

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 IPR2023-00480
Patent 7,713,947

PATENT OWNER'S SUR-REPLY

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I. INTRODUCTION¹

Petitioner asks the Board first to find that a POSA would have overlooked the field's overwhelming skepticism of cladribine, including that of its own declarant, Dr. Miller, so that the Board may find the challenged claims obvious over Bodor and Stelmasiak. But Bodor's regimen was attributable to the '947 patent inventors, not "by another"; thus, it is not prior art against the '947 patent. Even if Bodor were prior art, Petitioner's challenge fails.

Petitioner contends the challenged claims encompass flat and weight-based regimens. Reply 11-13. But Petitioner misconstrues the claims. The claims must be read in view of the '947 specification, which teaches administering cladribine based on patient weight. Ex. 1001, 14:41-44, 14:63-66. While the challenged claims do not expressly recite determining patient weight before drug administration, a POSA would have understood the claims require this when read in view of the specification. Ex. 1061, 144:20-145:3.

Further, despite basing its initial obviousness theory on Bodor's "improved" bioavailability and *ignoring* Bodor's bioavailability data (Pet. 23, 33), Petitioner now changes course to argue that "Bodor's bioavailability was *at least comparable* to Stelmasiak's." Reply 23. Petitioner's new bioavailability theory and related

¹ All emphases added.

arguments not only contradict its original obviousness theory, but also go beyond the proper scope of reply and should be disregarded.

Petitioner also attempts to revise the basis for its flawed routine-optimization argument—from evaluating efficacy (Pet. 41-42) to evaluating “cladribine’s effect” as measured by lymphocyte counts. Reply 26-27. But Petitioner fails to show how lymphocyte count would be linked to any efficacy parameter, or what lymphocyte level a POSA would look to for optimization. Petitioner’s revised routine-optimization argument thus fares no better.

Petitioner disregards coherence in outcome measures, and instead cherry-picks outcomes for support. Reply 14. For example, Petitioner focuses on Rice’s MRI outcomes, but ignores that Rice’s study failed to meet its primary and secondary clinical outcome measures such that Rice reported “clinical efficacy was not shown.” Ex. 1018, 1153.

Finally, Petitioner disparages objective indicia for allegedly lacking nexus. Reply 31-32. But Petitioner misunderstands the law—objective indicia evidence need only be reasonably commensurate with the claim scope.

For at least the foregoing reasons, patentability should be affirmed.

II. THE CITED PORTION OF BODOR IS NOT “BY ANOTHER”

Rather than address the evidence that the ’947 patent inventors developed Bodor’s regimen, Petitioner speculates about others and incorrectly suggests

Drs. Bodor and Dandiker co-invented the regimen just because they invented a formulation. Patent Owner's ("PO's") un rebutted evidence shows Bodor's regimen came from the '947 patent inventors. The Board should not allow their own work to be used against them.

A. The Burden Did Not Shift To PO

The Board held that "[t]he shifting burden of production is not applicable to ["by another"] analysis under § 102(e)." *Maxlinear, Inc. v. Cresta Tech. Corp.*, No. IPR2015-00594, Paper 90, at 14 (P.T.A.B. Aug. 15, 2016). Regardless, "the burden of persuasion is on the petitioner to prove" references qualify as prior art, "and that burden *never* shifts to the patentee." *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378-81 (Fed. Cir. 2015).

PO produced substantial, detailed evidence showing the '947 patent inventors developed Bodor's regimen and communicated it to at least Dr. Dandiker before February 4, 2004. After that, "the burden of production returned to [Petitioner] to prove that" the cited regimen is "by another." *Id.*, 1380. Petitioner has not met its burdens of production or persuasion.

B. Without Bodor's 6-Line Regimen, Petitioner's Sole Ground Fails

According to the Federal Circuit, at *Duncan* step 1, the Board must hold a petitioner to the specific disclosures it mapped to each limitation. *Ethicon LLC v. Intuitive Surgical, Inc.*, 847 F. App'x 901, 908-09 (Fed. Cir. 2021); *Google LLC v.*

IPA Techs. Inc., 34 F.4th 1081, 1086 n.3 (Fed. Cir. 2022) (excluding merely “relevant” citations from *Duncan* analysis). The 6-line regimen is the only portion of Bodor that Petitioner maps to several limitations, including the induction and maintenance periods—and is the only disclosure *from any source* mapped to the total doses and cladribine-free period. Pet. 45-52. Petitioner should be held to its exclusive reliance on these 6 lines.

Even if the Board considered Petitioner’s immaterial additional citations to Bodor, which Petitioner cited regarding “fine tuning,” motivation to combine, and expectation of success, those portions do not disclose any regimen. Pet. 3, 33, 41-45. Even if “relevance” were enough, those portions do not teach any induction/maintenance period, cladribine-free period, or total doses. Without the 6-line regimen, Petitioner has identified nothing teaching these claim limitations. Petitioner’s sole ground fails.

C. The Only Evidence Shows The Regimen In Bodor Was By Serono

Petitioner vaguely speculates that IVAX had approximately 10,000 employees who *could have* developed Bodor’s regimen yet identifies no evidence. Reply 8. The record shows Drs. Bodor and Dandiker did not work on any regimen, let alone one with 6-7 days of dosing. Ex. 2054, ¶26; Ex. 2055, ¶23; *see also* Ex. 2054, ¶¶11-18; Ex. 2055 ¶¶12-18. Instead, the ’947 patent inventors developed and communicated a regimen to IVAX, including at least Dr. Dandiker.

Ex. 2049; Ex. 2053, ¶¶17-53; Ex. 2048, 17-19; Ex. 2055, ¶¶18, 24-27. The 6-line flat-dosing regimen in Bodor is an (incomplete) excerpt of their disclosure. Ex. 1063, 100:2-16; 168:15-169:1; Ex. 2053, ¶48; Ex. 2055, ¶26.

Similarly, Petitioner questions Dr. De Luca's contribution (Reply 6), yet fails to rebut testimony showing Dr. De Luca was part of the Serono team that developed the regimen. Ex. 2053, ¶¶18-22, 34, 40.

Dr. Munafo's testimony is extensively corroborated—by detailed contemporaneous documents (Ex. 2048; 2049; 2050), Drs. Bodor and Dandiker's testimony (Ex. 2054; Ex. 2055), and the '947 patent (Ex. 1001). Contrary to Petitioner's argument, corroboration is judged under the "rule of reason," so "there need not be corroboration for every factual issue contested by the parties." *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1464 (Fed. Cir. 1998); *Fleming v. Escort Inc.*, 774 F.3d 1371, 1377 (Fed. Cir. 2014) (corroboration only requires "evidence that, as a whole, makes credible the testimony of the...inventor"). PO's corroborating evidence far exceeds *Ethicon's*. *Ethicon, Inc.*, 135 F.3d at 1464.

In contrast, Petitioner's theory that *unidentified* IVAX personnel independently invented the regimen is uncorroborated, unsupported, and contradictory to Petitioner's only ground. That is, if the flat-dosing regimen in

Bodor is materially different from Serono's regimen, as Petitioner alleges, then it cannot render the challenged claims' weight-based doses obvious. Reply 7.

D. Drs. Bodor And Dandiker Did Not Co-Invent The Regimen In Bodor

Petitioners do not explain how Drs. Bodor and Dandiker's involvement in a *formulation* renders them co-inventors of the dosing *regimen*. Petitioner's argument cites no law and is inconsistent with *In re Matthews*. 408 F.2d 1393, 1394-95 (C.C.P.A. 1969) (holding inventors of separate, but related inventions not co-inventors).

Serono's *regimen* (in Bodor) is distinct from Drs. Bodor and Dandiker's *formulation*. A product and process of use are distinct if either can be used without the other. MPEP §806.05(h); *see Novartis AG v. Ezra Ventures LLC*, 909 F.3d 1367, 1372 (Fed. Cir. 2018). Here, Bodor teaches that its formulation can be used to treat different diseases. Ex. 1022, 22:8-26. Further, Bodor (and its issued patents) do not claim the regimen. *Id.*, 40-53; Ex. 2029, 22:16-27:15; Ex. 2069, 22:20-26:32; *see also* Ex. 2054, ¶¶19-25; Ex. 2055, ¶¶19-22.

Indeed, the evidence shows that the regimen and formulation were distinct projects developed "in parallel," (Ex. 1063, 78:9-80:2), and that IVAX's formulation development was ongoing when the '947 patent inventors disclosed

their regimen to IVAX. Ex. 2049, 9, 27-34. Serono—**not** Drs. Bodor and Dandiker—worked on the regimen. Ex. 2054, ¶26; Ex. 2055, ¶23.

Even acknowledging Drs. Bodor and Dandiker’s formulation work, any incidental relation to the regimen was not “significant enough...to render [them] joint inventor[s] *of the applied portions*” of Bodor. *Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1358 (Fed. Cir. 2019). Petitioner has not shown the formulation work significantly contributed to key aspects of the regimen like the alleged induction period and cladribine-free period. Instead, both testified that they did not “develop[], research[], or invent[] the [cited] dosing regimen...[or] **any** cladribine dosing regimen for treating MS.” Ex. 2054, ¶26; Ex. 2055, ¶23.

Contrary to the excerpt Petitioner quotes out-of-context (Reply 5) Dr. Munafo testified that he knew IVAX’s formulation **could** have a “hypothetical...effect on...a dosing regimen.” Ex. 1063, 78:5-80:4, 164:11-18. But Serono disclosed its regimen to IVAX **before** Bodor’s formulation was complete. Ex. 2049, 27-34, 47-51; Ex. 1063, 165:6-14; Ex. 2055, ¶25-27. Petitioner has not shown the formulation changed Serono’s dosing regimen.

The portion of Bodor relied on by Petitioner is not “by another” and Petitioner’s sole ground fails.

III. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS

A. Bodor And Stelmasiak Fail To Disclose Or Suggest All Claim Limitations

1. No Disclosure Or Suggestion Of The Claimed Weight-Based Induction Or Maintenance Dosing

Petitioner contends the challenged claims encompass both flat and weight-based regimens because “the claims do not require ‘any active, *a priori*, steps of determining an individual patient’s weight and performing calculations to arrive at a mg/kg dosing before any drug is administered.’” Reply 12 (quoting Paper 10 (“DI”), n.17). Petitioner misconstrues the claims. “The claims...do not stand alone” and “must be read in view of the specification.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (*en banc*).

The specification explicates the claim term “the total dose of cladribine reached at the end of the [induction/maintenance] period is [from about 1.7 mg/kg to about 3.5 mg/kg/about 1.7 mg/kg].” Ex. 1001, 19:13-30. It states “patients in Groups 2 and 3 receives 3 mg or 10 mg 2-CdA (...*depending on the patient’s weight*)” and “[e]xamples of administration schemes for the induction period *depending on the patient’s weight* are given below in Tables 3 and 4[.]” *Id.*, 14:41-44, 14:63-66. Tables 3 and 4 specifically teach using *patient-weight* ranges to determine the number of cladribine pills to administer. *Id.*, 15:1-45. Further, the specification explains that “[t]he *dosage administered*...will vary” including

based on “**body weight.**” *Id.*, 5:30-35. The specification thus teaches weight-based dosing.

The MAVENCLAD® label, like the challenged claims, does not explicitly instruct determining a patient’s weight to arrive at a mg/kg dose before administration. Ex. 2001, 5 (“[t]he recommended cumulative dosage of MAVENCLAD is **3.5 mg per kg body weight administered** orally)... (see Table 1).” But it includes a table expressly using patient-weight ranges to determine the number of cladribine pills to give to the patient in accordance with the cumulative mg/kg dosage instruction, similar to the specification. *Compare id.*, with Ex. 1001, Tables 3-4.

Even without explicit instructions to determine patient weight, Petitioner’s declarant Dr. Miller testified that the label’s “instructions clearly **imply** that... somebody had to weigh the patient” and that “[o]f course it’s **required** that someone **weigh the patient**. How can you make a dosage by patient weight if somebody doesn’t weigh the patient?” Ex. 2079, 75:20-76:16. Like MAVENCLAD®’s label, the claims are no different. Indeed, Dr. Lublin testified that one must “know a patient’s weight before administering cladribine according to the methods claimed in the ’947 patent.” Ex. 1061, 144:20-145:3. Thus, in view of the specification, a POSA would have understood the challenged claims require determining patient weight to arrive at the claimed mg/kg dosing.

In contrast to the challenged claims’ weight-based dosing, Bodor and Stelmasiak only disclose *flat* dosing. POR 18-24; Ex. 2051, ¶¶18-19, 24, 85-97; Ex. 2052, ¶¶66-77. And Stelmasiak, where patients with different weights received the same dose, cladribine’s effect was *not* linked to dose in mg/kg—Stelmasiak reported that “[t]here was no indication that a ‘good response’ is related to the actual cladribine dose per body weight.” Ex. 1013, 7.

Even Dr. Miller considered MAVENCLAD®’s weight-based dosing “unique” (Ex. 2007, 3:53-4:18; Ex. 2008, 4:17-5:1). Despite Petitioner’s argument that this was limited to “*approved* MS drugs,” (Reply 13), Petitioner ignores that like Bodor, FDA-approved COPAXONE® had a fixed daily dose (20 mg/day), which Dr. Miller acknowledged did “not vary depending upon the patient’s weight.” Ex. 2009, 124:11-125:1.

2. No Disclosure Or Suggestion Of The Claimed Maintenance Period

Petitioner argues a POSA would have re-treated to maintain lymphocyte suppression achieved during an induction period. Reply 20. However, Petitioner fails to show lymphocytes would remain suppressed for the claimed 8-10 months between the induction/maintenance periods or explain why a POSA would have waited 8-10 months to re-treat to maintain lymphocyte suppression.

Only by improperly shifting its obviousness theory to now rely on Rice does Petitioner argue lymphocyte levels would remain suppressed. Reply 26; *infra* Sections III.B.2, III.B.3. Even then Petitioner's argument fails: Rice does not show maintaining lymphocyte suppression (<1000 cell/ μ L) for more than 6 months after the 0.7 mg/kg dosing phase. Ex. 1018, 1152.

The art did not suggest the claimed maintenance period 8-10 months after the claimed induction period.

First, the prior art demonstrates concerns about cladribine's safety and retreatment. POR 5-6, 25-27, 30-33; Ex. 2051, ¶¶72-73, 98-101, 113-115. Romine and Rice each set forth hematologic criteria before cladribine could be administered and require disease progression for re-treatment. Ex. 1031, 36, 43; Ex. 1018, 1146-1147. Rice also did not permit re-treatment until ***at least 12 months*** after the last cladribine dose. Ex. 1018, 1147.

Petitioner and Dr. Miller wrongly argue Romine's "long-term toxicity" discussion is "unrelated to cladribine." Reply 15; Ex. 1084, ¶57; Ex. 1031, 43-44. But even so, cladribine was not considered safe. As Beutler explained, "the ***possibility of malignancies*** occurring long after administration of [cladribine] ***cannot be dismissed.***" Ex. 1014, 1720. Dr. Miller admitted cladribine "raised safety concerns, particularly related to malignancies." Ex. 2078, 1402; Ex. 2079, 143:4-144:9.

Second, a POSA would have understood that in 2004, FDA-approved MS treatments were disease-modifying drugs dosed continuously to maintain the drug's pharmacological effects, efficacy, and safety. POR 27-30; Ex. 2051, ¶¶54-58, 103. Even for natalizumab (dosed 300mg once every four weeks), Dr. Miller admitted “you would not *discontinue* the medication *at any particular point*.” Ex. 2079, 182:21-183:7. Such continuous administration does not inform whether or when to retreat with cladribine. Ex. 2051, ¶¶102-110. Even accepting Petitioner's characterization of natalizumab and other drugs (e.g., Ex. 2061) as being dosed “cyclically,” Petitioner fails to explain how cladribine's pharmacological effects, efficacy, and risks, would have led to re-treatment as claimed. POR 27-30; Ex. 2051, ¶20; Reply 20.

Third, none of Romine, Rice, or Stelmasiak suggests the claimed maintenance period. POR 30-35. Petitioner's re-treatment argument ignores the re-treatment criteria of Romine and Rice (including Rice's timing requirement) and Stelmasiak's two-month cladribine-free period after its initial 6-month dosing phase.

B. No Motivation Or Reasonable Expectation Of Success

1. Petitioner's Routine-Optimization Argument Fails

Petitioner previously argued routine-optimization of cladribine dose/dosing length by “evaluating the efficacy” based on “change[s] in a patient's lymphocyte

count.” Pet. 41-42. But following Dr. Miller’s admission that “[l]ymphocyte suppression is not a measure of efficacy” (Ex. 2009, 121:14-18), Petitioner revised its flawed routine-optimization theory to argue a POSA would have optimized based on “cladribine’s effect”—not efficacy—as measured by lymphocyte counts. Reply 27. To distract from its revised theory, Petitioner alleges that “Merck wrongly posits routine-optimization must correlate with therapeutic efficacy[.]” *Id.*, 2. PO merely responded to Petitioner’s arguments. Nonetheless, the Board understood Petitioner’s argument as based on efficacy: “Petitioner argues[] it was known that cladribine’s dose and length of administration are result-effective variables that could be modified to achieve immunosuppression and *therapeutic efficacy, which can be measured*, for example, *by changes in a patient’s lymphocyte counts*.” DI 29; *see also id.*, 30, 40-41, 49.

Petitioner’s revised routine-optimization argument remains flawed.

First, neither Dr. Miller nor Dr. Lublin considers the “therapeutic” effect of lymphocyte suppression to include efficacy. Ex. 2079, 42:5-14; Ex. 2051, ¶¶21, 126, 136-144; *see also* POR 37-41.

Petitioner argues that “[p]rior studies routinely used lymphocyte counts to measure cladribine’s effect.” Reply 27. Stelmasiak explains, however, and Dr. Miller agrees, that lymphocyte levels are a “hematological *side effect*” of cladribine. Ex. 1013, 5; Ex. 2009, 37:19-38:9. Dr. Miller admits Rice measured

lymphocyte levels for *safety* and never connected them to clinical or MRI outcomes. Ex. 2009, 34:3-19, 36:5-15.

Second, Petitioner fails to show how a change in lymphocyte count would be linked to any parameter associated with efficacy. Reply 26-27. Dr. Miller admitted that the magnitude of lymphocyte suppression does not necessarily correlate with changes in EDSS, relapse rate, disease progression, or even MRI outcomes. Ex. 2079, 40:10-41:16. Petitioner does not identify any efficacy parameter linked to lymphocyte reduction that would allow for “fine-tuning” dose/dosing length based on lymphocyte count.

Third, Petitioner fails to identify *what lymphocyte level* a POSA would target in “fine-tuning” dose/dosing length or how to do so. Petitioner argues both that suppression to 1000 cells/ μ L is simply “exemplary,” (Ex. 1084, ¶90), with no “bright-line threshold” (Reply 22, 26) because “any percent [reduction] could be considered suppression” (Ex. 2079, 44:19-45:15), while simultaneously arguing the prior art provides guidance on threshold lymphocyte counts. Reply 27. Regardless, absent a clear threshold—which Petitioner has not identified—against which a POSA could measure a change in lymphocyte count correlating to “cladribine’s effect,” Petitioner cannot explain how a POSA would fine-tune dose/dosing length.

Fourth, Petitioner fails to show a reasonable expectation of success in achieving the claimed method via routine-optimization. Ex. 2051, ¶22-23. Petitioner argues “MRI scans can assess a positive treatment response in as little as 6 months” and relapse rates can be “measured over one year.” Ex. 1084, ¶83. Even accepting Petitioner’s 6 months-to-one year argument, this is an extended period of observation for each patient that does not allow for quick and easy “fine-tuning.” Ex. 2051, ¶127. Petitioner fails to account for sufficient sample size (including placebo/control) and duration to enable proper assessment of any outcome. Ex. 1061, 40:8-41:6, 63:6-16. As Dr. Miller admitted, the “trial must be of sufficient *duration* and *numbers*.” Ex. 2079, 97:8-98:4; *see also* Ex. 2051, ¶127 (relapses “require long follow-up of large patient numbers”).

Further, Dr. Miller testified that MRI outcomes do not necessarily demonstrate a treatment effect. Ex. 2009, 19:4-17 (“decrease in T2-lesion volume” may or *may not* be “a treatment response to cladribine”); Ex. 2079, 112:1-21 (more gadolinium-enhancing lesions could indicate “the patient is getting better, staying the same, or getting worse”). As an example, Dr. Miller testified he could not “draw a firm conclusion” about COPAXONE®’s efficacy from *nine months* of clinical trial MRI data, as one does not “know for sure” whether “any observed effect is actually the effect of Copaxone, as opposed to just normal progression of the disease.” Ex. 2079, 113:15-116:16, 120:2-5.

While Dr. Miller argues that relapse rate can be assessed in a year, he testified that relapse rate is a “flawed” outcome measure with “confounding issues,” including varying definitions of “relapse” subject to investigators’ interpretation. Ex. 2079, 91:10-22, 95:4-13, 103:2-20.

2. No Motivation To Start With Bodor’s Dose

a) Petitioner’s Revised Bioavailability Argument Is Improper

Petitioner now argues that “Bodor’s bioavailability was *at least comparable* to Stelmasiak’s” (Reply 23), having abandoned claims of Bodor’s “improved” or “enhanced” bioavailability. Pet. 3, 13, 23, 33, 43; Ex. 1002, ¶110. But “an IPR petitioner may not raise in reply ‘an entirely new rationale’ for why a claim would have been obvious.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1330-31 (Fed. Cir. 2019). To avoid “unfair surprise” to the PO, Petitioner is prohibited from raising a new obviousness theory not preserved in the petition even if the new theory is responsive to the PO’s response or the Board’s institution decision.

Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc., 853 F.3d 1272, 1286 (Fed. Cir. 2017); *Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1002 (Fed. Cir. 2023).

Petitioner’s new bioavailability arguments *contradict* its original obviousness theory. Dr. Miller initially ignored Bodor’s bioavailability data (Ex. 1002, ¶79 (citing the Examples without identifying results)), but nevertheless

testified a POSA would have understood Bodor's tablet to have "***better bioavailability***." Ex. 2009, 143:15-144:4. According to his first declaration:

[A] POSA would have understood Bodor's oral cladribine tablet to have an ***increased*** or ***enhanced*** bioavailability compared to earlier oral solutions..., such as Stelmasiak...a POSA would have understood the need to administer a ***lower dose of Bodor's oral cladribine tablets*** to achieve the ***same effect*** as compared to Stelmasiak's (and Grieb's) oral solution.

Ex. 1002, ¶110. Confronted with Bodor's data,² Petitioner completely changes its interpretation of Bodor's bioavailability. Reply 23; Ex. 1084, ¶¶15, 60, 91, 94.

² Petitioner argues PO misrepresented Bodor's bioavailability by stating Bodor's tablets have lower bioavailability than Stelmasiak's formulation. Reply 16-17; Ex. 1080, ¶¶17-18, 68-73; Ex. 1084, ¶¶15, 60. Dr. Miller, however, testified (1) "the bioavailability that Bodor reports for its 10 milligram tablets is 39.1 or 39.4 percent;" (2) "Liliemark's oral cladribine saline solution has about 50 percent bioavailability;" and (3) "Stelmasiak's oral cladribine...was the same dosage form disclosed by Liliemark." Ex. 2009, 61:13-18, 58:3-59:4; Ex. 1002, ¶110.

According to Dr. Miller then, Bodor's 10mg tablets have a ***lower*** bioavailability than Stelmasiak's oral formulation.

Additionally, Dr. Miller now argues that “a POSA would have reasonably expected Bodor’s dose to sufficiently suppress lymphocyte counts, in light of Stelmasiak’s and Rice’s data,” (Ex. 1084, ¶¶91, 94-96; Ex. 2079, 65:13-66:7), altering his opinion that a POSA would **not** have expected “the same” lymphocyte effects from Bodor’s dose based on Stelmasiak’s data. Ex. 1002, ¶110 (“A POSA would not have expected Bodor’s cladribine tablets to provide the same *in vivo* lymphocyte profile as Stelmasiak and Grieb report because of Bodor’s ‘improved cladribine absorption’ and ‘higher bioavailability.’”). Petitioner attempts to salvage its obviousness theory by belatedly arguing, for the first time, that a POSA would have started with Bodor’s dose because Rice’s “similar dose” lowered lymphocyte levels to ≤ 1000 cells/ μ L and reduced brain lesions. Reply 26. Yet, the Petition **never** relied on Rice—which is **not** a part of Petitioner’s obviousness grounds—to assert motivation to use Bodor’s 100-140mg dose, nor to assert a reasonable expectation of success. Pet. 33-45; Ex. 1002, ¶¶111-119.

Petitioner’s arguments that Bodor’s formulation has a bioavailability “comparable” to Stelmasiak’s and reliance on the purported efficacy of Rice’s “similar” dose to argue the effects of Bodor’s dose are improper new theories of obviousness and should be disregarded. *See Wasica*, 853 F.3d at 1286.

Petitioner’s deficient analysis disregarding Bodor’s bioavailability data in its Petition is no fault of PO. To permit Petitioner to introduce new expert testimony

in Reply to try to rehabilitate a faulty analysis it was aware of since the Petition—when PO cannot present rebuttal evidence—would be unfairly prejudicial and contrary to the rules governing IPR proceedings. PTAB Consol. Tr. Prac. Guide, 73 (November 2019).

Nevertheless, as discussed below, Petitioner’s revised bioavailability argument fails.

b) Petitioner’s New Bioavailability Argument Fails

Bodor discloses *absolute* bioavailability (~39%) for its 10mg tablet, but Petitioner, without explanation, looks to the *relative* bioavailability of Bodor’s 3mg tablet (35.7%-52.1%), to compare with Stelmasiak’s *absolute* bioavailability value. Reply 16-18; Ex. 1022, Tables VI, VIII; Ex. 1080, ¶¶75-76. Dr. Pinal also wrongly compared the *upper limit* of Bodor’s relative bioavailability *range* (52.1%) against Liliemark’s reported *average* bioavailability (55%), despite conceding a POSA “would have understood that Bodor’s oral dose” has a “bioavailability [of] (about 40%)[.]” Ex. 1080, ¶¶76, 81. Even if Bodor’s relative bioavailability *range* is considered, Stelmasiak (by citing Liliemark’s data), discloses an average bioavailability of 55% with a 72% upper limit (55% ± 17%) (Ex. 2043, 1516)—*higher* than Bodor’s 52.1% upper limit for relative bioavailability. Ex. 2080, 44:17-22 (“[H]aving higher bioavailability would be considered preferable”).

Nevertheless, even if Bodor and Stelmasiak's bioavailability is comparable, a POSA would not have been motivated to start with Bodor's 100-140mg dose. *See* POR 42, 49-53; Ex. 2051, ¶¶25, 172-177. According to Dr. Miller's revised testimony, Bodor and Stelmasiak would share the "same" lymphocyte profile for the same doses, (Ex. 2079, 65:21-66:7), but following Dr. Miller's theory, Bodor's 100-140mg cumulative dose would not have suppressed lymphocytes to <1000 cells/μL. Ex. 1002, ¶90 ("300 mg of cladribine suppressed the average lymphocyte count to less than 1000" cells/μL). Thus, in an attempt to show "cladribine's effect" via lymphocyte suppression, Petitioner now resorts to arguing Rice's 0.7 mg/kg dose is "similar to Bodor's" 100-140mg dose (Ex. 1080, ¶¶78-82), and that a POSA would have expected similar effects, i.e., "suppress[] lymphocytes to ≤ about 1000 cells/μL" and "lower[] brain-lesion numbers and volumes" based on MRI. Reply 26. But Rice reported "clinical efficacy was not shown," and MRI was not a designated outcome measure. Ex. 1018, 1147, 1152-53. Even assuming that MRI was a secondary outcome measure, Dr. Miller testified that if the study met the secondary outcome measure but not the primary, he is "not sure that a clinician could draw a conclusion [about efficacy] in that circumstance." Ex. 2079, 86:17-87:17. Indeed, Dr. Miller previously noted the dissociation between Rice's MRI and clinical results and was unable to recommend cladribine for treating MS. Ex. 2004, 341.

Further, Petitioner’s own exhibit (Ex. 1045) shows that co-authors of the Rice study, Drs. Rice and Filippi, later questioned the initially reported MRI results regarding brain-lesion numbers and volumes and looked instead to T1-hypointense lesion volume; however, they deemed the T1-hypointense lesion results “clinically unimportant.” Ex. 1045, 44. Rice’s MRI results would not have motivated a POSA to start with Bodor’s dose rather than Stelmasiak’s.

Lastly, Petitioner contends Stelmasiak alone teaches a “safe, effective, and convenient oral therapy for MS,” citing to Stelmasiak’s clinical results. Ex. 1084, ¶131; Ex. 2079, 179:4-9. Based on Petitioner’s premise, a POSA would not have been motivated to switch to Bodor’s dose that was only tested for pharmacokinetics, not efficacy.

3. No Motivation Or Reasonable Expectation Of Success To Re-Treat After Bodor’s 10-Month Cladribine-Free Period

Despite Petitioner’s revised bioavailability argument—that Bodor’s and Stelmasiak’s formulations have “comparable” bioavailability and would share the “same” lymphocyte profile for similar doses (Ex. 2079, 65:13-66:7; Ex. 1084, ¶92)—Petitioner still fails to explain why a POSA would have waited 10 months to re-treat after Bodor’s 140mg dose, when Stelmasiak waited only two months after administering its 300mg dose. POR 54-55; Ex. 2051, ¶¶26-27, 178-184.

Petitioner further argues that Bodor's dose and Rice's 0.7 mg/kg dose would suppress lymphocytes to "similar" levels (Reply 26; Ex. 1084, ¶92 (citing Rice at Figure 4); Ex. 1080, ¶82), but Rice's Figure 4 shows its dose cannot maintain lymphocytes below 1000 cells/ μ L for more than 6 months after the last dose. Ex. 1018, 1152 (Figure 4); Ex. 1084, ¶71. And whereas Petitioner argues for re-treatment after 10 months of no treatment, Rice did not permit re-treatment until after *at least 12 months* of no treatment, and further required disease progression and fulfilling hematologic dosing criteria. Ex. 1018, 1146. Petitioner does not explain why a POSA considering Bodor, Stelmasiak, and Rice would have been motivated to re-treat patients after 10 months of no treatment or have reasonable expectation of success in doing so.

While Petitioner relies on Stelmasiak's relapse results to argue efficacy (Reply 13-14), Stelmasiak provides no breakdown of relapse data that would inform re-treatment considerations. Petitioner suggests PO unduly focused on EDSS in assessing efficacy. *Id.*, 14 (citing POR 5-7, 54; Ex. 1061). However, PO acknowledged "*relapse rate and physical disability status...MRI outcomes*" as outcome variables for assessing efficacy. POR 5. Further, Dr. Miller admits, despite "mean" EDSS being "challenging" or "subjective," it does not change *EDSS*'s utility as an outcome measure. Ex. 2079, 81:4-17, 84:5-11. Indeed, relapse rate, although "flawed" is an accepted outcome measure. *Id.*, 95:4-13.

Lastly, contrary to Petitioner’s assertion (Reply 14; Ex. 1084, ¶54), whether a POSA would understand Stelmasiak’s outcome measures to demonstrate efficacy depends on the study design. Ex. 1061, 41:7-14 (“[Y]ou’ve got to meet that primary outcome measure before you consider any of the other outcomes.”). However, Stelmasiak did not specify which outcome measures were primary/secondary. Further, Stelmasiak lacks a placebo/control; thus, one cannot determine whether any observed effect is actually the effect of cladribine, “as opposed to just normal progression of the disease.” *Id.*, 41:15-42:7; Ex. 2079, 120:2-5.

IV. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

A. Skepticism

Petitioner disputes FDA had “concerns over higher cancer risks” for MAVENCLAD® (Reply 30; Ex. 1084, ¶114), but is contradicted by (1) Dr. Miller’s pre-IPR statement that “cladribine raised safety concerns, particularly related to *malignancies*, for *regulators*” (Ex. 2078, 1402-03 (citing CLARITY, Ex. 2033)); and (2) Ex. 2060, which Dr. Miller admitted states FDA “flagged *concerns of higher cancer risks* associated with Mavenclad.” Ex. 2079, 136:8-13, 162:22-163:9, 164:8-166:16; Ex. 2051, ¶201.

Petitioner argues *Neptune* is inapposite (Reply 30), but *Neptune* does not limit FDA skepticism to treatment strategy “changes.” Instead, “testimony that

third parties were ‘**worried**’ or ‘surprised’ was sufficient to establish skepticism.”

Neptune Generics, LLC v. Eli Lilly & Co., 921 F.3d 1372, 1378 (Fed. Cir. 2019).

FDA’s concerns over cancer risks based on CLARITY establish skepticism of the claimed regimen. Ex. 2060, 1-2; POR 60, 64-65; Ex. 2051, ¶¶199, 201.

Petitioner wrongly dismisses Drs. Miller’s, Noseworthy’s, and Lublin’s pre-IPR statements for being limited to progressive MS, (Reply 31-32), despite Petitioner’s reliance on progressive MS studies to argue cladribine’s efficacy, (e.g., Ex. 2030), Reply 1. Yet neither Dr. Miller nor Dr. Noseworthy could recommend cladribine to treat “patients with **multiple sclerosis**”; neither limited their clinical opinions to progressive MS. Ex. 2004, 341; Ex. 2031, 753; Ex. 2005, 45.

Petitioner also contends such pre-IPR statements were not made by a POSA “considering all pertinent art.” Reply 13, 15, 29, 31-32; Ex. 1084, ¶¶67, 105, 109. However, Drs. Miller, Noseworthy, and Lublin meet Petitioner’s POSA definition (Pet. 28-29) and their publications were directed to a POSA.

Petitioner disputes skepticism of cladribine’s efficacy or safety (Reply 13-15), but FDA’s and Drs. Miller’s, Noseworthy’s, and Lublin’s statements show otherwise. POR 25-27, 40-41, 58-60; Ex. 2051, ¶¶28, 64-73, 195-198. Petitioner focuses on **acute** toxicity, e.g., infections, and dismisses long-term safety issues, e.g., malignancies. Reply 15; Ex. 1084, ¶¶55-57. But FDA’s complete response letter and Dr. Miller’s pre-IPR statements (Ex. 2078, 1402 (cladribine carries “risk

of potentially very serious or even fatal adverse events”); Ex. 2079, 143:4-22) show significant concerns. Dr. Miller’s pre-IPR statements contradict his IPR opinions, which should be discounted.

B. Unexpected Results

Petitioner argues Bodor is the closest prior art (Reply 31), but Bodor does not teach the claimed weight-based dose/dosing or maintenance period. POR 18-35; Ex. 2051, ¶¶85-129. Regardless, unexpected results are shown by comparing the *results* of the closest prior art. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Even assuming that art is Bodor, Bodor provides no results for its regimen for comparison with CLARITY. Ex. 2051, ¶75; Ex. 2009, 71:15-20; Ex. 2079, 170:7-171:4. Nevertheless, Dr. Lublin considered Bodor in his unexpected results opinion. Ex. 1061, 113:9-13.

Petitioner’s position that CLARITY’s results were not superior to Stelmasiak’s (Reply 31; Ex. 1084, ¶122-123) ignores (1) Stelmasiak’s non-responders’ EDSS scores increased relative to baseline (Ex. 1013, 6; Ex. 2051, ¶174) and (2) CLARITY’s results were *relative to placebo*. Ex. 2033, 422. Stelmasiak reported a 10-patient study with no control/placebo and Dr. Miller agreed that its results “should be interpreted with caution.” Ex. 2079, 96:4-19.

Regarding Romine, Dr. Miller’s argument that CLARITY’s results were not superior overlooks the overlapping confidence intervals reported for exacerbation

rates in cladribine (0.37-1.05) and placebo (0.90-1.93) groups (Ex. 1031, 39-40), leading Dr. Miller to “**not** believe...there was a statistically meaningful result.” Ex. 2079, 188:10-189:1. Further, Romine reported no clinical benefit based on EDSS/SNRS, in contrast to CLARITY’s statistically significant reduction in relapse rates and risk of disability progression. *Id.*, 123:15-20; Ex. 2033, 416; Ex. 1031, 40, 42; Ex. 2051, ¶67.

C. Long-Felt, Unmet Need

Petitioner argues the long-felt, unmet need “must exist as of the ‘filing date of the challenged invention.’” Reply 31. But as the ’947 patent explains, “it would be desirable to have a method for treating [MS] comprising the *oral* administration of Cladribine...A *sustained benefit of Cladribine* treatment...is also desirable.” Ex. 1001, 3:22-30. Thus, the need for “a more convenient method” of administration with “a short [treatment] commitment” and “a long-lasting possibility [for] relief” (Ex. 2042, 1, 4) existed as of the filing date.

D. Nexus

Petitioner argues objective evidence must be “coextensive” with the claims (Reply 31); however, it “need only be ‘reasonably commensurate with the scope of the claims.’” *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013). “[T]he *claimed combination* as a whole [can] serve[] as a nexus for the objective evidence[.]” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330 (Fed. Cir. 2016).

Petitioner's position that CLARITY's results lack nexus is unreasonable. Petitioner's argument would require a clinical trial testing every embodiment within the scope of the claims. Reply 31-32. Further, Dr. Miller suggests that evidence of skepticism must express skepticism about the *exact regimen* as claimed. Ex. 1084, ¶110. But to establish nexus, courts "have not required absolute identity of scope," *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308 (Fed. Cir. 2011), nor required applicants "to test every embodiment within the scope of [their] claims," *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Here, the Board must "properly consider the evidence of objective indicia of nonobviousness," including the aggregate weight of objective evidence factors. *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1215 (Fed. Cir. 2023).

Lastly, Petitioner relies on mischaracterization to argue MAVENCLAD®'s durability is inherent. Reply 32; POR 62-63; Ex. 2051, ¶212. But it was not until PO's CLARITY results led to FDA approval of MAVENCLAD® that a safe, durably effective, and convenient oral MS treatment method became available. Ex. 2070, 2.

V. 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
2072	Supplemental Declaration of Fred D. Lublin, M.D. (SERVICE ONLY)
2073	D. S. Goodin et al., <i>Disease Modifying Therapies in Multiple Sclerosis</i> , 58 NEUROLOGY 169, Supplementary Material (2002) (SERVICE ONLY)
2074	The 2002 Product Development and License Agreement between IVAX International GMBH and Ares Trading S.A. (SERVICE ONLY)
2075	Declaration of David Mlaver in Support of Motion for Admission <i>Pro Hac Vice</i>
2076	Declaration of Mary Pheng in Support of Motion for Admission <i>Pro Hac Vice</i>
2077	Stephen Krieger et al., <i>Issues in the Design and Interpretation of Multiple Sclerosis Clinical Trials</i> , in PRIMER ON MULTIPLE SCLEROSIS 435-450 (B. S. Giesser, ed., 2011)
2078	Aaron E. Miller, <i>Multiple Sclerosis Should be Treated Using a Step-Down Strategy Rather than a Step-Up Strategy—Commentary</i> , 22 MULTIPLE SCLEROSIS J. 1402 (2016)

Exhibit No.	Description
2079	Transcript of Deposition of Aaron E. Miller (May 13, 2024)
2080	Transcript of Deposition of Rodolfo Pinal (April 26, 2024)

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Sur-Reply contains 5,587 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. §42.24(d), excluding the parts exempted from the word count by 37 C.F.R. §42.24(a)(1).

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

CERTIFICATE OF SERVICE

I hereby certify that on May 21, 2024, I caused a true and correct copy of the following materials:

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- Exhibits 2077-2080
- Word Count Certification Under 37 CFR §42.24(d)

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