

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

MERCK SERONO S.A.,
Patent Owner.

Case IPR2023-00481
Patent 8,377,903

PATENT OWNER'S RESPONSE

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STATUTES, RULES, AND REGULATIONS

Pre-AIA 35 U.S.C. § 102	<i>passim</i>
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I. INTRODUCTION

By 2004, skilled artisans in the field of neurology, including Petitioner’s declarant Dr. Miller, did not expect cladribine to be of clinical benefit in treating multiple sclerosis (“MS”), much less with any durability and without dangerous side effects. Ex. 2005, 45, 67; Ex. 2031, 753; Ex. 2004, 341; Ex. 2011, 3. Several studies had reported that cladribine was either not clinically effective, or had inconsistent outcome measure readouts, or raised significant safety concerns. *See, e.g.*, Ex. 1018, 1153; Ex. 1016, 432; Ex. 1031, 43-44; Ex. 1023, 326. Nonetheless, the ’903 patent’s inventors persisted in designing a dosing regimen for cladribine that would be safe and effective, ultimately discovering the novel and unique dosing regimen claimed in the challenged claims, which is unexpectedly effective not just during treatment, but with sustained benefits for up to almost ***11 years*** after treatment, while maintaining patient safety. *See* Ex. 2036, 719, 728.

The centerpiece of Petitioner’s evidence is the declaration of Dr. Miller, but his opinion that the challenged claims are allegedly obvious should be given no weight because it conflicts with pre-IPR statements by Dr. Miller establishing exactly the opposite. Petitioner’s single ground of invalidity—alleged obviousness over Bodor and Stelmasiak—fails.

Bodor discloses in passing a dosing ***regimen*** that was disclosed ***by the inventors of the ’903 patent*** (on a confidential basis) to Bodor’s assignee IVAX as

part of a joint research program between IVAX and Serono.¹ Because Bodor's dosing regimen was attributable to the inventors of the '903 patent and not "by another," it cannot be used as prior art against the '903 patent. But even if Bodor *were* prior art, Bodor and Stelmasiak do not teach or suggest the claimed weight-based dosing or maintenance period.

Moreover, there is nothing that would have motivated a person of ordinary skill in the art ("POSA") to modify the teachings of Bodor or Stelmasiak to arrive at the disclosed regimens. Nor would a POSA have recognized that Bodor's or Stelmasiak's dosing regimen was *effective*: Bodor discloses no clinical results for its regimen, and Stelmasiak discloses only *partial* patient response.

There is even less motivation to cobble together Petitioner's cherry-picked parts of the regimens disclosed in Bodor and Stelmasiak to achieve the claimed regimen. Relying impermissibly on hindsight, Petitioner fails to show that a POSA would have been motivated to select those features, much less combine them with a reasonable expectation of success.

Hindsight also infects Petitioner's contention that the claimed regimen would have resulted from "routine optimization." The complex and variable

¹ Serono is used herein to collectively refer to the challenged patent's owner and its affiliates, including Ares.

nature of MS, its slowly evolving disability over years, and the gradual, long-term nature of disease-modifying agents (“DMAs”) combine to ensure that the treatment effects of any dosing schedule of a DMA can likewise only be assessed over a long time. A POSA would have understood that it would require *years* to evaluate how changes made to an MS drug’s dose and/or dosing schedule would impact clinical outcomes, making “optimization” of the dosing regimen anything but “routine.”

For at least the foregoing reasons, Patent Owner (“PO”) respectfully requests that the Board uphold the challenged claims.

II. STATE OF THE ART

A. MS

In MS, the body’s immune system attacks the central nervous system (CNS), causing destruction of myelin insulating nerve fibers. Ex. 2010, 1, 18, 56; Ex. 1001, 1:26-30; Ex. 1007, 131. By 2004, it was thought that “auto-reactive” lymphocytes, a type of white blood cell, and “[m]any cells and molecules of the immune system ... participate in demyelination.” Ex. 2010, 6, 44; Ex. 1016, 421; Ex. 1007, 131; Ex. 2051, ¶¶39-40.

1. MS Clinical Course and Treatment as of 2004

The clinical subtypes of MS include relapsing remitting MS (“RRMS”) and secondary progressive MS (“SPMS”), which includes an initial, transitional stage

that can be referred to as early SPMS. Ex. 1001, 1:48-50; Ex. 2051, ¶¶41-46; Ex. 1038, 60-63.

By 2004, FDA had approved six DMAs for MS: three beta interferons (Betaseron[®]; Avonex[®]; Rebif[®]), glatiramer acetate (Copaxone[®]), mitoxantrone (Novantrone[®]), and natalizumab (Tysabri[®]). Ex. 2014, 12; Ex. 2015, 3; Ex. 2016, 17; Ex. 2017, 19; Ex. 2018, 29; Ex. 2019, 10; Ex. 2051, ¶50. All were injectables—none was approved for oral administration—and none was dosed by bodyweight.² Ex. 2051, ¶53. These drugs are either immunosuppressants or immunomodulators. *Id.*, ¶¶50-52. Immunosuppressants cause general immune system suppression and are characterized by relatively nonspecific down-regulation of immune function, whereas immunomodulators have more targeted effects and are usually less toxic. *Id.*, ¶49; Ex. 2006, 273. By 2004, all FDA-approved MS drugs were dosed continuously to maintain the pharmacologic and clinical effects of the drug. *See* Ex. 2024, 9; Ex. 2020, 571, 573; Ex. 2025, 1879, 1883; Ex. 2017, 3; Ex. 2051, ¶¶54-57. That is, they were dosed “continuously, without an intended interruption in dosing, because clinical efficacy is tightly linked to the period of dosing.” Ex. 2032, 1923. No FDA-approved MS drug was administered based on the “cyclical” nature of MS. Ex. 2051, ¶¶58-59.

² The recommended dosage of mitoxantrone is 12 mg/m².

2. Outcome Measures In MS Clinical Trials

The mainstay for assessing MS treatment efficacy are clinical outcome variables such as relapse rate and physical disability status, while MRI outcomes can be indicative of disease activity. Ex. 2051, ¶¶60-61; Ex. 2011, III/4. The most widely used measure of physical disability is the Kurtzke Expanded Disability Status Scale (“EDSS”), which measures disability status based on neurologic examination of functional systems throughout the body. Ex. 1010, 1445-49; Ex. 1016, 425-426; Ex. 2051, ¶60.

When assessing MS treatment efficacy, a POSA would have understood that outcome measures should be considered collectively, not individually. Ex. 2051, ¶62. For example, MS studies have shown a dissociation between MRI effects and clinical outcomes. *See, e.g.*, Ex. 1018, 1145. A POSA would have understood that “[a]n important principle when interpreting clinical trial data is that of *coherence*,”³ i.e., all outcomes point to the same effect to confirm treatment efficacy. Ex. 2011, III/4; Ex. 2051, ¶62.

3. Cladribine Investigations For MS

The MS clinical studies on cladribine through 2004 left skilled artisans skeptical about cladribine’s utility for treating MS, including RRMS and early

³ Hereinafter, all emphasis is added unless otherwise noted.

SPMS, due to (1) the reported lack of cladribine clinical efficacy and (2) safety concerns arising from cladribine’s lymphocytotoxic activity. Ex. 2051, ¶¶64-71. For example, in 2000, Petitioner’s declarant Dr. Miller explained that “[i]n recently completed trials of oral myelin, *cladribine*, and sulfasalazine, these agents were found not to be of benefit.” Ex. 2005, 45; *see also* Section VIII.A, *infra*.

A POSA also would have understood that cladribine posed significant long-term safety concerns due to its lymphocytotoxic activity. Ex. 2051, ¶¶72-73. Further, “[r]epeated treatment raises long-term toxicity issues.” Ex. 1031, 43-44.

By 2004, there was at best a “hypothesis” that cladribine “acts by reducing the number of activated lymphocytes,” but the basis for cladribine’s therapeutic effect had not been established. Ex. 2051, ¶74; Ex. 1016, 432; *see also* Ex. 1031, 42.

B. Alleged Prior Art

1. Bodor (Ex. 1022)

Bodor is a PCT application, filed March 2004, teaching and claiming cladribine formulations. Ex. 1022, 5-6. Although the invention in Bodor is clearly directed to cladribine formulations, Petitioner focuses on a 6-line example regimen for treating MS, which teaches neither weight-based dosing nor a maintenance period. *Id.*, 23:15-20; Ex. 2051, ¶75. What it does disclose, however, is the work of the ’903 patent inventors. Ex. 2053, ¶53; Ex. 2055 ¶¶23-27.

As described below, the '903 patent inventors confidentially communicated their work on dosing regimens to IVAX before February 2004. Ex. 2053, ¶¶30-53; Ex. 2055, ¶¶15-18; *infra*, Section VI. This communication from the '903 patent inventors resulted in the 6-line disclosure in Bodor on which Petitioner relies. Ex. 2053, ¶¶50-54; Ex. 2054 ¶¶26-29; Ex. 2055, ¶¶23-27. Because the relevant portion of Bodor is thus not “by another,” as required by 35 U.S.C. § 102(a) and (e), it is not prior art to the '903 patent.

2. Stelmasiak (Ex. 1013)

Stelmasiak is a publication disclosing a cladribine study, without any placebo group, in 10 RRMS patients, in which 4 patients received a high (300 mg), flat oral cladribine dose, followed by 50 mg at month nine and month twelve or fifteen. Ex. 1013, 5; Ex. 2051, ¶77. While some patients “responded” to treatment as assessed by EDSS scores, others did not, and Stelmasiak advised that “[i]ts results concerning the effic[ac]y of the treatment ... be interpreted with great caution.” Ex. 1013, 6-7; Ex. 2051, ¶78.

III. THE '903 PATENT INVENTION

Claims 17, 19, 20, and 22-27 of the '903 patent (“challenged claims”) are directed to an oral dosing regimen for treating RRMS or early SPMS, comprising (i) an induction period having a total cladribine dose of about 1.7-3.5 mg/kg and lasting about 2-4 months; (ii) a cladribine-free period lasting from about 8 months

to about 10 months; (iii) a maintenance period having a total cladribine dose of about 1.7 mg/kg and lasting about 2-4 months; and (iv) a cladribine-free period.

Ex. 1001, 18-7:51; Ex. 2051, ¶¶79-80.

The claimed dosing regimen overcame the challenges and drawbacks of earlier cladribine clinical studies and provides a safe and effective method for treating MS, now approved by FDA in MAVENCLAD®. Ex. 2051, ¶81. The Cladribine Tablets Treating Multiple Sclerosis Orally (“CLARITY”) study, a placebo-controlled clinical trial implementing embodiments of the claims, demonstrated that “[t]reatment with cladribine tablets significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks.” Ex. 2033, 416. CLARITY not only showed positive clinical *and* MRI outcomes, but also unexpectedly yielded a dosing regimen “sweet spot,” i.e., a minimal dosing period (two years) that achieved the same clinical benefits as four-year dosing with a lower incidence of lymphopenia, as demonstrated by the CLARITY EXTENSION trial. Ex. 2051, ¶¶82-83; Ex. 2035, 1594; *infra*, Section VIII.B.

IV. PERSON OF ORDINARY SKILL IN THE ART

A POSA would have an M.D. with at least two years of experience treating neurological conditions, with a focus on autoimmune disorders, including but not limited to multiple sclerosis, and prescribing immunotherapies to treat such

neurological conditions. Ex. 2051, ¶29. A POSA would also be part of a team including individuals with experience in investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, pharmaceutical drug development, and clinical trial design. *Id.*

This definition is more accurate than Petitioner's. Under either definition the claims are non-obvious for the reasons stated herein, and Dr. Fred Lublin qualifies as a POSA. Ex. 2051, ¶¶30-31.

V. CLAIM CONSTRUCTION

For the reasons identified in its Preliminary Response, PO agrees with the Board adopting PO's proposed constructions for "an induction period" and "a maintenance period." Paper 10, 13-17.

VI. THE CITED PORTION OF BODOR IS NOT "BY ANOTHER"

A. The Cited Portion of Bodor is not Prior Art Under Pre-AIA 35 U.S.C. § 102(a) or (e).

It is black letter law that "an [inventor's] own work may not be used against" them unless it was published over a year before their application.⁴ *In re DeBaun*, 687 F.2d 459, 462 (C.C.P.A. 1982) (internal citation omitted). But that is

⁴ Bodor was published on October 14, 2004, less than a year before the December 22, 2004 filing date of the '903 patent priority applications, U.S. 60/638,669 and EP04106909, and is not prior art under pre-AIA 35 U.S.C. § 102(b).

what Petitioner seeks here: Bodor includes the work of named inventors of the '903 patent, Drs. Munafo, Lopez-Bresnahan, Ythier, and De Luca, which IVAX, assignee of Bodor, obtained through a joint research agreement between IVAX and Serono. The dosing regimen in Bodor, the only Bodor disclosure Petitioner contends renders the challenged claims obvious, was solely the work of the inventors of the '903 patent, and *not* the work of Bodor's inventors, Dr. Bodor or Dr. Dandiker. Consequently, it is not prior art "by another" within the meaning of 35 U.S.C. § 102(a) or (e), and Petitioner's sole ground fails.

1. Petitioner bears the burden to prove Bodor is "by another."

A disclosure is not prior art under pre-AIA Section 102(a) or (e) unless it is "by another."⁵ The Federal Circuit has established a three-step framework for assessing whether a disclosure is "by another" under Section 102(a) or (e):

[T]he Board must (1) determine what portions of the reference patent were relied on as prior art to anticipate the claim limitations at issue, (2) evaluate the degree to which those portions were conceived "by

⁵ The relevant part of Section 102(a) requires knowledge or use "by others." A patent disclosure that is not "by another" under Section 102(e) is likewise not evidence of knowledge or use "by others" under Section 102(a). *In re Land*, 368 F.2d 866, 877-79 (C.C.P.A. 1966).

another,” and (3) decide whether that other person’s contribution is significant enough, when measured against the full anticipating disclosure, to render him a joint inventor of the applied portions of the reference patent.

Duncan Parking Techs., Inc. v. IPS Grp., Inc., 914 F.3d 1347, 1358 (Fed. Cir. 2019).

Petitioner bears the burden of proving any alleged prior art, or a portion relied upon is “by another” and “that burden never shifts to the patentee.”

Dynamic Drinkware, LLC v. National Graphics, Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015). Petitioner thus must prove that the cited regimen upon which Petitioner relies is attributable to Dr. Bodor or Dr. Dandiker, not the inventors of the ’903 patent. *Riverwood Int’l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1356 (Fed. Cir. 2003). If the inventors of the challenged patent communicated their ideas to someone else, mere publication of the inventor’s ideas by the recipient in a reference publication is not “by another.” For example, in *In re Mathews*, two coworkers told each other about their inventions and each filed separate patent applications including descriptions of the other’s invention. 408 F.2d 1393, 1394-95 (C.C.P.A. 1969). The Court of Customs and Patent Appeals held that the disclosure of Mathews’s invention in his coworker’s application was not prior art

“by another” because it merely reflected Mathews’s own work communicated to his coworker, not the coworker’s independent work. *Id.*, 1395.

2. Petitioner fails to show Bodor’s regimen is “by another.”

Under step 1 of *Duncan*, Petitioner’s sole ground relies upon 6 lines of Bodor to allegedly disclose the treatment regimen and dosage in the challenged claims. Pet. 46-48. Petitioner cites no other portion of Bodor that it contends discloses the claimed regimen or dosage limitations. *Id.*

Turning to *Duncan* step 2, Petitioner offers no argument that these 6 lines in Bodor were “by another.” Indeed, as described in more detail below, Bodor inventors did not invent any dosing regimen at all.

The analysis should end here, and the Board should hold that Petitioner’s sole ground fails because Petitioner failed to prove the portion of Bodor it relies on is prior art.

3. Bodor’s regimen is not “by another.”

Even if Petitioner had satisfied step 2 of *Duncan*, the evidence demonstrates that the disclosure in Bodor relied on by Petitioner was first developed by inventors of the ’903 patent who communicated it to IVAX before February 2004. The cited disclosure in Bodor states:

At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant

complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.

Ex. 1022, 23:15-20.

Both of Bodor's inventors—Drs. Bodor and Dandiker—declare they did not invent this regimen. Ex. 2054, ¶26; Ex. 2055, ¶23. One of the Serono inventors, Dr. Munafo, explains that he and his co-inventors developed this regimen first and communicated it to IVAX before the effective filing date of Bodor's relevant disclosure. Ex. 2053, ¶¶17-53. Dr. Munafo's explanation is corroborated by documents showing communications from Serono to IVAX.

Serono and the assignee of Bodor (IVAX) entered into a joint research agreement in October 2002 to develop oral cladribine for treating MS. Ex. 2048, 19-22; Ex. 2055, ¶14; Ex. 2054, ¶18; Ex. 2053, ¶23; Ex. 2056; Ex. 2057, 22, 137; Ex. 2058. Under the agreement, IVAX would “develop an oral dosage formulation of [cladribine] in tablet or capsule form suitable for use in clinical trials and commercial sale.” Ex. 2048, 19. Serono agreed to “conduct clinical trials” to determine “the dose, safety, and/or efficacy” of IVAX's oral tablets or capsules,

“obtain necessary health authority approvals, and market the final product[.]” *Id.*, 2, 17-18.

Under this agreement, IVAX and Serono regularly and confidentially exchanged substantial information about their work, including via emails and meetings. Ex. 2054, ¶28; Ex. 2055, ¶¶15-18; Ex. 2053, ¶¶27-32; Ex. 2048. Those emails and meetings included Dr. Dandiker, a named co-inventor of the Bodor reference, and others at IVAX. Ex. 2053, ¶28-32; Ex. 2055, ¶15-18; Ex. 2049; Ex. 2050.

On December 17, 2003, Isabelle Emery of Serono emailed a Briefing Document containing a clinical trial design invented by the Serono inventors, including Drs. Munafo and Lopez-Bresnahan, disclosing the regimen in Bodor, to Dr. Dandiker and IVAX. Ex. 2049; Ex. 2053, ¶¶29, 39-48; Ex. 2055, ¶¶18, 26.

This Briefing Document explained that Serono’s study would include three treatment groups, who would receive either a high dose (2.1 mg/kg), a low dose (0.7 mg/kg), or placebos. Ex. 2049, 47-48; Ex. 2053, ¶41; Ex. 2055, ¶26. Patients receiving the low dose would receive daily 10 mg oral cladribine tablets for 5 consecutive days in each of the first 2 months. Ex. 2053, ¶¶43-46; Ex. 2055, ¶26. At this rate, patients would have received the low dose over two months of dosing, one-third as many months as the high dose which was three-times larger. Ex. 2053, ¶44; Ex. 2055, ¶26; Ex. 2049, 47-49. This is consistent with an August 2003

meeting in Amsterdam, where Dr. Lopez-Bresnahan explained to the IVAX team that patients receiving the same low dose would receive oral cladribine for 5 consecutive days per month for 2 months. Ex. 2050, 4; Ex. 2053, ¶¶35-38. Patients would receive another dose starting after month 12, leaving a 10-month cladribine-free period after the first 2 months. Ex. 2049, 48-49; Ex. 2053, ¶¶45-46; Ex. 2055, ¶26.

Although the Briefing Document says the “duration of treatment” was 6 months for all patients, that included placebos to keep the study “double blind.” Ex. 2049, 47-49; Ex. 2053, ¶¶42-43. As Dr. Munafo explains, the low dose arm (who received one-third the dose) had to receive 4 months of placebos to bring their apparent treatment to 6 months, thus concealing which patients received which doses, followed by 6 months with no “treatment.” Ex. 2053, ¶¶42-44; Ex. 2055, ¶26; Ex. 2050, 4; Ex. 2049, 47-49. Consequently, patients receiving the low dose would be administered 5-days of cladribine for 2 months, followed by 4 months of placebos and another 6 months with no “treatment.” Ex. 2053, ¶¶43-44; Ex. 2055, ¶26.

As Dr. Munafo further explains, Serono also communicated to the IVAX team Serono’s alternative dosing regimen of daily oral cladribine tablets for 5 days per month for 6-months followed by an 18-month cladribine-free period, which is

also disclosed in the Bodor PCT as an “alternative” regimen. Ex. 2053, ¶¶36-38, 51; Ex. 1022, 23:20-24.

As Dr. Munafo further explains, the Serono inventors’ “Study Design” was in draft form, and they discussed with IVAX the possibility of adjusting certain parameters, including dosing 10 mg oral cladribine tablets for 6 or 7 days per month. Ex. 2053, ¶47. Thus, Serono communicated to IVAX the same dosing regimen later disclosed in Bodor—daily 10 mg oral cladribine tablets for 5-7 days per month for 2-months followed by a 10-month cladribine-free period. Ex. 2053, ¶53; Ex. 2049, 47-49.

Drs. Bodor and Dandiker corroborate that the cited regimen is attributable to the Serono inventors. Drs. Munafo, Bodor, and Dandiker all confirm that IVAX had a joint research agreement with Serono under which IVAX would develop an oral cladribine formulation while Serono would design dosing regimens and conduct clinical trials. Ex. 2053 ¶¶23-29; Ex. 2054, ¶¶18, 27; Ex. 2055, ¶¶14-18. Drs. Bodor and Dandiker confirm that, consistent with the agreement, neither they

nor anyone else on their team at IVAX developed, researched, or invented any cladribine dosing regimen for treating MS. Ex. 2054, ¶26; Ex. 2055, ¶23.⁶

Instead, Dr. Dandiker recalls receiving the August 2003 presentation and December 2003 Briefing Document from Serono and believes the Serono inventors disclosed the regimen disclosed in Bodor to him and others at IVAX. Ex. 2055, ¶¶16-18, 25-27. Dr. Bodor agrees it is “highly likely” the Serono inventors communicated the dosing regimen in Bodor to IVAX in meetings and emails. Ex. 2054, ¶28. That Serono communicated Bodor’s regimen to IVAX is further corroborated by the fact that before Serono disclosed its August 2003 presentation and December 2003 Briefing Document to IVAX, Bodor’s first two provisional applications, U.S. Nos. 60/458,922 (filed March 28, 2003) and 60/484,756 (filed July 2, 2003), did not contain such dosing regimen; while after Serono’s disclosures, Bodor’s third provisional application, U.S. No. 60/541,247 (filed February 4, 2004), did contain this dosing regimen. Ex. 2044; Ex. 2045; Ex. 2046, 20:6-10.

⁶ Neither Dr. Bodor nor Dr. Dandiker was aware of the two IVAX provisional applications cited in Bodor, both of which were later abandoned. Ex. 1022, 23:24-29; Ex. 2055, ¶20; Ex. 2054, ¶22; Ex. 2047, 10-12.

The Board need not reach step 3 of *Duncan*, because there is no evidence that Drs. Bodor or Dandiker made **any** contribution to the regimen in Bodor on which Petitioner relies, significant or not; instead, both state that they did not invent any dosing regimen.

In fact, the inventors of the '903 patent provided the regimen in Bodor that Petitioner relies on. That regimen was included, but not claimed, in Bodor after the '903 patent inventors communicated their work to IVAX. Ex. 1022, 40-55; Ex. 2029, 22:16-27:15; Ex. 2069, 22:20-26:32. This work by the '903 patent inventors therefore cannot be used against them. *In re DeBaun*, 687 F.2d at 462. The Board should hold that Petitioner's sole ground fails because the portion of Bodor on which Petitioner relies is not "by another" and thus not prior art.

VII. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER BODOR AND STELMASIAK

Even if Bodor were prior art (which it is not), Petitioner fails to establish that Bodor and Stelmasiak, even in combination, teach or suggest all limitations of the challenged claims, including claimed weight-based dosing or maintenance period. 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. Ex. 2051, ¶84.

A. Bodor And Stelmasiak Do Not Disclose Or Suggest All Claim Limitations

1. Bodor And Stelmasiak Do Not Disclose Or Suggest The Claimed Weight-Based Induction Or Maintenance Dosing

Petitioner's argument relying on "the average weight of a person being about 70 kg," (Pet. 51), incorrectly assumes that every disclosed dose is being given specifically to an average-weight patient, but no such thing is disclosed in Bodor. Bodor does not disclose the weight of any patient nor any weight-based dosing, let alone any specific dose(s) ever given to 70-kg patients, or any patient or class of patients (whether defined by weight or otherwise) that would allow the calculation of a dose-by-weight as Dr. Miller purports to do. Ex. 1002, ¶83. Doses-by-weight within the claimed range are also not inherently disclosed (and Petitioner does not argue that they are) because Bodor does not disclose any patient weight.

Indeed, a POSA would have understood that flat and weight-based dosing are fundamentally different. Ex. 2051, ¶¶91-93; Ex. 2052, ¶¶20, 73. In weight-based dosing, the dose each patient receives is based on that individual's weight. Ex. 2051, ¶91; Ex. 2052, ¶35. In contrast, in flat dosing all patients, regardless of weight, receive the same amount of a drug. Ex. 2051, ¶91; Ex. 2052, ¶35.

Drs. Lublin and Meibohm opine that 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. Ex. 2051, ¶90; Ex. 2052, ¶¶66-69, 75.

Despite recognizing weight-based cladribine dosages for treating MS in prior art *subcutaneous* dosing regimens (e.g., Rice), Bodor expressly teaches a flat-dosing method. *Compare* Ex. 1022, 22:19-26, with, 23:15-24. A POSA would have understood that Bodor considered weight-based dosing in the art but still chose flat dosing. Ex. 2051, ¶87, 132; Ex. 2052, ¶69. The Board’s preliminary findings state that Bodor uses weight-based dosing in “defining the terms ‘therapeutically effective amount’ and ‘effective amount.’” Paper 10, 35-36. However, Bodor expressly defines these terms as “dosages effective to achieve the therapeutic result sought” and references weight-based “therapeutically effective dosages” that have been reported in the literature for hairy cell leukemia and MS. Ex. 1022, 24:17-26. A POSA considering Bodor as a whole would not have understood this “definition” in Bodor to teach or suggest a method of treating MS that encompasses weight-based dosing. Ex. 2051, ¶87; Ex. 2052, ¶68.

First, Bodor expressly teaches flat dosages for treating MS, *not* weight-based dosages. Bodor discloses that “for the treatment of [MS], 10 mg of cladribine ... would be administered ...,” i.e., flat, fixed doses of cladribine, regardless of weight. Ex. 1022, 23:15-20. Whether administered for 10 or 14 days, the dosage remains *flat*. Because Bodor does not disclose any relationship between dosage and patient weight, a POSA would have understood that the disclosed 100, 120, and 140 mg doses are *flat* for all patients and not weight-based,

i.e., the dose does not vary depending upon a patient's weight. Ex. 2051, ¶¶85-86; Ex. 2052, ¶¶66-67.

Second, a POSA would have understood that Bodor's examples confirm administration based on flat, fixed dosing. Ex. 2051, ¶88; Ex. 2052, ¶¶67-69. Example 4 discloses "[p]atients received randomly three different *fixed oral doses* (3.0 mg)" and Example 5 discloses "patients received randomly two different *fixed oral doses* (3.0 mg and 10.0 mg) and a fixed intravenous dose of 3.0 mg." Ex. 1022, 33:25-27, 36:18-20. A POSA would have understood that nowhere does Bodor suggest administering its formulation of cladribine based on patient weight. Ex. 2051, ¶88; Ex. 2052, ¶¶66-69.

Third, although Dr. Miller's statement of Bodor's "equivalent" dose based on a 70 kg adult (Ex. 1002, ¶83) is impermissible hindsight based on knowledge of the claimed invention, as there is no express or inherent disclosure in Bodor of a patient weighing 70 kg, let alone of selecting a dose based on any such patient weight. Ex. 2051, ¶¶89-90, 131.

Indeed, Dr. Miller himself characterized MAVENCLAD[®]'s weight-based dosing regimen as "unique," in contrast to the regimens of prior FDA-approved MS drugs, even though a POSA *could have* calculated a corresponding weight-based dosage. *See* Ex. 2007, 3:53-4:12; Ex. 2008, 4:17-5:1; Ex. 2009, 127:5-14;

Ex. 2051, ¶¶92-93. In a 2019 video for the National Multiple Sclerosis Society authenticated by Dr. Miller (Ex. 2009, 132:4-16), he admits:

The treatment regimen for MAVENCLAD[®] is *rather unique* ... the dose of MAVENCLAD[®] is dependent on an individual's weight. *This is the only MS medicine that we have that is not given in a fixed dose but rather the dose is determined by how much the individual weight is.*

Ex. 2007, 3:53-4:12; Ex. 2008, 4:17-5:1. Given Dr. Miller's video contrasting the MAVENCLAD[®] dosing regimen with other MS drugs, his current testimony can only be explained by hindsight. And while the Board credited Dr. Miller's opinion in support of the Petition "that a POSA would understand that [Bodor's dose] is readily convertible to a dose reported on a mg/kg basis" (Paper 10, 35), Dr. Miller's pre-IPR statements demonstrate that even he did not equate a flat dosing regimen with MAVENCLAD[®]'s "unique" dose, "determined by how much the individual weighs." Ex. 2007, 3:53-4:12; Ex. 2009, 127:5-20.

Petitioner thus fails to establish that Bodor teaches or suggests a method of treating MS with a weight-based dosage of about 1.7 or 1.7-3.5 mg/kg cladribine in an induction period, or about 1.7 mg/kg cladribine in a maintenance period as claimed. Only by rewriting Bodor with hindsight knowledge of the claimed dosing regimen; ignoring Bodor's express teaching of flat, fixed-dose dosing (Ex. 1022,

23, 33, 36); and disregarding Dr. Miller's prior inconsistent statements 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. Ex. 2051, ¶¶95-97. Stelmasiak discloses that patients received 300 mg oral cladribine (i.e., 10 mg/day for 5 days/month for six months), followed by 50 mg at month 9 and 12 or 15. Ex. 1013, 5. Stelmasiak does not suggest weight-based dosing but instead reports the opposite: that “[t]here was *no indication* that a ‘good response’ is related to the actual cladribine dose per body weight.” *Id.*, 7. Thus a POSA would not have been motivated to adopt weight-based dosing as claimed because Stelmasiak teaches away from it. Ex. 2051, ¶96. As Dr. Meibohm opines, “Stelmasiak teaches against weight-based dosing and [one] would not be motivated by Stelmasiak’s teachings to convert Stelmasiak’s fixed, flat dose to weight-based dosing.” Ex. 2052, ¶90. *See In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). 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 **4.0-5.7 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 induction dosing. Ex. 2052, ¶75; Ex. 2051, ¶¶95-97.

While the '903 patent specification states that the Grieb reference, which has substantially the same disclosure as Stelmasiak (*compare* Ex. 1023, 324 (“Materials and Methods”), *with* Ex. 1013, 5 (“Materials and Methods”)), discloses a cladribine study in which “a total dose of about 4–5.7 mg/kg (patients of about 52 and about 75 kilos, respectively)” was administered (Ex. 1001, 3:3–21), this characterization of Grieb’s dosing is that of the '903 patent *inventors*, not that of a POSA. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (“Inventors, as a class, . . . possess something – call it what you will – which sets them apart from the workers of ordinary skill[.]”). Here, regardless of how the *inventors* characterized Grieb’s dosing, both Grieb and Stelmasiak administer the same flat doses regardless of patient bodyweights. Ex. 1013, 5; Ex. 1023, 324.

Accordingly, neither Bodor nor Stelmasiak teaches or suggests a method of treating MS with a weight-based induction dosage of about 1.7 or 1.7-3.5 mg/kg, or a weight-based maintenance dosage of about 1.7 mg/kg.

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

a) Bodor Does Not Teach or Suggest Re-Treatment

In its preliminary findings, the Board acknowledged that Bodor does not explicitly describe a “maintenance period” but found “that a POSA would have

understood Bodor to suggest retreatment.” Paper 10, 33. However, Bodor does not state that re-treatment with cladribine should occur upon completion of the 10-month cladribine-free period (or otherwise). Ex. 2051, ¶98.

As opined by Dr. Lublin, given the state of MS treatment in 2004, cladribine safety concerns, the lack of safe and effective cladribine dosing regimen, and alternative MS treatments, “a POSA considering Bodor would not have understood Bodor to teach re-administering cladribine at the end of the 10-month cladribine-free period.” Ex. 2051, ¶¶99-119.

(1) Cladribine Safety

A POSA would have understood that Bodor’s disclosure of a 10-month cladribine-free period after a two-month dosing period likely relates to safety considerations, especially given that “cladribine causes prolonged, profound suppression of lymphocyte counts.” Ex. 2051, ¶99; Ex. 1016, 420. As discussed above, a POSA would have understood that cladribine’s lymphocytotoxic activity posed significant safety concerns. Ex. 2051, ¶100. For example, Romine explains that “[*r*]epeated treatment [with cladribine] raises long-term toxicity issues including” increased cancer risk, hematologic toxicity, and bone marrow suppression. Ex. 1031, 43-44; *see also* Ex. 1001, 2:59-3:2, 3:22-30; Ex. 1014, 1720; Ex. 1016, 430; Ex. 1013, 7; Ex. 1023, 326.

Indeed, Dr. Miller acknowledges that after a cladribine dosing period, a POSA would have “followed” with a “drug-free period” “because cladribine toxicity was a concern” and that a POSA would have “mitigate[d] side effects” of cladribine during a cladribine-free period. Ex. 1002, ¶¶95, 103. As Dr. Lublin explains, a cladribine-free period allows a physician to evaluate a patient’s condition, including safety markers such as lymphocyte levels, to evaluate safety risks. Ex. 2051, ¶100. If lymphocyte levels remain suppressed below safe levels, a POSA would not have further treated a patient with cladribine. *Id.* Dr. Miller has stated that “for safety reasons,” a patient’s “lymphocyte count [needs to] be up to 1,000” before receiving cladribine treatment. Ex. 2009, 135:18-137:1; Ex. 2008, 12:2-9 (“we may need to wait to get that lymphocyte count back into the safe range[.]”). However, as of 2004, it was unclear how long cladribine-induced lymphocyte suppression would last. *See* Ex. 1047, 297 (“**one year** after completion of cladribine ... [t]he mean total lymphocyte ... had shown **some recovery** ... but were still **significantly below baseline** level”); Ex. 1013, 4 (Stelmasiak reporting that “a trend toward recovery [was] **evident only at 24 months.**”); Ex. 2051, ¶100.

Given the safety concerns arising from the prolonged suppression of lymphocytes induced by cladribine and safety concerns associated with re-treatment, a POSA considering Bodor would not have assumed it would be safe to

re-treat patients with cladribine immediately after the 10-month cladribine-free period. Ex. 2051, ¶101. Accordingly, Bodor does not teach or suggest the claimed maintenance period following the 10-month cladribine-free period. Bodor's disclosure of 10 months of no treatment is neither an express nor an inherent disclosure of *treatment* following the cladribine-free period.

(2) Dosing of Approved DMAs For MS Was Based on Pharmacological Effects and Safety

Dr. Miller states that “a POSA would have understood that a common strategy for treating MS involved cyclically administering a therapy for a period of time, stopping the therapy for a period of time, and retreating for a period of time.” Ex. 1002, ¶¶63, 87. As support, Dr. Miller relies on treatment with corticosteroids and cyclophosphamide, but Dr. Miller mischaracterizes the art. Ex. 2051, ¶102.

First, a POSA would have understood that in 2004, MS treatment focused on DMAs, which were dosed continuously to maintain the drugs' pharmacological effects, maximize their efficacy, and minimize associated risks. *Id.*, ¶¶54-58, 103; *supra*, Section II.A.1. For example, frequent dosing of beta interferons is “*necessary to sustain the activity* of intracellular molecular signalling pathways.” Ex. 2024, 9. A POSA would have understood that the dosing schedule for an MS drug is based on the drug's pharmacological effects, mechanism of action (if known), therapeutic benefits, and safety risks. Ex. 2051, ¶103. Indeed, as Dr.

Miller admitted, administration of DMAs such as beta interferon and glatiramer acetate “did not involve administering a therapy for a period of time, stopping the therapy for a period of time, and retreating for a period of time.” Ex. 2009, 78:20-73:15. Thus, a POSA would not have “re-administer[ed] cladribine again after the specified cladribine-free period” simply because “MS is a chronic disease that typically requires ongoing care and repeat treatment,” at least because none of the FDA-approved DMAs by 2004 was dosed in a “cyclic” manner. Ex. 2051, ¶103; Ex. 1002, ¶87.

Second, a POSA would have understood that corticosteroid and cyclophosphamide treatments fail to inform cladribine treatments. Ex. 2051, ¶¶104-119. Before DMAs were developed for MS, corticosteroids were used to reduce the severity of relapses but were “*not effective* at reducing the relapse rate or the rate of disease progression.” Ex. 2011, 3; Ex. 2051, ¶¶47-48.

Corticosteroids have not been proven to alter the natural course of MS and were administered as needed to treat relapses. Ex. 2006, 273; Ex. 1016, 431; Ex. 2013, 176; Ex. 2051, ¶105. A POSA would have understood that a drug used to treat the severity of relapses *by definition* would have to be re-administered during a patient’s lifetime. Ex. 2051, ¶105. But such a treatment approach does not inform treatment with DMAs such as cladribine, which alter the MS disease course. *Id.*, Ex. 2006, 273, 279.

Dr. Miller also relies on pulsed intravenous methylprednisone (“IVMP”) treatment to support “re-treatment” in MS patients (Ex. 1002, ¶¶59-60) but does not explain the rationale for IVMP dosing or why it would inform re-treatment with cladribine. Further, Dr. Miller agreed that “[a]dministration of regularly scheduled intermittent doses of pulse steroids has not been established as effective therapy for the prevention of clinical worsening in MS.” Ex. 2009, 90:20-91:3, 92:13-93:13; *see also* Ex. 2005, 48; Ex. 2004, 342 (citing pre-2004 publications). Like general corticosteroid treatment, IVMP appears to be effective for treating relapses when they occur, but a POSA would have understood that such a treatment approach does not inform treatment with DMAs such as cladribine. Ex. 2051, ¶106.

Dr. Miller also relies on cyclophosphamide dosing to show MS “re-treatment.” Ex. 1002, ¶58. But again, Dr. Miller does not provide any mechanistic or pharmacologic rationale for the cyclophosphamide dosing of “every 2 months for a 2-year period” (*id.*) or why this regimen would inform re-treatment with cladribine, especially in view of his prior statement that “[m]any trials have confirmed that the clinical benefits of cyclophosphamide therapy for MS are restricted to the short term and are marginal at best” and concluded that “cyclophosphamide is an unlikely candidate for long-term therapy” for MS. Ex. 2037, 371; Ex. 2051, ¶¶107-108. Indeed, Dr. Miller admitted that

“cyclophosphamide proved too toxic for widespread acceptance by physicians for their patients.” Ex. 2005, 68. A POSA would not have looked to the dosing of a drug with limited short-term benefits to inform the dosing of cladribine, which induces prolonged lymphocyte suppression. Ex. 2051, ¶108.

Accordingly, nothing in Bodor or the art would have led a POSA to re-administer cladribine after Bodor’s 10-month cladribine-free period. *Id.*, ¶110.

(3) The Art Did Not Suggest A Maintenance Period As Claimed

Even if a POSA had considered re-treatment, the art did not suggest repeating or resuming treatment immediately after the cladribine-free period. *Id.*, ¶111.

First, a POSA would have known that by 2004, most MS clinical trials studying cladribine used a single intravenous- or subcutaneous-dose dosing phase without re-treatment. *Id.*, ¶112; Ex. 1016, 425 (Table III).

Second, any re-treatment plan would have specified the criteria for re-treatment. Ex. 2051, ¶113. For the few cladribine MS trials that re-treated patients, the published trial protocols expressly disclosed the re-treatment criteria, and did not automatically re-treat patients after a specified treatment-free period. For example, while Rice discloses that patients in one arm received cladribine for two months, followed by six months of placebo, these patients were not re-treated

immediately after the six-month placebo period. Ex. 1018, 1146. Instead, as Dr. Miller admitted, “Rice describes several criteria for that retreatment,” including “hematologic dosing criteria . . . , [that] at least 12 months had elapsed since the last dose of cladribine and there was evidence of *disease progression*.” *Id.*; Ex. 2009, 99:7-100:17. Dr. Miller agreed that patients in this arm “could not receive re-treatment until month 18 at the earliest.” Ex. 2009, 103:20-104:4. Such patients also had to satisfy “hematologic dosing criteria,” which a POSA would have understood relate to safety concerns about cladribine. Ex. 2051, ¶113; Ex. 1018, 1151-52 .

Likewise, as Dr. Miller admitted, Romine discloses that a subset of patients were re-treated “because of a *recurrence of disease worsening*.” Ex. 2009, 95:11-18; Ex. 1031, 43. At best, a POSA would have understood that any re-treatment would have been based on evidence of disease progression rather than automatically re-treating after a set period of time. Ex. 2051, ¶113.

Third, given the safety and toxicity concerns associated with cladribine (Ex. 1031, 43-44), a POSA would have been concerned about resuming cladribine treatment. Ex. 2051, ¶114. For example, Rice was concerned with “hematologic” criteria, and allows re-treatment only if “*at least 12 months had elapsed* since the last dose of cladribine” *Id.*; Ex. 1018, 1146. Even Dr. Miller acknowledges that a POSA would have considered patient safety when assessing when to re-treat:

“[a] POSA would have had the skill to monitor a patient’s lymphocyte count and side effects associated with lymphocyte and myelosuppression” so as to “mitigate side effects.” Ex. 1002, ¶104. A POSA thus would have been concerned about re-treating a patient who had “significant overall lymphocytopenia” and would not have automatically resumed treatment at the end of Bodor’s 10-month cladribine-free period without further indication that it was both needed and safe to do so. Ex. 2051, ¶115.

Fourth, there was no consensus in the art as to when cladribine re-treatment would occur, if at all. Ex. 2051, ¶116. Although Dr. Miller states that cladribine’s effect is “not permanent” because “lymphocyte counts eventually rebounded after a cladribine-free period” (Ex. 1002, ¶95), this does not suggest re-treatment *with cladribine*, or that any re-treatment would occur immediately after Bodor’s 10-month cladribine-free period. Ex. 2051, ¶116. Indeed, the reference cited by Dr. Miller, Selby (Ex. 1047), discloses that “*one year after* completion of cladribine ... [t]he mean total lymphocyte ... counts had shown some recovery ... but were still *significantly below baseline level*.” Ex. 1047, 297. As Dr. Lublin explains, a POSA would have understood that Selby does not suggest lymphocytes return to baseline levels one year after the last dose of cladribine, but that it would be necessary to wait more than a year after the last cladribine dosing for the patient’s lymphocyte level to further recover before considering any re-treatment. Ex. 2051,

¶116. Thus, a POSA would not have resumed cladribine treatment after 8-10 months of no treatment as claimed. Indeed, by 2004 there has been no reported safe and effective cladribine dosing regimen. Ex. 2051, ¶117.

Even if there was a need for retreatment, the art does not suggest that a POSA would have re-treated with cladribine as a POSA could have looked to other available MS drugs. Ex. 2051, ¶118. Dr. Miller admitted that “many people with MS start on a medication and then need to change medication, at some point, for one reason or another.” Ex. 2009, 94:8-15; *see also* Ex. 2008, 11:17-19.

Therefore, 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.

b) Stelmasiak Does Not Teach Or Suggest A Maintenance Period As Claimed

Stelmasiak does not remedy the deficiencies of Bodor. Ex. 2051, ¶¶120-124.

First, while Stelmasiak teaches treatment after two months of no treatment, neither Stelmasiak alone nor the combination of Bodor and Stelmasiak teaches or suggests a maintenance period occurring about 8-10 months after the induction period. *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.”); Ex. 2051, ¶121.

Nevertheless, Petitioner argues that Stelmasiak and Bodor would have led a POSA to treat MS according to a “general treatment framework” that provides for “maintenance” after a 2-month induction period and 10 months of no treatment. Pet. 37; Ex. 1002, ¶105. However, 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. Ex. 2051, ¶122.

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 disclosing 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; Ex. 2051, ¶123. 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 VII.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, not the claimed about 1.7 mg/kg total maintenance dosing. Ex. 2051, 124.

Lastly, as discussed below, Petitioner's routine-optimization theory would not have suggested a maintenance period as claimed. *See* Section VII.B.1, *infra*; *see also* Ex. 2051, ¶¶125-129, 131-163.

Thus, Bodor and Stelmasiak combined do not disclose or suggests all elements of the challenged claims.

B. No Motivation To Combine Bodor With Stelmasiak To Arrive At The Challenged Claims Or Reasonable Expectation Of Success In Doing So

Petitioner fails to establish motivation for a POSA to modify Bodor's *flat* cladribine dosing method in view of Stelmasiak's *flat* cladribine dosing method to arrive at the claimed *weight-based* dosing method, or how a POSA would have had a reasonable expectation of success in doing so. 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 (1) adopts weight-based dosing; (2) effectively reduces the initial treatment length and dose of Stelmasiak; (3) prolongs Stelmasiak's initial drug-free period; and (4) extends Stelmasiak's month-long 2nd treatment phase; or how a POSA would have reasonably expected success in doing so. *See* Ex. 2051, ¶130.

1. Petitioner's Routine Optimization Arguments Fail

Petitioner argues 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. Pet. 40 (quoting *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003)). Petitioner is wrong because there is ***no overlap*** between Bodor's doses and the claimed doses. If the prior art teachings do not 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, a POSA would have understood that 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. *See* Pet. 50-51; *supra*, Section VII.A.1; Ex. 2051, ¶¶85-97. Petitioner identifies purported overlap only through improper hindsight, arguing that a POSA would have understood "for an average adult weighing about 70 kg, Bodor's dose is equivalent to approximately 1.4 to 2 mg/kg." Ex. 1002, ¶83. While the Board noted in its preliminary findings that "[PO's] reading of Bodor would *exclude* the average-weight patient from Bodor's disclosed method for treating MS" (Paper 10, 35 (emphasis in original)), PO is ***not*** arguing that the average-weight patient is "excluded" but that Bodor does not teach or suggest consideration of ***any*** patient weight, let alone a 70 kg person. Nor would a POSA have understood Bodor to teach or suggest consideration of patient weight in its dosing. Ex. 2051, ¶¶85-94; Ex. 2052, ¶¶66-69. Petitioner's own declarant distinguished the claimed weight-based dosing regimen, practiced by MAVENCLAD[®], from the "fixed dos[ing]" of

other MS drugs where the dose “does not vary depending upon the patient’s weight.” *See* Ex. 2009, 118:12-119:2; Ex. 2007, 3:53-4:12; Ex. 2008, 4:17-5:1; Ex. 2051, ¶133. Thus, absent improper hindsight, there is **no** overlap between Bodor’s doses and the claimed doses. Petitioner’s argument based on overlapping ranges fails. Ex. 2051, ¶131.

Petitioner further argues that a POSA would have optimized the maintenance dose and dosing length, which are “result-effective” variables and “readily-optimized parameters,” “by regularly measuring the patient’s lymphocyte counts and evaluating the efficacy of a given dose based on the change[] in the count.” Pet. 41-43. As an initial matter, Petitioner fails to show that Bodor’s teaching of “fine tuning” the daily dose means shifting completely to a weight-based dosing method—which it does not. *See supra*, VII.A.1; Ex. 2051, ¶¶125-129, 134.

Petitioner’s routine optimization arguments fail for at least the following additional reasons.

First, Petitioner fails to establish why or how a POSA would have been motivated to optimize any alleged maintenance dosing or dosing length based on a patient’s lymphocyte count, or reasonably expected success in doing so, especially when Dr. Miller admitted that “[l]ymphocyte suppression is not a measure of efficacy.” Ex. 2009, 121:14-18.

Petitioner characterizes lymphocyte suppression as a measure of cladribine's "efficacy." Pet. 16, 43. But while Dr. Miller refers to lymphocyte suppression as a "treatment response" and a "therapeutic effect," (Ex. 1002, ¶¶16, 31, 35, 38, 48, 106), he does not associate lymphocyte count with "efficacy," and instead testified that in his view a "treatment response" or "therapeutic effect" includes side effects. Ex. 2009, 30:12-31:15, 37:3-40:3. In its preliminary findings, the Board appears to have credited Petitioner's suggestion that a POSA could have optimized cladribine dose and length to achieve therapeutic efficacy by "measur[ing] ... changes in a patient's lymphocyte counts." Paper 10, 29-31 40-41, 47-49. However, as Dr. Miller admitted during his deposition, "[l]ymphocyte suppression is not a measure of efficacy." Ex. 2009, 121:14-18. Accordingly, a POSA would not and could not have used lymphocyte count to evaluate the efficacy of any "optimization" to a dosing regimen. Ex. 2051, ¶¶126, 136-137.

Petitioner does not show otherwise. Dr. Miller cites to Exhibits 1018 (Rice), 1013 (Stelmasiak), and 1014 (Beutler) to support his opinion that "neurologists commonly *assessed the therapeutic effect* of cladribine by monitoring a patient's lymphocyte count." Ex. 1002, ¶16. But none of the references suggests lymphocyte count is a metric of therapeutic efficacy. Ex. 2051, ¶¶138-142; *see also id.*, ¶¶143-148.

Dr. Miller agreed that Rice “discuss[es] lymphocyte levels in the context of the safety evaluation” and that Rice’s reference to lymphocyte counts at Ex. 1018, 1146, “does not talk about measurements of therapeutic effects.” Ex. 2009, 27:3-28:1, 28:19-30:14; Ex. 2051, ¶139.

Stelmasiak discusses “lymphocyte counts” in the context of other “hematological side effects.” Ex. 1013, 5. Further, while Stelmasiak’s Figure 1 shows that lymphocyte levels were *lower* at month 24 than month 3, Table 1 shows that the corresponding EDSS scores were *worse* at month 24 than month 3 (4.3 ± 2.0 and 3.4 ± 1.5 , respectively). *Id.*, 5-6. In fact, Stelmasiak shows that while “EDSS scores were significantly reduced during the treatment,” the final EDSS score (month 24) returned to *baseline*, even though lymphocyte levels remained suppressed. *Id.* Stelmasiak also reported two “non-responders” who showed lymphocyte “reduction of approximately the same magnitude as in some of the ‘responders,’” further demonstrating that suppressing lymphocyte count does *not* correlate with cladribine efficacy. *Id.*, 6. A POSA would have thus understood from Stelmasiak that neither lymphocyte count nor change in lymphocyte count measures cladribine’s therapeutic efficacy. Ex. 2051, ¶140. Indeed, Dr. Miller agreed that “Stelmasiak did not identify lymphocyte count as a measure of cladribine efficacy.” Ex. 2009, 42:8-12.

Lastly, Beutler discloses that “[l]ymphocyte subset evaluation was done monthly during the course of drug administration” as part of its “[h]ematologic evaluation,” which Dr. Miller admits is “simply ... about blood counts.” Ex. 1014, 1717; Ex. 2009, 47:1-20. Beutler also discusses “[c]hanges in lymphocyte subsets” under “Toxicity and adverse events[.]” Ex. 1014, 1719. Thus, the art consistently shows that lymphocyte count is a metric of *safety*, not therapeutic efficacy for cladribine treatment. Ex. 2051, ¶142.

Despite relying on Rice to allege that lymphocyte count is a metric of therapeutic effect, Dr. Miller has elsewhere disparaged Rice for its lack of treatment “promise” and “unconvincing clinical benefit,” stating in 2008 :

Initial trials with cladribine [i.e., Sipe] *showed promise* in the treatment of SPMS *but these results were not seen* in the subsequent blinded, randomized, placebo-controlled trial [i.e., Rice]. Furthermore, studies of cladribine continue to show an enigmatic dissociation between positive effects on MRI and *unconvincing clinical benefit*. Another drawback to the use of cladribine is the profound and very long-lasting lymphopenia induced by the drug ... At this point, it seems *prudent to await the results* of a prospective, randomized, blinded trial of oral cladribine *before recommending its use in patients with MS*.

Ex. 2004, 341, 350.⁷ Dr. Miller also warned of the “drawback” of cladribine-induced lymphopenia—despite opining in this proceeding that lymphocyte suppression is a metric of therapeutic effect. While the Board noted in its preliminary findings that “[p]rior studies may not have universally pointed to cladribine’s promise or efficacy but much of the reporting in the literature did” (Paper 10, 49-50), Dr. Miller’s prior statements suggest otherwise. *See* Ex. 2005, 45, 67; *see also* Ex. 2031, 753 (reviewing pre-2004 trials and concluding, “[w]e **remain to be convinced** that cladribine is useful, and **do not recommend its use in the management of patients with [MS].**”).

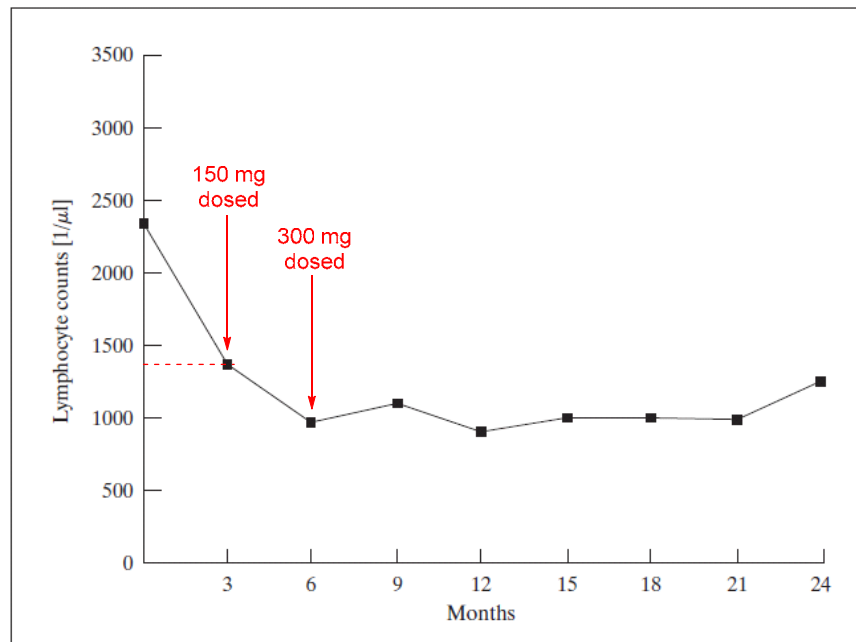
Second, Petitioner fails to show *what level* of lymphocyte suppression would have been sufficient to show efficacy. Dr. Miller opines that a sustained reduction of lymphocytes to $\leq 1,000$ cells/ μ L indicates a “treatment response” (Ex. 1002, ¶16), but admitted that 1,000 cells/ μ L is simply “the lower limit of normal” and “[l]ymphocyte suppression is not a measure of efficacy.” Ex. 2009, 31:16-20, 121:14-18. While the Board noted in its preliminary findings that “it is not evident

⁷ At deposition, Dr. Miller initially disagreed that the dissociation between MRI effects and lack of clinical benefit was “enigmatic.” Ex. 2009, 21:13-22:1. Dr. Miller also disagreed that cladribine-induced lymphopenia was a “drawback,” but acknowledged his 2008 book chapter stating otherwise. *Id.*, 51:11-52:3.

that a sustained reduction to below 1000 cells/ μ L would be necessary before a therapeutic effect is observed” (Paper 10, 47), Stelmasiak’s data shows that a reduction in lymphocyte count does not correlate with cladribine efficacy. Ex. 2051, ¶149. Petitioner fails to show how a POSA would have been able to optimize cladribine dose or dosing length based on lymphocyte count (Pet. 43) with ***no guidance*** as to a threshold lymphocyte level that would correspond to therapeutic efficacy. Ex. 2051, ¶149.

To the extent Petitioner requires suppressing lymphocyte levels to ≤ 1000 cells/ μ L to show efficacy, a POSA would not have expected Bodor’s dosing regimen to meet this threshold. Ex. 2051, ¶150. 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 ***above*** 1000 cells/ μ L (~1350 cells/ μ L). Ex. 1013, 5. Following Dr. Miller’s definition of suppression, a POSA if anything 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/ μ L, especially in view of the lower bioavailability (39%; *infra*, Section VII.B.3) reported in Bodor. Ex. 2051, ¶150; Ex. 2052, ¶¶85, 88-89.

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



Third, even if lymphocyte count were a measure of efficacy (which it is not), a POSA would not have been motivated to optimize cladribine dosing “by adjusting the *daily dose* administered,” as Petitioner argues. Pet. 43; Ex. 2051, ¶¶151-154.

As Dr. Lublin explains, the art does not suggest that any change in daily lymphocyte count would provide meaningful information on cladribine dosing. Ex. 2051, ¶152. As an initial matter, lymphocyte count was not measured daily precluding a POSA from determining whether any change in lymphocyte count was a result of the adjusted dose or of the pre-adjustment dose. *Id.*; *see, e.g.*, Ex. 1018, 1146 (“lymphocyte count[s]” “were obtained at *baseline and months 6 and*

12”); Ex. 1014, 1717 (“Lymphocyte subset evaluation was done *monthly*”).

Nevertheless, any changes in daily lymphocyte count would not provide sufficient information to evaluate the extent to which the change in dose or dosing length was beneficial for a patient, given the “marked and sustained reduction in lymphocyte counts [that] appears to occur regardless of the total cladribine dose.” Ex. 1016, 422; Ex. 2051, ¶152.

Fourth, aside from lymphocyte suppression, which “is not a measure of efficacy” (Ex. 2009, 121:14-18), Petitioner never identifies any other alleged recognizable result associated with “the therapeutic effect” of cladribine. *See* Pet. 42. While Dr. Miller notes that Rice discloses “a small, dose-dependent, median percent decrease in T2 lesion volume” (Ex. 1002, ¶91), Petitioner fails to explain how a POSA would have optimized a cladribine dose or dosing length based on this effect, which Dr. Miller testified is “possibly not” “a treatment response to cladribine therapy.” Ex. 2009, 19:8-17; *see also* Ex. 2004, 341. For at least these reasons, Rice would not have led a POSA to reasonably expect success in arriving at the claimed dosing regimen using routine optimization based on lymphocyte count or MRI results. Ex. 2051, ¶¶155-156.

Fifth, a POSA would have understood that due to the complexity, variable nature, and slowly evolving disability of MS, it would require years to evaluate how changes made to an MS drug dosing regimen would affect clinical outcomes

and to obtain meaningful information regarding efficacy and safety. *Id.*, ¶¶63, 127, 157. As Dr. Miller admitted, even “open trial[s] in a few patients with known disease,” which are “of much shorter duration than later studies ... still take *many months to a year or longer*[.]” Ex. 2009, 114:17-116:16; Ex. 2005, 49. Further, as Dr. Miller also admitted, disease-modifying drugs “are designed to ... slow disease progression *over the long term*” (Ex. 2005, 61 (emphasis in original)) and thus “it is not possible to evaluate the extent to which any of these drugs is working for any one individual at any particular point in time.” *Id.*, 60; *see* Ex. 2009, 116:18-117:22, 118:16-119:8. A POSA thus would have understood that the treatment benefits of any dosing schedule of a disease-modifying drug can only be assessed over years, and that for each adjustment in dose and/or dosing length, a separate dosing schedule would need to be studied to assess the impact of such a change. Ex. 2051, ¶¶63, 127, 157.

Sixth, Petitioner’s routine optimization suggestion ignores the numerous possible combinations of dose, dosing period length/number, and drug-free period length/number that a POSA could have “optimized.” *Id.*, ¶¶158-162. Petitioner argues “Bodor’s [two-/ten-]month [treatment/cladribine-free] period as a starting point for optimization” (Pet. 60-61) but as discussed above, (1) under Petitioner’s theory a POSA would not have started with Bodor’s regimen at least because Bodor’s maximum 140 mg cladribine dose likely would have been insufficient to

reduce lymphocytes to below 1000 cells/ μ L and (2) a POSA would not have been motivated to resume treatment after Bodor's 10-month cladribine-free period. Ex. 2051, ¶¶98-119, 150. Petitioner fails to explain why, "[g]iven Stelmasiak's success" (Pet. 6), a POSA would not have considered *Stelmasiak* as a starting point.

Indeed, even if a POSA would have considered re-treating after starting with Bodor's 140 mg dose, a POSA could have considered Stelmasiak's 2- or 5-month cladribine-free period (Ex. 1013, 5), Rice's 12-month minimum cladribine-free period (Ex. 1018, 1146), or any other length of the cladribine-free period. Ex. 2051, ¶158. For the maintenance period dose, Dr. Miller opts for a "lower" dose, but *any* dose less than Bodor's 140 mg maximal dose would have been "lower," or if a POSA would have started with Stelmasiak's oral dose as an induction period dose, any dose less than 300 mg would have been "lower." *Id.*, ¶159. And if a POSA were considering a cladribine-free period, they could have considered Rice or Stelmasiak's cladribine-free period, or any length in between. Ex. 2051, ¶158.

Thus, Petitioner's simplistic suggestion that a POSA would have arrived at the claimed method by routine optimization ignores the numerous combinations of dose/dosing period length and number/drug-free period length and number. Ex. 2051, ¶¶161-162. Petitioner fails to establish that there were a finite number of identified and predictable solutions and provides no motivation as to *which*

specific combination to pick or any expectation as to which combination would work.

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, 1070-71 (Fed. Cir. 2012) (alteration in original) (internal quotations and citations omitted). As of 2004, ***nothing*** in the art taught a POSA how the combination of different variables—dose, length and number of dosing periods or drug-free periods—would impact the treatment of MS (including RRMS and early SPMS) or what specific combination (if any) would result in a safe and effective method for treating RRMS or early SPMS. Ex. 2051, ¶162. Instead, the art taught that “[w]e remain to be convinced that cladribine is useful, and ***do not recommend its use in the management of patients with multiple sclerosis.***” Ex. 2031, 753. “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).

For at least the above reasons, Petitioner fails to show how a POSA would have been motivated to arrive at the specific combination of (a) an about 2-4 month induction period and an about 2-4 month maintenance period, (b) about 1.7-3.5 mg/kg induction dose and about 1.7 mg/kg maintenance dose, and (c) about 8-10 month cladribine-free period between the induction and maintenance periods, as claimed in the '903 patent, simply by “regularly measuring the patient’s lymphocyte counts and evaluating the efficacy of a given dose based on the change[] in the count.” Paper 10, 30-31.

2. A POSA Would Not Have Been Motivated To Adopt Weight-Based Dosing Or Reasonably Have Expected To Arrive At The Claimed Weight-Based Dosing Regimen

Petitioner fails to explain why a POSA would have shifted from Bodor and Stelmasiak’s flat dosing method to a weight-based dosing method when neither Bodor nor Stelmasiak teaches or suggests weight-based dosing. *Supra*, Section VII.A.1. A POSA would have understood that Bodor considered weight-based dosing in the art but *still* chose flat dosing; and Stelmasiak teaches the effects of cladribine were *unrelated* to its dose per body weight, thus teaching away from it. *Supra*, Section VII.A.1; Ex. 2051, ¶¶85-97, 132. For at least these same reasons, a POSA 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. Ex. 2051, ¶¶164-166.

3. A POSA Would Not Have Been Motivated To Combine Bodor With Stelmasiak To Arrive At The Claimed Induction Doses Or Have Had A Reasonable Expectation Of Success In Doing So

Petitioner identifies “oral drug delivery” and “increased bioavailability” as reasons for a POSA “to use Bodor’s form to treat MS.” Pet. 35. However, a POSA would have understood that Stelmasiak’s oral cladribine method provides a *higher* bioavailability than Bodor’s. Ex. 2051, ¶¶167-171; Ex. 2052, ¶¶81-84.

Drs. Lublin and Meibohm, and even Dr. Miller, all agree that both Stelmasiak and Liliemark studied the same cladribine formulation in the same phosphate-buffered pH 7.4 saline solution. *See* Ex. 2043, 1514, 1515; Ex. 1013, 5; Ex. 2051, ¶168; Ex. 2052, ¶¶82-83; Ex. 1002, ¶110 (admitting that “a POSA would have understood [Stelmasiak’s solution] was the same dosage form disclosed by Liliemark”); Ex. 2009, 57:11-53:5. Liliemark determined, and Dr. Miller agreed, that “the bioavailability of [its] CdA [solution] administered orally is only approximately 50%.” Ex. 2043, 1516; *see* Ex. 2009, 57:15-58:11. As Dr. Meibohm opines, because the Liliemark and Stelmasiak formulations use identical dosing route (oral), identical ingredients (cladribine in saline solutions), identical buffer (PBS), and identical pH (7.4), their formulations have the same

bioavailability, i.e., 50% as reported in both Liliemark and Stelmasiak. Ex. 2051, ¶168; Ex. 2052, ¶¶64-65, 82-83. Indeed, Stelmasiak reports 50% for its oral formulations. Ex. 2052, ¶¶57, 64-65; Ex. 1013, 5; *see also* Ex. 1023, 325.

In contrast, as Dr. Meibohm explains, Bodor determined that its 10 mg tablet has **39.1-39.4%** bioavailability. Ex. 2052, ¶46. Dr. Miller also admitted that “the bioavailability that Bodor reports for its 10 milligram tablets is 39.1 or 39.4 percent.” Ex. 2009, 61:13-18. While Dr. Miller asserts that “Bodor states that this form of cladribine would have better oral absorption and, therefore, would have better bioavailability,” (Ex. 2009, 143:22-144:4), as Dr. Meibohm opines, “oral absorption” is just part of the bioavailability determination, which Bodor determined to be about 39% for its 10 mg cladribine tablets. Ex. 2052, ¶93.

Thus, a POSA would have understood Bodor’s 10 mg cladribine formulation has 39.1-39.4% bioavailability, which is **less** than the 50% bioavailability of Stelmasiak’s formulation. Ex. 2051, ¶¶76, 167-171; Ex. 2052, ¶¶81-84.

Given Bodor’s 10 mg formulation had lower bioavailability (~39%) than Stelmasiak’s (50%), Petitioner’s argument that there is a “[p]reference for ... increased bioavailability” (Pet. 35) suggests a POSA would not have been motivated to start with Bodor’s oral cladribine dose, especially in view of Petitioner’s praise of “Stelmasiak’s success” and Petitioner’s and Dr. Miller’s acknowledgement that Bodor lacks efficacy data for its dosing regimen. Pet. 6, 34

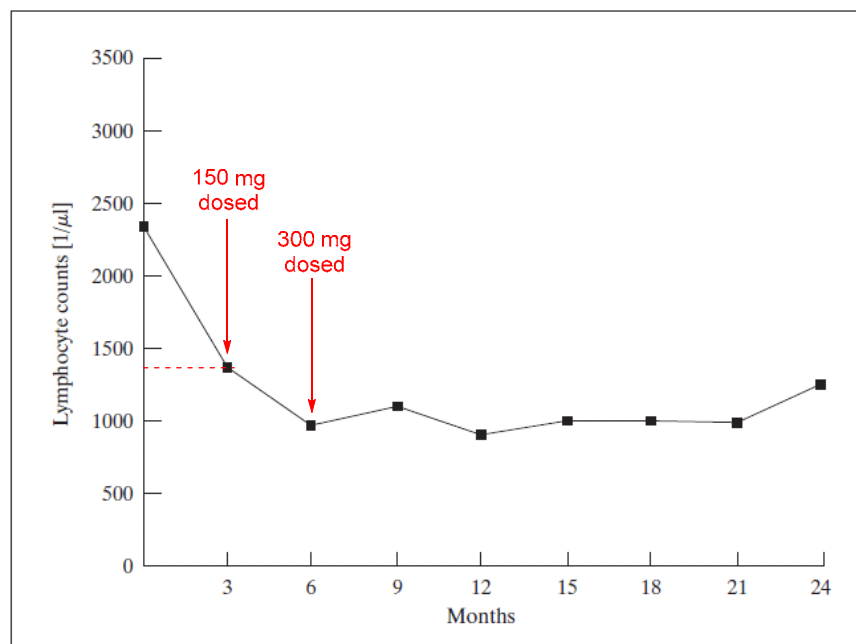
n.9; Ex. 2009, 70:10-71:20; Ex. 2051, ¶¶172-175; Ex. 2052, ¶¶84-89 (also opining that there is no safety concerns with Stelmasiak's initial dose that will motivate a POSA to reduce its dose).

Here, Stelmasiak's 300 mg dose and 150 mg dose reportedly resulted in reduced EDSS scores, but the higher dose resulted in a better EDSS score (2.9 ± 1.7 versus 3.4 ± 1.5 at months 6 and 3, respectively). Ex. 1013, 6 (Table 1). Further, as reported by Stelmasiak, the lymphocyte count reached a nadir at month 6 only after 300 mg was administered, decreasing to 968 cells/ μ L, versus ~ 1350 cells/ μ L at month 3 after 150 mg was administered (annotated Figure 1 of Stelmasiak below). Thus, given Bodor's lower bioavailability, and particularly in view of Petitioner's lymphocyte theory (Pet. 16), a POSA if anything would have expected Bodor's lower dose and two-month dosing period to be *less effective* than Stelmasiak's first three months' dosing regimen. Ex. 2051, ¶¶172-173; Ex. 2052, ¶¶85, 88.

Even if a POSA would have considered Stelmasiak's 150 mg dose efficacious, Stelmasiak reported only partial response from patients. Ex. 1013, 6. Thus, as Drs. Lublin and Meibohm opine, a POSA if anything would have wanted to further increase Stelmasiak's dose, not decrease it to Bodor's 100-140 mg dose. Ex. 2051, ¶174; Ex. 2052, ¶¶85 ("Stelmasiak did not identify a reason to reduce its dose for safety and a POSA would not have been motivated to reduce Stelmasiak's cumulative dose . . ."), 89.

As such, a POSA 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 have had a reasonable expectation of success in doing so. Ex. 2051, ¶175; Ex. 2052, ¶¶86-89.

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



Further, even if a POSA were to convert Stelmasiak's flat dose into mg/kg based on the reported patient weight (52-75 kg), Stelmasiak's 300 mg initial dose corresponds to 4.0-5.7 mg/kg -- significantly higher than the claimed induction period doses of about 1.7-3.5 or 1.7 mg/kg. See Ex. 1013, 5; Ex. 2052, ¶75. Even Stelmasiak's high 300 mg dose ultimately resulted in *no change in EDSS score* at month 24. Ex. 1013, 6 (Table 1). Given that "the most important therapeutic aim

of any disease-modifying treatment of MS is to prevent or postpone long-term disability” (Ex. 2013, 169), a POSA would therefore not have been motivated to *lower* or modify Stelmasiak’s dose to arrive at the claimed induction period dose of about 1.7-3.5 or 1.7 mg/kg, or have had a reasonable expectation of success in doing so. Ex. 2051, ¶¶176-177; Ex. 2052, ¶¶86-89.

4. A POSA Would Not Have Been Motivated To Re-Treat Patients After Bodor’s 10-Month Cladribine-Free Period With A Reasonable Expectation Of Success

Petitioner argues that a POSA would have resumed treatment after Bodor’s cladribine-free period because of “the general immunosuppression framework common with MS therapies” and patients’ relapses. Pet. 37; Ex. 1002, ¶100. However, as discussed above, Bodor does not teach or suggest *any* re-treatment, let alone re-treatment with cladribine immediately after its 10-month cladribine-free period. *Supra*, Section VII.A.2; Ex. 2051, ¶¶98-119. Stelmasiak does not remedy this deficiency. Ex. 2051, ¶¶120-124, 178-184.

First, a POSA would have understood that there was no “general immunosuppression framework common with MS therapies” and the nature of MS treatment is not “cyclical” as Petitioner alleged. Ex. 2051, ¶179; Pet. 16-18, 37. For example, the art shows that dosing of approved disease-modifying treatments for MS was *continuous* so as to *maintain the drug’s pharmacological effects*. *Supra*, Section VII.A.2(a)(2).

In the context of cladribine, a POSA would have looked to the studies in which cladribine was re-treated, e.g., Rice and Romine. Ex. 2051, ¶180. As explained above, the art did not teach repeating treatment absent a specific pharmacological rationale. *Supra*, Section VII.A.2(a)(3). A POSA would not have simply retreated a patient for relapse, absent a showing of patient need, in view of cladribine’s mechanism of action, pharmacologic effects, and safety risks. *Id.*; Ex. 2051, ¶¶180-181.

Second, Petitioner relies on Stelmasiak to teach a “cyclical” regimen. *See* Pet. 4-5, 54. But 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).

Stelmasiak only teaches the “maintenance” of both EDSS and lymphocyte levels when cladribine is re-administered at month 9 (after 2 months of no treatment) and month 12 or 15 (after either 2 or 5 months of no treatment). Ex. 1013, 5-6. Stelmasiak does not teach “maintaining” efficacy levels after 10 months of no treatment. Instead, after 9 months of no treatment (months 16-24), EDSS scores **worsened**, returning to the baseline value for all patients. *Id.*, 6. And while Dr. Miller opines that a POSA would have simply “**believed** Bodor’s dosing regimen to have a sufficient immunosuppressive effect to **treat** MS” (Ex. 1002,

¶99), Bodor offers no supporting data⁸ and Stelmasiak if anything suggests otherwise as its higher dose of a higher bioavailability formulation was not reported to maintain efficacy over a 9-month cladribine-free period. Ex. 2051, ¶183. Thus, Stelmasiak would not have provided motivation to retreat patients after Bodor's 10-month cladribine-free period with a reasonable expectation of success.

Third, as described above, even if there were a need for retreatment, the art does not suggest that a POSA would have re-treated with cladribine as a POSA could have looked to other available MS drugs. Ex. 2051, ¶182; *supra*, Section VII.A.2(a)(3).

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

As the Board correctly indicated, the challenged claims do not require that the total maintenance dose be lower than the total induction dose. Paper 10, 13-17. Nevertheless, Petitioner argues that a POSA would have “lower[ed] the total dose of cladribine administered during the maintenance period” because Stelmasiak's

⁸ While Dr. Miller cited Bodor for cladribine's “clinical efficacy” (Ex. 1002, ¶115; citing Ex. 1022, 23:15-20), at deposition he admitted that Bodor “does not provide efficacy data in those lines.” Ex. 2009, 70:5-15.

data indicates “a lower dose of cladribine would suffice” to maintain an immunosuppressive effect after induction. Pet. 39. But Stelmasiak’s “immunosuppressive effect” is based on a high initial dose (300 mg). Ex. 1013, 5, 7; Ex. 2015, ¶185. Further, as discussed in the previous section, Stelmasiak only teaches the “maintenance” of both EDSS and lymphocyte levels when cladribine is re-administered after a 2- or 5-month drug-free period (at month 9 and 12 or 15). Ex. 1013, 5-6. Notably, after 9 months of no treatment (months 16-24), EDSS scores returned to their starting value, even though lymphocyte levels continued to be suppressed. Ex. 1013, 6.

Turning to Bodor, as discussed above, a POSA would not have expected Bodor’s maximal 140 mg dose, having *lower* bioavailability, to have the same immunosuppressive effect as Stelmasiak’s 150 mg dose. *Supra*, Section VII.B.1 and 3; Ex. 2051, ¶¶150, 158, 167-175. As such, it would have been unclear to a POSA what immunosuppressive effects, if any, would be maintained. Ex. 2051, ¶186. Thus, a POSA would not have been motivated to select an about 1.7 mg/kg weight-based dose, by “lowering” the initial dose, or otherwise. This is especially true when both Bodor and Stelmasiak teach and focus on flat dosing. *Id.*, ¶188.

Lastly, regardless of whether any purported maintenance dose would have been “lowered” or otherwise, neither Bodor nor Stelmasiak provides a POSA with any teaching or guidance as to what dose would have been required to maintain the

treatment effects (if any) of Bodor's 100-140 mg cladribine dose. Given the various possible re-treatment doses, and the complexity, variable nature, and slowly evolving disability of MS, it would require years to evaluate the effects of a re-treatment dose change to determine which (if any) re-treatment dose would have resulted in a safe and effective MS treatment method, all without guidance from the prior art in an unpredictable field. Ex. 2051, ¶187; *supra*, Section VII.B.1.

Petitioner thus fails to establish motivation for a POSA to modify Bodor's method based on Stelmasiak to arrive at a method for treating MS as claimed, or any reasonable expectation of success in doing so.

C. The Dependent Claims Would Not Have Been Obvious Over Bodor And Stelmasiak

For at least the same reasons as discussed above, Bodor and Stelmasiak would not have rendered obvious claims 17, 19, 20, and 22-27.

Additionally, claim 20, requiring the induction and maintenance period doses to be "about 1.7 mg/kg" (Paper 10, 14), would not have been obvious over Bodor and Stelmasiak for at least the following additional reasons. Petitioner argues a POSA would have "retreat[ed] the patient using a *lower* cladribine dose." Pet. 57-58. But for the reasons discussed above in Sections VII.A.1 and VII.B.2, Bodor does not teach or suggest any weight-based dosing for its method, nor would a POSA have understood Bodor to teach or suggest as such. Additionally,

none of the references cited by the Petition teaches or even suggests a cladribine dosing regimen having the same induction and maintenance dose; and the only reference relied on by the Petition for teaching re-treatment, Stelmasiak, requires different dose in the second treatment period. Ex. 2051, ¶¶189-192. There is no motivation or reasonable expectation of success for a POSA to repeat the same dose. *Id.*

VIII. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

“Objective indicia of nonobviousness must be considered in every case where present.” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc); *see also Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1215-16 (Fed. Cir. 2023). Here, nonobviousness is confirmed by at least (1) the skepticism of others, (2) the unexpected durable efficacy and safety of the claimed dosing regimen, and (3) the satisfaction of a long-felt unmet need. Ex. 2051, ¶¶193-229.

A. Skepticism Of Others

“Evidence of industry skepticism weighs in favor of non-obviousness.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016).

The record includes multiple reports of skepticism, including by Petitioner’s own declarant, demonstrating non-obviousness. Ex. 2051, ¶195. In 2000, Dr. Miller explained that “[i]n recently completed trials. . . , cladribine. . . [was] found

not to be of benefit” for treating MS and that “[a] trial of cladribine failed to show benefit in progressive disease.” Ex. 2005, 45, 67. And in a 2008 review referencing pre-2004 trials, Dr. Miller expressed skepticism that cladribine would be useful for treating MS, suggesting “it seems *prudent to await the results* of a prospective, randomized, blinded trial of oral cladribine before recommending its use in patients with MS.” Ex. 2004, 341. In a contemporaneous book chapter regarding MS, the renowned MS specialist Dr. Noseworthy expressly recommended against cladribine for MS patients: “We remain to be convinced that cladribine is useful, and *do not recommend its use in the management of patients with multiple sclerosis.*” Ex. 2031, 753.

In reaching their conclusions, Drs. Miller and Noseworthy referenced cladribine clinical trials for MS, including by Sipe, Grieb, Beutler, Romine, and/or Rice, that “proved unsuccessful” according to Dr. Lublin. Ex. 2051, ¶¶195-197; Ex. 2004, 341; Ex. 2031, 753; Ex. 2011, III/3. Dr. Miller, Dr. Noseworthy, and Dr. Lublin confirm the skepticism of skilled artisans regarding cladribine’s utility to treat MS. Ex. 2051, ¶¶195-198.

Even after the CLARITY trial provided positive results for the claimed dosing regimen based on significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity (Ex. 2033, 416), skepticism remained. Ex. 2051, ¶199. In 2011, FDA issued a complete response letter

“conclud[ing] that substantial evidence of Cladribine Tablets’ effectiveness was provided by the CLARITY[] study,” but raised concerns over higher cancer risks associated with Mavenclad®. Ex. 2038, 1; Ex. 2039, 11. FDA’s skepticism provides further evidence that the claimed dosing regimen was nonobvious. *See Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019) (finding no error in the Board’s finding “that evidence of skepticism of others, *particularly the FDA*, supported a conclusion of nonobviousness”).

B. Unexpected Results

MAVENCLAD® has offered unexpected durable efficacy and safety in treating RRMS. The CLARITY Extension study showed that the two-year dosing regimen from the original CLARITY trial, in which patients received a total cladribine dose of 3.5 or 5.25 mg/kg over two years followed by two years of placebo, resulted in *durable* clinical efficacy that was comparable to the four-year regimen in which patients further received an additional 3.5 mg/kg dose of cladribine over years three and four, with improved safety profiles. Ex. 2035, 1594, 1603. “[T]he response achieved at the end of CLARITY in the proportion of patients free from relapses or sustained disability progression was *maintained* in the Extension.” *Id.*, 1603. Such durability was unexpected. Ex. 2042, 3 (“What became clear . . . was this drug [i.e., cladribine] has a *durability* of effect that was *unexpected*.”); Ex. 2051, ¶205.

Moreover, CLARITY Extension showed that further dosing of cladribine after two years of treatment is not needed because “there was no significant incremental benefit from additional treatment with cladribine tablets in Years 3 and 4.” Ex. 2035, 1603. And “[i]mportantly, there was no evidence of increased clinical activity (i.e. disease rebound) after treatment discontinuation (e.g. in the CP 3.5 mg/kg group), as reported for other therapies in MS with a direct effect on lymphocytes.” *Id.* Notably, the long-term efficacy of cladribine tablets in patients from CLARITY/CLARITY Extension was confirmed in the CLASSIC-MS study, finding “sustained long-term mobility and disability benefits of cladribine tablets” during the median **10.9 years**’ follow-up period. Ex. 2036, 719; Ex. 2051, ¶206. The identification of an optimal dosing length of two years is surprising, especially since it had been expected that cladribine’s “beneficial effect should eventually decline and would not be expected to last much beyond 2 years” for chronic progressive MS. Ex. 1031, 43; Ex. 2051, ¶207.

Thus, the CLARITY trials studying the claimed dosing regimen not only demonstrated significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity, but also yielded a nonobvious dosing regimen “sweet spot,” i.e., a minimal dosing period that achieved the same clinical benefits as four-year dosing but with a lower incidence of lymphopenia. Ex. 2051, ¶207. MAVENCLAD®’s unexpected durability provides a short-duration dosing regimen

that “allows for reduced treatment and management burden for patients and providers,” (Ex. 2023, 1924), which “facilitate[s] treatment adherence, a significant challenge for patients with MS.” Ex. 2035, 1603. One clinical neurologist described the impact of MAVENCLAD®’s dosing regimen as follows:

It’s huge ... once they invest in the initial 5 days, and then the second 5 days, their commitment for a year is over. A year later, you commit yourself for another 5 days and another 5 days, and that’s the end of the treatment. To be able to do that and not to have to worry about, “Did I miss my drug? Did I take it?” You can go on vacation. You can leave your home for 6 months or even a year and you don’t have any problems. That convenience for them is really, really big.

Ex. 2042, 4.

Surprisingly, in 2020, “[c]ladribine tablets are postulated to be an immune reconstitution therapy,” i.e., cladribine causes a transient reduction in lymphocytes “followed by a recovery period during which cells gradually repopulate and immune function is restored.” Ex. 2032, 1923. It has been hypothesized that the “reconstituted lymphocyte population is ... less autoreactive towards the CNS component, resulting in prolonged efficacy, as demonstrated in the cladribine tablets clinical studies[.]” *Id.* Whereas other FDA-approved MS treatments generally required continuous dosing (*supra*, Section II.A.1; Section

VII.A.2(a)(2)), the effects of cladribine “persist long after the drug is eliminated from the body[.]” Ex. 2032, 1923.

C. Satisfaction of a Long-Felt, Unmet Need

MAVENCLAD®’s “unique dosing regimen has offered patients a more convenient method of medication administration” that provides “the benefit of a short commitment to the treatment and a long-lasting possibility to offer relief.” Ex. 2042, 1, 4. MAVENCLAD® offers patients a treatment commitment of only about 10 days in 2 month per year for two years, with long-lasting clinical benefits of up to about 10 years without further treatment. MAVENCLAD®’s unique dosing regimen satisfied the long-felt, unmet need for a short, convenient treatment with long-lasting clinical benefits without further treatment, as all other MS drugs require inconvenient, continuous dosing of the drugs to maintain pharmaceutical effects, providing further evidence that the claimed dosing regimen was anything but obvious. Ex. 2051, ¶209-216.

D. Nexus

The skepticism of others, unexpected results, and satisfaction of a long-felt, unmet need bear a direct nexus to the claimed invention. Objective evidence supporting non-obviousness “need only be ‘reasonably commensurate with the scope of the claims.’” *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013). Objective evidence has a nexus to the claims when the evidence is the “direct

result of the unique characteristics of the claimed invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1374 (Fed. Cir. 2019); *see also Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417-18 (Fed. Cir. 2022).

Here, the CLARITY trial evaluated the method recited in at least claims 17 and 20. As Dr. Lublin explains, the CLARITY results have a nexus to at least claims 17 (induction period (about 1.7-3.5 mg/kg, 2-4 months) + maintenance period (about 1.7 mg/kg; 2-4 months), which corresponds to total dose (about 3.4-5.2 mg/kg)) and 20 (induction period (about 1.7 mg/kg, 2-4 months) + maintenance period (about 1.7 mg/kg; 2-4 months), which corresponds to total dose (about 3.4 mg/kg)). The unexpected durable efficacy and safety of the claimed dosing regimen as studied in CLARITY is a direct result of the two-year dosing regimen, in which ***both*** the ***3.5 and 5.25 mg/kg*** two-year regimens were ***equally efficacious*** and comparable to the four-year cladribine regimen, but with an ***improved safety*** profile. Ex. 2051, ¶¶218-219; Ex. 2033, 425-26; Ex. 2035, 1594, 1599 (Table 2), 1603.

The FDA-approved method of administering MAVENCLAD[®] also practices the method recited in at least claims 17 and 20. As Dr. Lublin explains, there is a nexus between MAVENCLAD[®] and at least claims 17 and 20. Ex. 2051, ¶¶223-226. The efficacy and safety of MAVENCLAD[®]'s method is a direct result of the claimed dosing regimen, which provides significant benefits in relapse rate,

disability progression, and MRI measures, and was comparable to the four-year cladribine regimen but with an *improved safety* profile. Ex. 2033, 425-26; Ex. 2035, 1594, 1599 (Table 2), 1603.

Lastly, as Dr. Lublin explains, FDA's skepticism regarding malignancies arising in CLARITY was tied to the tested dosing regimen, which embodies the claims of the '903 patent. Ex. 2051, ¶228; Ex. 2033, 424.

IX. CONCLUSION

Patentability of the challenged claims should be confirmed.

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PATENT OWNER'S UPDATED LIST OF EXHIBITS

Exhibit No.	Description
2001	MAVENCLAD [®] (cladribine) Package Insert (2022)
2002	Declaration of David B. Bassett in Support of Motion for Admission <i>Pro Hac Vice</i>
2003	Declaration of Vinita Ferrera in Support of Motion for Admission <i>Pro Hac Vice</i>
2004	H. El-Moslimany et al., <i>Escape Therapies and Management of Multiple Sclerosis</i> in C. S. Raine MULTIPLE SCLEROSIS A COMPREHENSIVE TEXT 333 (2008) (Excerpt)
2005	A. E. Miller et al., <i>Treatment Issues</i> in R. C. Kalb MULTIPLE SCLEROSIS: THE QUESTION YOU HAVE – THE ANSWERS YOU NEED 43 (2d ed. 2000) (Excerpt)
2006	M. J. Tullman et al., <i>Immunotherapy of Multiple Sclerosis – Current Practice and Future Directions</i> , 39 J. REHAB. RES. DEV. 273 (2002)
2007	Video: A. Miller, <i>What You Need to Know About Mavenclad[®]</i> (https://www.nationalmssociety.org/Treating-MS/Medications/Mavenclad) (2019); image of USB Drive containing video
2008	Transcript of Video, A. Miller, <i>What You Need to Know About Mavenclad[®]</i> (2019)
2009	Deposition Transcript of Dr. Aaron Miller (December 12, 2023)
2010	J. E. Joy et al., <i>Multiple Sclerosis: Current Status and Strategies for the Future</i> , 17 (2001) (Excerpt)
2011	F. Lublin, <i>History of Modern Multiple Sclerosis Therapy</i> , 252 (SUPPL 3) J. NEUROL. III/3 (2005)

Exhibit No.	Description
2012	<i>Reserved</i>
2013	D. S. Goodin et al., <i>Disease Modifying Therapies in Multiple Sclerosis</i> , 58 NEUROLOGY 169 (2002)
2014	Betaseron [®] (Interferon beta-1b) Package Insert (1993)
2015	Avonex [™] (Interferon beta-1a) Package Insert (1996)
2016	Rebif [®] (Interferon beta-1a) Package Insert (2003)
2017	Copaxone [®] (glatiramer acetate) Package Insert (2001)
2018	Novantrone [®] (mitoxantrone) Package Insert (2000)
2019	Tysabri [®] (natalizumab) Package Insert (2004)
2020	R. A. Rudick et al., <i>Natalizumab: α_4-Integrin Antagonist Selective Adhesion Molecule Inhibitors for MS</i> , 4 EXPERT REV. NEUROTHER. 571 (2004)
2021	R. A. Rudick et al., <i>Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis</i> , 354 NEW ENG. J. MED. 911 (2006)
2022	<i>Reserved</i>
2023	<i>Reserved</i>
2024	L. Durelli, <i>Dose and Frequency of Interferon Treatment Matter</i> , 250 J. NEUROL. (SUPPL 4) IV/9 (2003)
2025	D. S. Alberts et al., <i>Disposition of Mitoxantrone in Cancer Patients</i> , 45 CANCER RES. 1879 (1985)

Exhibit No.	Description
2026	M. Caporro et al., <i>Two Decades of Subcutaneous Glatiramer Acetate Injection: Current Role of the Standard Dose, and New High-Dose Low-Frequency Glatiramer Acetate in Relapsing-Relapsing Multiple Sclerosis Treatment</i> , 8 PATIENT PREFER. ADHERENCE 1123 (2014)
2027	<i>Reserved</i>
2028	<i>Reserved</i>
2029	U.S. Patent No. 8,785,415
2030	J. C. Sipe et al., <i>Development of Cladribine Treatment in Multiple Sclerosis</i> , 1 MULT. SCLER. 343 (1996)
2031	J. Noseworthy et al., <i>Disease-Modifying Treatments in Multiple Sclerosis</i> in A. Compston MCALPINE'S MULTIPLE SCLEROSIS 729 (4 th ed. 2005) (Excerpt)
2032	K. Rammohan et al., <i>The Development of Cladribine Tablets for the Treatment of Multiple Sclerosis: A Comprehensive Review</i> , 80 DRUGS 1901 (2020)
2033	G. Giovannoni et al., <i>A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis</i> , 362 NEW ENG. J. MED. 416 (2010)
2034	G. Giovannoni et al., <i>Supplementary Appendix to A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis</i> , 362 NEW ENG. J. MED. 416 (2010)
2035	G. Giovannoni et al., <i>Safety and Efficacy of Cladribine Tablets in Patients with Relapsing-Relapsing Multiple Sclerosis: Results from the Randomized Extension Trial of the CLARITY Study</i> , 24 MULT. SCLER. J. 1594 (2018)

Exhibit No.	Description
2036	G. Giovannoni et al., <i>Long-Term Follow-Up of Patients with Relapsing Multiple Sclerosis from the CLARITY/CLARITY Extension Cohort of CLASSIC-MS: An Ambispective Study</i> , 29 MULT. SCLER. J. 719 (2023)
2037	A. Miller et al., <i>Current and Investigational Therapies Used to Alter the Course of Disease in Multiple Sclerosis</i> , 90 SOUTH. MED. J. 367 (1997)
2038	<i>Merck Receives Complete Response Letter From FDA on Cladribine Tablets New Drug Application</i> , FIERCEBIOTECH.COM (March 2, 2011) (https://www.fiercebiotech.com/biotech/merck-receives-complete-response-letter-from-fda-on-cladribine-tablets-new-drug-application), accessed on December 20, 2023
2039	<i>Reserved</i>
2040	FDA News Release: <i>FDA Approves New Oral Treatment For Multiple Sclerosis</i> (March 29, 2019) (https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-treatment-multiple-sclerosis), accessed on November 25, 2023
2041	ClinicalTrials.gov publication and Record History, NCT00213135 <i>A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-Relapsing Multiple Sclerosis (RRMS) (CLARITY)</i> (2014) (https://clinicaltrials.gov/study/NCT00213135 ; https://clinicaltrials.gov/study/NCT00213135?tab=history&a=13), accessed on November 25, 2023
2042	M. Hoffman, K. Rammohan Interview: <i>Short-Term Dosing Regimen Gives Cladribine an Advantage in MS</i> , NEUROLOGYLIVE (July 1, 2020) (https://www.neurologylive.com/view/shortcommitment-dosing-regimen-gives-cladribine-an-advantage-in-ms), accessed on November 10, 2023

Exhibit No.	Description
2043	J. Liliemark et al., <i>On the Bioavailability of Oral and Subcutaneous 2-Chloro-2'-Deoxydenosine in Humans: Alternative Routes of Administration</i> , 10 J. CLIN. ONCOL. 1514 (1992)
2044	U.S. Provisional Patent Application No. 60/458,922
2045	U.S. Provisional Patent Application No. 60/484,756
2046	U.S. Provisional Patent Application No. 60/541,247
2047	U.S. Patent No. 8,785,415 File History, Response to Rule 312 Communication Post Allowance, filed on June 12, 2014
2048	The 2002 Product Development and License Agreement between IVAX International GMBH and Ares Trading S. A. (PROTECTIVE ORDER MATERIAL)
2049	December 17, 2003 email and Cladribine Briefing Document (PROTECTIVE ORDER MATERIAL)
2050	August 27, 2003 Meeting Minutes for the Oral Cladribine for MS Project Joint Meeting (PROTECTIVE ORDER MATERIAL)
2051	Declaration of Fred D. Lublin, M.D.
2052	Declaration of Bernd Meibohm, Dr.rer.nat.
2053	Declaration of Alain Munafo, Ph.D.
2054	Declaration of Nicholas Bodor, Ph.D., D.Sc., d.h.c.
2055	Declaration of Yogesh Dandiker, Ph. D.
2056	Serono Press Release, <i>Serono and IVAX to Develop Oral Therapy for Multiple Sclerosis</i> (October 30, 2002)

Exhibit No.	Description
2057	Serono S.A. Form 20F (2003)
2058	C. Sargent, <i>Serono Purchases Rights to Experimental MS Drug</i> , Wall Street Journal (October 31, 2002) (https://www.wsj.com/articles/SB1035995148253461151), accessed on December 14, 2023
2059	Copaxone® (glatiramer acetate) Package Insert (2014)
2060	A. Liu, <i>Better 8 Years Late Than Never: Merck KGaA Nabs FDA Nod for MS Drug Mavenclad</i> , FIERCEPHARMA.COM (April 1, 2019) (https://www.fiercepharma.com/pharma/better-8-years-late-than-never-merck-kgaa-nabs-fda-nod-for-ms-drug-mavenclad), accessed on December 18, 2023
2061	The Canadian Cooperative Multiple Sclerosis Study Group, <i>The Canadian Cooperative Trial of Cyclophosphamide and Plasma Exchange in Progressive Multiple Sclerosis</i> , 337 LANCET 441 (1991)
2062	J. W. Hainer et al., <i>Dosing in Heavy-Weight/Obese Patients with the LMWH, Tinzaparin: A pharmacodynamic Study</i> , 87 THROMB HAEMOST. 817 (2002) (Excerpt)
2063	B. Meibohm et al., <i>Clinical Pharmacodynamics & Pharmacokinetics</i> , In: R. A. Helms, RA et al. TEXTBOOK OF THERAPEUTICS: DRUG AND DISEASE MANAGEMENT 1 (8 th ed. 2006) (Excerpt)
2064	<i>Reserved</i>
2065	<i>Reserved</i>
2066	<i>Reserved</i>
2067	Declaration of Asher S. McGuffin in Support of Exhibits 2056, 2057, and 2058

Exhibit No.	Description
2068	Declaration of Cindy Kan in Support of Exhibits 2038, 2040, 2041, 2042, 2060, and 2070
2069	U.S. Patent No. 7,888,328
2070	SAFETY & SIDE EFFECTS Learn about the possible risks of MAVENCLAD (https://www.mavenclad.com/en/home/why-mavenclad/safety-and-side-effects.html#:~:text=It) (last updated November 2022), accessed on December 18, 2023
2071	Declaration of Willem de Weerd in Support of Exhibits 2048, 2049, and 2050

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response contains 13,929 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/
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CERTIFICATE OF SERVICE

I hereby certify that on December 21, 2023, I caused a true and correct copy of the following materials:

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