would a POSA have expected giving an even lower dose during any alleged re-treatment period to be effective in maintaining reduced lymphocyte levels. As such, a POSA would not have been motivated to reduce the dose in Bodor to arrive at the claimed 1.7 mg/kg maintenance dosing during the maintenance period.

Further, even assuming a POSA would have been motivated to lower Bodor’s 100-140 mg dose, which Petitioner alleges corresponds to 1.4-2 mg/kg (*id.*, 40), Petitioner’s routine optimization argument (*id.*, 41, 55) does not establish

why or how a dose “lower” than 1.4-2 mg/kg would have led a POSA to arrive at the claimed about 1.7 mg/kg maintenance period dosing. *See* Section V.B.5, *infra*.

5. Petitioner’s Routine Optimization Arguments Fail To Explain How A POSA Would Have Been Motivated To Arrive At Claimed Dosing Methods

Petitioner argues that the claimed total induction dose would have been obvious because about 1.7-3.5 mg/kg overlaps with Bodor’s alleged dosing range of about 1.4-2 mg/kg and “[i]t is settled law that ‘even a slight overlap in range establishes a prima facie case of obviousness.’” Pet. 40 (quoting *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003)). But Petitioner is wrong because there is ***no overlap*** between Bodor’s doses and the claimed doses. If the prior art teachings do not at least overlap with claimed subject matter, there is nothing that can be optimized to result in the claims. *See In re Peterson*, 315 F.3d at 1330.

As discussed above, Bodor and Stelmasiak expressly disclose flat, fixed dosing and do not disclose ***any*** weight-based dosing, let alone the alleged weight-based range of about 1.4-2 mg/kg and Petitioner fails to identify any passages to the contrary. *See* Pet. 50-51. As the *TWi* Board held, the “Petitioner has not shown, nor do we find, that Bodor’s teaching of increasing or decreasing the daily dose means shifting to a weight-based dosing method or arriving at a total dosage based on a patient’s weight.” *TWi*, IPR2023-00050, Paper 8 at 21. The only way Petitioner can identify any purported overlap is through improper hindsight, by

arguing that a POSA would have understood that “for an average adult weighing about 70 kg, Bodor’s dose is equivalent to approximately 1.4 to 2 mg/kg.” Ex. 1002, ¶83 (footnote omitted). Thus, there is no overlap between Bodor’s doses and the claimed doses. Petitioner’s argument based on overlapping ranges fails.

Petitioner further argues that the maintenance dose and dosing length are “result-effective” variables and thus “readily optimized parameters” Pet. 41. Petitioner relies on Bodor’s disclosure that cladribine doses can be “fine tun[ed]” and Beutler’s disclosure that “one can tailor the dosage and duration” of cladribine to argue that a POSA would “take Bodor’s two-month treatment period as a starting point for optimization” and “would have arrived at a suitable dose and length of administration[.]” *Id.*, 42-43 (citations omitted). But “obviousness concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations or modifications of prior art to arrive at the claimed inventions.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphasis in original). Here, Bodor does not teach or suggest switching from a flat dosage to a weight-based dosage or fine tuning a weight-based dosage. “Bodor recognized methods involving weight-based dosing in the prior literature and expressly disclosed a different method of treating MS orally with a flat daily dosage of its cladribine complex, independent of a patient’s weight.” *TWi*, IPR2023-00050, Paper 8 at 21. Instead, Bodor suggests fine tuning its daily flat

dosage of 10 mg, without any consideration of patient weight. Petitioner fails to show that Bodor's teaching of fine tuning the daily dose means shifting to a weight-based dosing method or arriving at a total dosage based on a patient's weight.

Further, Petitioner fails to establish why a POSA *would have been motivated* to start from Bodor's flat dose or shorter dosing period given that based on Petitioner's own arguments a POSA would have expected Bodor's dose and dosing length to yield less lymphocyte suppression, relative to Stelmasiak. *Supra*, Section V.B.2. Indeed, as of 2004, nothing in the prior art taught a POSA how the combination of the different variables—dose, length and number of dosing periods or drug-free periods—would impact the treatment of MS or what specific combination (if any) would result in a safe and effective MS treatment method. Instead, the art taught that “[t]here is still more to be learned about optimal cladribine dosages, ideal timing for retreatment and how cladribine compares with other agents used to treat MS.” Ex. 1016, 431.

Petitioner's simplistic suggestion that a POSA would have arrived at the claimed method by routine optimization ignores the infinite number of combinations of dose/dosing period length and number/drug-free period length and number. Petitioner fails to establish that there would have been a finite number of

identified and predictable solutions and provides no motivation as to **which** specific combination to pick.

Where ... a defendant urges an obviousness finding by merely throw[ing] metaphorical darts at a board in hopes of arriving at a successful result, but the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, courts should reject hindsight claims of obviousness.

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig., 676 F.3d 1063, 1070 (Fed. Cir. 2012) (alteration in original) (internal quotations and citations omitted); *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007) (claims not obvious where there was not “a finite number of identified, predictable solutions”).

Importantly, even if a POSA would have been motivated to optimize Bodor’s dose, based on Petitioner’s own theories, she would have been motivated to increase Bodor’s 100-140 mg dose (at 39.1-43.1% bioavailability) to **more than** Stelmasiak’s 300 mg oral dose (at 50% bioavailability), and to shorten the cladribine-free period to a maximum of 2 months, to ensure sufficient lymphocyte reduction (≤ 1000 cells/ μL) and to improve upon the “partial” response in Stelmasiak. *See* Ex. 1013, 6-7.

Thus, Petitioner’s contention that a POSA would have modified Bodor’s method of dosing its cladribine-complex to depend on patient weight or to provide a total induction dosage of about 1.7-3.5 mg/kg or a total maintenance dosage of about 1.7 mg/kg as claimed, is improperly guided by hindsight and not suggested by the teachings of Bodor and Stelmasiak, or the knowledge in the art. As discussed above, the Board in *TWi* denied institution of an obviousness ground based on Bodor and Rice, where Rice teaches subcutaneous weight-based dosing. *See TWi*, IPR2023-00050, Paper 8 at 21 (“[I]t is apparent that [the] Petitioner’s contention that a skilled artisan would have modified Bodor’s method of dosing its cladribine-complex to depend upon a patient’s weight or to provide a total dosage that is about 1.7 mg/kg at the end of the induction period and at the end of the maintenance period, as recited by the challenged claims, is improperly guided by hindsight and not the teachings of Bodor, or in view of the knowledge in the art.”), 26 (“In other words, the motivation to modify Bodor’s method of dosing to a weight-based dosage or to achieve a total dose based on weight remains missing.”). Here, Petitioner’s obviousness ground is solely based on art teaching *flat* dosing (Bodor and Stelmasiak)—neither reference teaches or suggests weight-based dosing—and thus the deficiencies are even more evident than the combination of Bodor and Rice in *TWi*. Petitioner fails to establish any motivation for a POSA to modify Bodor’s method based on Stelmasiak to arrive at a method for treating

RRMS or early SPMS comprising a total induction period dose of about 1.7 or 1.7-3.5 mg/kg and a maintenance period about 8-10 or 10 months after the induction period, lasting about 2- or 2-4 months with a total dose of about 1.7 mg/kg, as claimed.

C. Petitioner Has Not Established Any Reasonable Expectation Of Success In Combining Bodor's Method With Stelmasiak To Arrive At The Challenged Claims

Petitioner's cursory two-page discussion of a reasonable expectation of success is far from sufficient to demonstrate that a POSA would have "reasonably expected to treat MS by orally administering Bodor's cladribine following the claimed steps of an induction, cladribine-free, maintenance, and cladribine-free periods." Pet. 44-46. Particularly in view of Petitioner's reliance on "Stelmasiak's success" (*id.*, 6) and Petitioner's arguments that cladribine "can reduce the number of relapses by causing prolonged, profound suppression of lymphocyte counts" (*id.*, 36 (quotations and citations omitted)), where a decrease in lymphocyte levels to ≤ 1000 cells/ μ L constitutes "suppression" and a "positive response" (Ex. 1002, ¶32; Pet. 16, n.6), Petitioner fails to show how a POSA would have reasonably expected success in modifying Bodor's method based on Stelmasiak.

1. A POSA Would Not Have Reasonably Expected To Arrive At The Claimed Weight-Based Dosing

As discussed above (Section V.A.1), Bodor and Stelmasiak fail to teach or suggest weight-based dosing as claimed. Furthermore, Stelmasiak not only teaches flat dosing rather than weight-based dosing, but also reinforces flat dosing by explaining that “[t]here was *no indication* that a ‘good response’ is related to the actual cladribine dose per body weight.” Ex. 1013, 7. For example, “there was *no correlation* between the depth of lymphocyte nadir, or the magnitude of lymphocyte count reduction from the initial value, and the *drug dose expressed per kg of body weight*[.]” *Id.*, 6. A POSA would have understood that Stelmasiak teaches the effects of cladribine were unrelated to the cladribine dose per body weight, and thus would not have had a reasonable expectation of success in modifying Bodor and Stelmasiak to arrive at the weight-based dosing of the challenged claims.

2. A POSA Would Not Have Reasonably Expected To Arrive At The Claimed 1.7-3.5 Mg/Kg Total Induction Dose By Modifying Bodor’s Method In View Of Stelmasiak

As discussed above, based on Dr. Miller’s “*direct correlation*” opinion, a POSA would not reasonably have expected Bodor’s oral cladribine dose of 100-140 mg (39-43% bioavailability) to yield “a *sustained reduction* of lymphocytes, e.g. below 1000/ μ L” for treating RRMS or early SPMS. *See* Section V.B.2

(annotated Figure 1 showing administration of Stelmasiak's 150 mg oral cladribine (50% bioavailability) and corresponding lymphocyte levels well above 1000 cells/ μ L (~1350 cells/ μ L)).

Further, even if a POSA calculated Stelmasiak's flat dosage based on patient weight, Stelmasiak's 300 mg "induction" dosing would correspond to 4.0-5.8 mg/kg, well above the claimed weight-based induction dose. *See* Ex. 1013, 5. As discussed above in Section V.B.2, (1) given that these dosages were reported to only result in a "partial" response and (2) based on Dr. Miller's "direct correlation" opinion and Petitioner's statement that lowering lymphocytes to $\leq 1,000$ cells/ μ L constitutes "[a] positive response," a POSA would have had concerns that decreasing Stelmasiak's dose could result in insufficient lymphocyte suppression and not effectively treat RRMS or early SPMS, and thus would not have had a reasonable expectation of success in arriving at the claimed dosing regimen based on Bodor and Stelmasiak.

3. A POSA Would Not Have Reasonably Expected To Treat RRMS Or Early SPMS Using The Claimed About 8-10- Or 10-Month Cladribine-Free Period By Modifying Bodor's Method In View Of Stelmasiak

As discussed above (Section V.B.3), Figure 1 of Stelmasiak indicates that after the two-month cladribine-free period, i.e., at month nine, the lymphocyte count had already increased beyond 1000 cells/ μ L and did not decrease until after

another dose of cladribine was administered. Based on Dr. Miller's opinion that "a sustained reduction of lymphocytes, e.g. below 1000/ μ L, [is] characteristic of a treatment response" and the "***direct correlation*** [that] exists between the dose and length of administration of cladribine and level of lymphocyte suppression," a POSA would not have reasonably expected that prolonging Stelmasiak's cladribine-free period to arrive at the claimed cladribine-free period of about 8-10 or 10 months would be effective to treat RRMS or early SPMS. *See* Ex. 1002, ¶¶16, 91; Pet. 16, n.6. Rather, under Petitioner's own theory, a POSA would have expected that doing so would have led to elevated lymphocyte levels, i.e., above 1000 cells/ μ L, which under Petitioner's theory would not be sufficient to treat RRMS or early SPMS.

Additionally, under Petitioner's theory, a POSA would have expected that prolonging Stelmasiak's two-month cladribine-free period to about 8-10 months and combining it with Bodor's 100-140 mg dose would not have sufficiently suppressed lymphocyte levels. *See* Section V.B.2 (annotated Figure 1), *supra*. As such, according to Petitioner's theories, a POSA would not have reasonably expected that prolonging Stelmasiak's two-month cladribine-free period to about 8-10 month as claimed would have been effective at maintaining lymphocyte levels to ≤ 1000 cells/ μ L or treating RRMS or early SPMS.

4. A POSA Would Not Have Reasonably Expected To Arrive At The Claimed About 1.7 Mg/Kg Maintenance Dose By Modifying Bodor's Method In View Of Stelmasiak

Petitioner repeatedly argues that Stelmasiak shows a “lower dose of cladribine in the maintenance period, compared to the induction period, was sufficient to maintain the decreased lymphocyte count.” Pet. 5-6, 38-39. But Stelmasiak’s data is based on an initial dose of 300 mg over six months. Figure 1 in Stelmasiak shows that giving 150 mg oral cladribine failed to lower lymphocyte levels to ≤ 1000 cells/ μ L. Section V.B.2, *supra*. As such, based on Dr. Miller’s “direct correlation” theory (Ex. 1002, ¶91), a POSA would not have reasonably expected that re-treatment with a lower dose (especially after ten months of no treatment), would have “maintain[ed] the decreased lymphocyte count” at ≤ 1000 cells/ μ L.

Thus, based on Petitioner’s theory, a POSA considering Bodor and Stelmasiak would not have reasonably expected that a maintenance dose of less than 100-140 mg cladribine, after using 100-140 mg for induction, would have been effective to hold lymphocyte levels at ≤ 1000 cells/ μ L to treat RRMS or early SPMS. Based on Petitioner’s theory and Stelmasiak’s teachings, a POSA would not have reasonably expected to arrive at the claimed about 1.7 mg/kg maintenance period dose by modifying Bodor’s method in view of Stelmasiak.

5. A POSA Would Not Have Reasonably Expected To Arrive At A Safe And Effective Method Of Treating RRMS Or Early SPMS As Claimed By Modifying Bodor's Method In View Of Stelmasiak

Petitioner relies on studies that showed cladribine “to cause prolonged, profound suppression of lymphocyte counts” to argue a POSA would have had a reasonable expectation of success in modifying Bodor’s method based on Stelmasiak’s study. Pet. 45 (internal quotations and citations omitted). But as of December 2004, numerous MS clinical trials concluded that high doses equivalent to at least 4.1 mg/kg oral cladribine (i.e., intravenous or subcutaneous doses of 2.1, 2.8, or 3.65 mg/kg (*supra* n.2)) were “*not found to be effective against MS* clinical deterioration.” See Ex. 1015, 1754; Ex. 1001, 2:37-42; Ex. 1016, 425 (Table III).

In addition to the reportedly ineffective MS trials, a POSA would have been concerned about cancer risks associated with using cladribine. See Ex. 1031, 43-44 (“Repeated treatment [with cladribine] raises long-term toxicity issues including ... an increase in the incidence of malignancy, known to occur in association with other long-term immunosuppressive treatments.”); Ex. 1014, 5 (“[S]ince [cladribine] is incorporated into DNA, the possibility of malignancies occurring long after administration ... cannot be dismissed.”). Given the concern about malignancy risk associated with cladribine and the absence of guidance from the prior art, a POSA would not have had any reasonable expectation of success in

selecting a dosing regimen from among numerous possible combinations of different variables (dose, length and number of dosing periods or drug-free periods) to arrive at the claimed specific combination of these variables as a safe and effective cladribine treatment for MS. *See* Ex. 2001, 5-6 (“Recommended Dosage”), 24-25 (“Clinical Studies”). A POSA would not have had any reasonable expectation that modifying Bodor’s method in view of Stelmasiak would have led to a safe and effective treatment for RRMS or early SPMS.

Further, Petitioner’s simplistic suggestion that “[a] POSA would have arrived at a suitable dose and length of administration, for example, by regularly measuring the patient’s lymphocyte counts and evaluating the efficacy of a given dose based on the changed in the count” (Pet. 43), ignores the infinite number of combinations of dose/dosing period length and number/drug-free period length and number, and provides no reasonable expectation as to *which* specific combination would work. As of 2004, nothing in the prior art taught a POSA how the combination of the different variables—dose, length and number of dosing period or drug-free periods—would impact the treatment of MS or what specific combination (if any) would result in a safe and effective MS treatment method. Instead, the art taught that “[t]here is still more to be learned about optimal cladribine dosages, ideal timing for retreatment and how cladribine compares with other agents used to treat MS.” Ex. 1016, 431. “When a field is unreduced by

direction of the prior art, and when prior art gives no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, an invention is not obvious to try.” *Unigene Lab ’ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (quotations and citations omitted). In light of the infinite number of combinations of dose, dosing periods, and drug-free periods, with no predictability as to which combination would work, Petitioner fails to present a reasonable expectation of success in arriving at the claimed specific regimen to treat RRMS or early SPMS.

In sum, given (1) the express teachings of Bodor and Stelmasiak on flat dosing; (2) the lack of any reasonable expectation of success in arriving at the claimed about 1.7-3.5 or 1.7 mg/kg induction period dosing, the claimed about 8-10 or about 10 month cladribine-free period, or the claimed about 1.7 mg/kg maintenance period dosing; and (3) the infinite number of potential combinations of doses, dosing period length and number, and drug-free period length and number, Petitioner fails to establish how or why a POSA would have reasonably expected success in modifying Bodor’s flat-dosing regimen in view of Stelmasiak’s high-dose, flat-dosing method to arrive at the claimed method.

VI. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

The FDA-approved method of using PO’s successful MAVENCLAD[®] product practices the method recited in the challenged claims, and has been shown

to surprisingly “significantly lower[] the annualized relapse rate” for treated patients and was approved by the FDA for treating MS patients. *See* Ex. 2001, 5-6 (“Recommended Dosage”), 24-25 (“Clinical Studies”). PO reserves the right to argue objective indicia at a later stage in this proceeding, should the Board institute trial.

VII. THE PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 325(d)

Under *Advanced Bionics*, the Board may exercise its discretionary denial by considering “whether the same or substantially the same art [or arguments] previously was presented to the Office;” and “if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential). Both prongs strongly favor discretionary denial.

A. The Office Already Considered Petitioner’s Alleged Prior Art And Arguments

In evaluating whether the same or substantially the same art or arguments were presented previously to the Office, the Board considers *Becton Dickinson* factors (a), (b), and (d): (a) similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative

nature of the asserted art and the prior art evaluated during examination; and (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or PO distinguishes the prior art. *See id.* at 9-10; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017)). Here, all three factors favor denial.

1. *Becton Dickinson* Factors (a) And (b): Asserted Art Was Considered During Examination

Petitioner's single ground relies on Bodor and Stelmasiak. Bodor was considered during examination. The Examiner raised rejections based on Bodor in Office Actions during prosecution of the '903 patent and its parent patent, the '947 patent, which were overcome by PO, and the Examiner allowed the claims of the '903 and '947 patents. Ex. 1004, 100-103, 105-106, 120-127, 135-138, 140-141, 148-153, 157-158, 174-178; Ex. 1025, 220-226, 246-255, 298-304. Thus, Bodor was fully evaluated and overcome during examination.

Petitioner acknowledges "Stelmasiak was cited in an IDS[.]" Pet. 65; *see also* Ex. 1004, 114. Further, during prosecution, the Examiner relied on Grieb. Notably, Grieb co-authored the Stelmasiak publication, and Stelmasiak co-authored the Grieb publication and their disclosures are not materially different. *Compare* Ex. 1023, 323 (author list), *and* 324 ("Materials and Methods"; Fig. 1),

with Ex. 1013, 4 (author list), and 5 (“Materials and Methods”; Figure 1).

Accordingly, Stelmasiak was before the Office and the substance was considered during Examination, thus satisfying *Advanced Bionics* step one and demonstrating that *Becton Dickinson* Factors (a) and (b) weigh strongly in favor of denial.

2. *Becton Dickinson* Factor (d): Petitioner’s And The Examiner’s Arguments Are Not Materially Different

Petitioner attempts to repackage the same arguments already evaluated and overcome during prosecution.

First, as the Examiner did during prosecution, Petitioner argues that Bodor teaches the treatment periods as claimed. *Compare* Pet. 50 (“a POSA would have understood the first two months of Bodor’s treatment regimen to be ‘an induction period’”), 51 (“Bodor teaches ‘a cladribine-free period of between about 8 and about 10 months’”), 52 (“Bodor teaches a retreatment period after the cladribine-free period”), and Ex. 1002, ¶86 (Bodor teaches “that cladribine is re-administered at the end of the specified cladribine-free period—otherwise, the specified length of time of the cladribine free period is meaningless”), with Ex. 1004, 100 (“[B]ecause Bodor states ‘10 months of no treatment’, it is implied that following these 10 months, treatment with cladribine is resumed”), and Ex. 1025, 221 (“[Bodor] ... address[es] the following recited limitations ...: an induction period ... the cladribine-free period ... lasts up to 10 months ... the maintenance period

lasts up to 4 months”). Accordingly, the Examiner already considered Petitioner’s arguments as to whether Bodor taught the claimed treatment periods.

Second, Petitioner relies on Stelmasiak to allegedly teach “cyclical” regimens that “included an induction, a cladribine-free, and a maintenance period,” in which “cycles (or courses) of cladribine administration are repeated at a given interval.” Pet. 5, n.1; *id.*, 35. However, Petitioner’s argument based on Stelmasiak is substantially the same as the Examiner’s argument based on Grieb (Ex. 1023)—that Grieb “clearly indicate[s] a repetitive treatment regimen comprising periods of cladribine therapy separated by periods of no treatment[.]” Ex. 1004, 138. As discussed above, Grieb has substantially the same disclosure as Stelmasiak and discloses the same cladribine dosing regimen as Stelmasiak. *Compare* Ex. 1023, 324 (“Materials and Methods”), *with* Ex. 1013, 5 (“Materials and Methods”). Given Petitioner’s reliance on a dosing method (i.e., Stelmasiak’s) that is identical to Grieb’s, Petitioner relies on the same prior art and arguments evaluated by the Examiner. Further, during prosecution of the parent ’947 patent, the Examiner argued that Beutler ’214 (Ex. 1026) discloses that “[c]ourses (cycles) of administration can also be repeated at monthly intervals.” Ex. 1025, 222. Thus, Petitioner makes the same argument raised by the Examiner and overcome by PO, now based on a different reference, Stelmasiak.

Third, Petitioner further relies on Stelmasiak to “teach[] that the total [maintenance] dose ... is lower than the total [induction] dose ... the limitation that the Examiner expressly found missing from Bodor and Beutler[.]” Pet. 55, 65. However, Petitioner acknowledges the Examiner relied on Bloom (Ex. 1033) for this limitation. Pet. 10. Indeed, the Examiner argued “Bloom teaches that treatment dosages are lowered with each successive use of the drug[.]” Ex. 1004, 104; *see also* Ex. 1025, 226. Thus, Petitioner again simply makes the same argument raised by the Examiner and overcome by PO, now based on a different reference, Stelmasiak. *See Dafron Elecs. Corp. v. Shipman*, IPR2022-01008, Paper 11 at 13-14 (P.T.A.B. Dec. 2, 2022) (denying institution under § 325(d) because “the art presented in the Petition is cumulative and is substantially the same as those previously presented to the Office” and the Petitioner has not demonstrated material error by the Office).

Fourth, Petitioner also relies on Stelmasiak’s lowering of lymphocyte levels to ≤ 1000 cells/ μ L to assert a reasonable expectation of success. Pet. 45; Sections V.C.2-V.C.4, *supra*. Likewise, the Examiner argued that Grieb’s treatment—the same as Stelmasiak’s—“was effective to provide a progressive reduction in lymphocytes to around 1000/ μ L on average” and that a POSA “would be successful in the treatment of MS based upon the demonstrated effectiveness in *reducing activated lymphocytes* reported by Grieb[.]” Ex. 1004, 102, 105, 140

(“Grieb indicat[es] that cladribine treatment significantly reduced lymphocyte numbers[.]”). Indeed, Stelmasiak and Grieb disclose substantially the same lymphocyte results. *Compare* Ex. 1013, 5 (“Lymphocyte counts dropped from ... 2336 ± 595 per μl (mean $\pm$ S.D.) to 968 ± 229 per μl at 6 months[.]”), *with* Ex. 1023, 323 (“Progressive lymphocyte reduction to 1000/ μl on average ... was observed[.]”), *and* 324 (“[T]he nadir of lymphocyte counts [was] after 6 months of the study[.]”). The Examiner thus considered the same argument based on substantially the same art.

Thus, the Examiner considered Petitioner’s arguments as to whether the prior art disclosed a total maintenance period dose lower than the total induction period dose, now based on Stelmasiak rather than Bloom, and Petitioner’s arguments as to a reasonable expectation of success in treating MS based on lymphocyte levels, now based on Stelmasiak rather than Grieb. The Petition at best repeats the same arguments overcome by the PO during prosecution based on different references that were before the Examiner.

Accordingly, *Becton Dickinson* Factor (d) weighs strongly in favor of denial.

B. Petitioner Has Not Identified A Material Error By The Examiner

In evaluating whether Petitioner has demonstrated material error by the Office, the Board considers *Becton Dickinson* factors (c), (e), and (f): (c) the extent to which the asserted art was evaluated during examination, including whether the

prior art was the basis for rejection; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 9-10. Petitioner has failed to identify any material error or present additional evidence or facts that warrant institution.

1. *Becton Dickinson* Factor (c): Asserted Art Was Evaluated During Examination

Factor (c) favors denial because Petitioner's asserted art was evaluated thoroughly during prosecution. As discussed above (Section VII.A.1), Bodor was fully evaluated during prosecution of the '903 and '947 patents.

Although the claims were not rejected over Stelmasiak, Factor (c) does not require that "each and every argument set forth in the petition must have been previously presented[.]" *Ziegmann v. Stephens*, IPR2015-01860, Paper 13 at 19 (P.T.A.B. Sept. 6, 2017). As shown by the signed IDS and admitted by Petitioner, the Examiner considered Stelmasiak. Ex. 1004, 114; Pet. 65; *see also R.J. Reynolds Vapor Co. v. Fontem Holdings I B.V.*, IPR2017-01642, Paper 10 at 6 (P.T.A.B. Jan. 16, 2018) (references listed on an IDS and signed off by Examiner but not discussed were "considered").

Nevertheless, Petitioner argues the Examiner “failed to apply Stelmasiak” even though Stelmasiak allegedly teaches “the limitation the Examiner expressly found missing from Bodor and Grieb,” i.e., a lower, total maintenance dose.

Pet. 65. But according to Petitioner, the Examiner “rel[ied] in part on Bloom” for that missing claim limitation. *Id.*, 9-10. Thus, under Petitioner’s theory, Stelmasiak is cumulative: the Examiner would not have needed Stelmasiak for its alleged “lower” dosage teachings.

Further, the Examiner rejected the claims over the combination of Bodor, Bloom, and Grieb. As discussed above (Sections V.B.2, VII.A.1, and VII.A.2), Grieb and Stelmasiak disclose the same dosing schedule and substantially the same lymphocyte count results—their disclosures are not materially different. Thus, the subject matter of Stelmasiak was evaluated, and the Examiner’s rejections based on this subject matter were overcome during examination.

Accordingly, based on Petitioner’s own arguments, the addition of Stelmasiak does not warrant reconsideration of prior art and arguments previously considered by the Office.

2. *Becton Dickinson* Factor (e): Petitioner Has Not Identified Material Examiner Error

Material error can include “misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the

challenged claims” or legal error. *Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9, n.9.

Petitioner fails to identify any error by the Examiner.

Petitioner first argues that PO had “argued to the Examiner that Grieb taught the use of a 6-month induction period” and the Examiner erred by “accept[ing] Merck’s incorrect application of Grieb’s uninformative teachings to dismiss Bodor’s express teachings of a two-to-four month induction period.” Pet. 64. According to Petitioner, Grieb “does not inform a POSA as to how long of an induction period to use with Bodor’s improved tablet.” *Id.* But as discussed above (Section V.B.2), a POSA would have understood Grieb’s oral cladribine formulation provides higher bioavailability (50%) than Bodor’s (39.1-43.1% bioavailability), and Petitioner’s own argument of a “[p]reference for ... increased bioavailability” (Pet. 35), suggests that a POSA would have been motivated to start with Stelmasiak’s oral cladribine formulation administered over six months, rather than Bodor’s formulation administered over two months. Further, as discussed above (Section V.B.2), under the “direct correlation” theory of Petitioner’s declarant, a POSA would not have expected Bodor’s oral dose (100-140 mg) to similarly lower lymphocyte levels. Thus, Petitioner’s own arguments and the opinion of its declarant suggest that the Examiner did not err. Petitioner’s disagreement with the Examiner’s conclusion does not render its argument new,

nor does it indicate any error on behalf of the Examiner. As the Board explained in *Advanced Bionics*, even “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Advanced Bionics*, IPR2019-01469, Paper 6 at 9.

This is far different than the situation in *Agrofresh Solutions, Inc. v. Lytone Enterprise, Inc.*, cited by Petitioner (Pet. 64), in which the Board found that additional evidence not considered by the Examiner sufficiently showed a reasonable expectation of success, thereby undermining the Examiner’s conclusions. *See* IPR2021-00451, Paper 11 at 13-14, (P.T.A.B. Jul. 27, 2021). As discussed above, Petitioner fails to show that the Examiner erred in her application of Bodor or Grieb. Petitioner merely disagrees with the Examiner’s conclusions; this does not amount to material error.

Petitioner next alleges the Examiner erred by “failing to apply [Stelmasiak’s] teachings regarding lowering the total dose for the maintenance phase[.]” Pet. 63. But as discussed above in Section VII.B.1, (1) the Examiner would not have needed Stelmasiak because the Examiner had Bloom and under Petitioner’s theory, Stelmasiak is cumulative; (2) during examination, the Examiner also applied Grieb, which discloses the same dosing schedule as Stelmasiak.

Here, unlike *Vudu Inc. v. Ideahub, Inc.*, cited by Petitioner (Pet. 65), the Examiner evaluated Petitioner’s cited art and applied the same or substantially the same art in rejecting the claims. *See* IPR2020-01689, Paper 16 at 19 (P.T.A.B. Apr. 19, 2021); *see also* *Dafron Elecs.*, IPR2022-01008, Paper 11 at 13-14. Accordingly, based on Petitioner’s own arguments, the Examiner did not err by not applying Stelmasiak in a rejection.

Lastly, Petitioner erroneously claims that “Merck did not, and could not, dispute that Bodor taught a cyclical treatment of MS using cladribine[.]” Pet. 10. But during prosecution, PO argued Bodor “fail[s] to teach a cladribine-free period of between about 8 and 10 months followed by a ‘maintenance period’” and “nowhere in [Bodor] is there any discussion about *repeating* a treatment course at any point in time ... that could be construed as a ‘maintenance period’.” Ex. 1004, 121. Based on Petitioner’s own interpretation of “cyclical” treatment—i.e., cyclical dosing regimens “included an induction, a cladribine-free, and a maintenance period[.]” (Pet. 5)—PO clearly disputed that Bodor taught a cyclical MS treatment using cladribine.

Petitioner has not established any examiner error and Factor (e) favors denial.

3. *Becton Dickinson* Factor (f): Additional Evidence Does Not Warrant Reconsideration

Petitioner has not presented any additional evidence that warrants reconsideration of the prior art and arguments previously considered by the Office.

Thus, the above analysis of *Becton Dickinson* factors (c), (e), and (f) demonstrates Petitioner has not shown that the Office materially erred in allowing the challenged claims. Accordingly, the Board should deny institution under § 325(d).

VIII. CONCLUSION

For at least the reasons stated herein, PO respectfully requests that the Board deny institution.

/Emily R. Whelan/
Emily R. Whelan (Reg. No. 50,391)

PATENT OWNER'S LIST OF EXHIBITS

Exhibit No.	Description
2001	MAVENCLAD [®] Package Insert (September 2022)

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response contains 13,978 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. §42.24(d), excluding the parts exempted from the word count by 37 C.F.R. §42.24(a)(1).

By: /Emily R. Whelan/
Emily R. Whelan (Reg. No. 50,391)

CERTIFICATE OF SERVICE

I hereby certify that on June 26, 2023, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibit 2001
- Word Count Certification Under 37 CFR §42.24(d)

to be served via e-mail, as consented to by Petitioner, on the following attorneys of record:

cellison-PTAB@sternekessler.com
opartington-PTAB@sternekessler.com
cvira-PTAB@sternekessler.com
jcrozendaal-PTAB@sternekessler.com
PTAB@sternekessler.com

By: /Cindy Kan/

Cindy Kan (Reg. No. 76,385)
Wilmer Cutler Pickering Hale and Dorr LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
Tel: 212-295-6470
Email: cindy.kan@wilmerhale.com