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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.

IPR2023-00480
Patent 7,713,947 B2

Before ZHENYU YANG, ROBERT A. POLLOCK, and
TIMOTHY G. MAJORS, *Administrative Patent Judges.*

MAJORS, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Granting Parties' Motions to Seal (Papers 19, 54, 55)
Denying without Prejudice Petitioner's Motion to Seal (Paper 42)
37 C.F.R. § 42.14

I. INTRODUCTION

Hopewell Pharma Ventures, Inc. ("Petitioner" or "Hopewell") filed a Petition (Paper 2, "Pet.") requesting *inter partes* review of claims 36, 38, 39, and 41–46 of U.S. Patent No. 7,713,947 B2 (Ex. 1001, "the '947 patent"). Pet. 1, 33.

We instituted trial on September 22, 2023. Paper 10 ("Inst. Dec."). During trial, Merck Serono S.A. ("Patent Owner" or "Merck") filed a Patent Owner Response. Paper 20 ("PO Resp."). Petitioner filed a Reply (Paper 41 ("Pet. Reply")) and Patent Owner filed a Sur-reply (Paper 51 ("PO Sur-reply")). An oral hearing was held on June 25, 2024, and a transcript is of record. Paper 61 ("Tr."). With authorization, Petitioner and Patent Owner also filed post-hearing supplemental briefs providing further argument about the asserted prior-art status of a reference asserted herein. Paper 59 (PO Suppl. Br.); Paper 60 (Pet. Suppl. Br.).

Unopposed motions to seal also remain pending (Papers 19, 42, 54, and 55). We resolve those motions as set forth in Section IV below.

We have jurisdiction under 35 U.S.C. § 6(b). After considering the full record developed through trial, we determine that Petitioner has proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a).

II. BACKGROUND

A. Real Parties-in-Interest

Petitioner identifies itself and the following entities as real parties-in-interest: Hopewell Pharma Ventures LLC; Levy SPV, LLC; GLS Capital Partners Fund I, LP; GLS Capital Partners GP, LLC; and GLS Capital, LLC.

Pet. 68–69. Merck identifies itself along with Merck KGaA and Ares Trading SA as the real parties-in-interest. Paper 3, 1.

B. Related Matters

The parties identify the following lawsuits involving assertions of the '947 patent: *Merck KGaA et al. v. Accord Healthcare, Inc. et al.*, 1-22-cv-00974 (D. Del.); *Merck KGaA et al. v. Hopewell Pharma Ventures, Inc.*, 1-22-cv-01365 (D. Del); *Merck KGaA et al v. Aurobindo Pharma USA, Inc. et al.*, 1-23-cv-00039 (D. Del.). Pet. 69; Paper 3, 1.

The parties also identify other related matters before the Board. Pet. 69–70; Paper 3, 1–2. We instituted trial in IPR2023-00481, which matter was filed by Petitioner and challenges U.S. Patent No. 8,377,903 ("the '903 patent"), and we enter a final written decision in IPR2023-00481 concurrent with this Decision. Additionally, the parties identify IPR2023-00049 and IPR2023-00050, which were filed by a different petitioner (TWi Pharmaceuticals, Inc. ("TWi")), challenging the '947 and '903 patents.[1] *Id.*

C. The '947 Patent & Technology Background

The '947 patent, titled "Cladribine Regimen for Treating Multiple Sclerosis," issued on May 11, 2010. Ex. 1001, codes (45), (54). The application that matured into the '947 patent was filed December 20, 2005, and claims the priority benefit of a provisional patent application filed December 22, 2004. *Id.* at codes (22), (60).[2]

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[1] The Board initially denied institution on the TWi-filed petitions, but granted institution on rehearing. IPR2023-00049, Papers 10 and 15; IPR2023-00050, Papers 8 and 13. Those proceedings remain pending.

[2] In this case, Petitioner assumes December 22, 2004, is the priority date. Pet. 2–4, 7–8 n.3, 13–28. Absent argument to the contrary, the Board applies December 22, 2004, as the priority date for the challenged claims.

According to the '947 patent, the "present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis . . . wherein the preparation is to be orally administered and wherein re-treatments are possible." *Id.* at Abstr.; *see also id.* at 1:17–20 ("The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.").

Cladribine is a chlorinated purine analogue, 2-chloro-2´deoxyadenosine (also known as 2-CdA). *Id.* at 2:24–27. Cladribine was known in the prior art, as were oral, i.v., and subcutaneous formulations including it. *See, e.g.*, *id.* at 6:20–25 (noting formulations for oral administration described in, for example, US Patent No. 5,506,214[3]). The '947 patent notes that cladribine has also been suggested previously in the art as useful for treating multiple sclerosis. *Id.* at 2:24–3:21 (discussing prior studies on cladribine's use in patients with multiple sclerosis); *see also* Pet. 19–21; Ex. 1002 ¶¶ 33–52 (testimony of Dr. Aaron Miller on studies by Beutler, Stelmasiak, Rice, and others).

As described in the '947 patent, "[m]ultiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans." Ex. 1001, 1:25–27. "Over time, MS may result in the accumulation of various neurological disabilities" and "[c]linical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy." *Id.* at 1:30–34. The patent states that "MS is manifested in physical symptoms (relapses

[3] Beutler, U.S. Patent No. 5,506,214, issued April 9, 1996 (Ex. 1026).

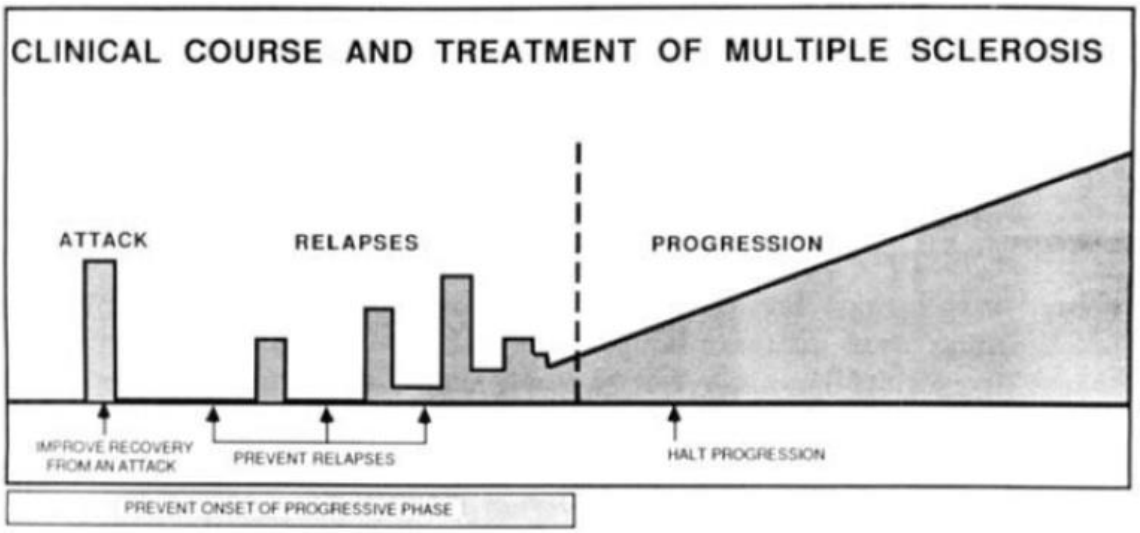
and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment." *Id.* at 1:35–37; Ex. 2051 ¶ 39 (testimony of Patent Owner's declarant, Dr. Fred Lublin, explaining that "multiple sclerosis," meaning "many scars," is an autoimmune disease where the immune system attacks the CNS, particularly myelin, which is an insulating substance that surrounds and protects nerve fibers/axons).

By December 2004, it was known that lymphocytes (especially T cells), which cells are part of the body's acquired immune system, play a role in the pathophysiology of MS. Ex. 1002 ¶¶ 28–29; Ex. 2051 ¶ 40 (testifying that "by 2004, MS was thought to be a lymphocyte-dependent autoimmune disease" involving autoantigen-specific T lymphocytes). According to Petitioner's declarant, Dr. Miller, "[p]atients with MS 'harbor T cells that react with CNS autoantigens'" and, "[a]lthough these T cells (a type of lymphocyte) may 'remain dormant for decades, at some point they are activated in the periphery,'" allowing the cells to "migrate through the blood-brain barrier to the brain and spinal cord." Ex. 1002 ¶¶ 28–29 (citing Ex. 1044, 1–3; Ex. 1007, 131). "Once these T cells are reactivated in the CNS . . . they 'release pro-inflammatory Th1 cytokines and orchestrate the destruction of the myelin sheath by various types of immune cells.'" *Id.* (citing Ex. 1007, 131). As Dr. Miller further explains, inflammation and resulting demyelination creates "lesions" in the affected tissues that can be detected and monitored. *Id.* ¶¶ 15, 24, 27 (discussing detection of active/enhancing lesions with MRI); Ex. 2051 ¶ 39 (explaining "lesions" reflect accumulated dead nerve cells in the brain and spinal cord).

According to the '947 patent, MS is "considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are

infrequently permanent." Ex. 1001, 1:43–46. Moreover, the patent states, "[f]our courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis." *Id.* at 1:47–50. "More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by recovery that may or may not be complete." *Id.* at 1:51–56 (noting that disability arises from incomplete recovery from relapses). "Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the disease[] onset." *Id.* at 1:56–62 (noting that worsening of disability in the progressive phase results from "accumulation of residual symptoms after exacerbation but also from insidious progression between exacerbations").

There is no known cure for MS. Ex. 1002 ¶ 22 (citing Ex. 1024). Because MS is a chronic disease, patients ordinarily require ongoing care and repeated treatments designed to alter or suppress the immune system. *Id.* ¶ 53 (citing Ex. 1008, 211–213). To illustrate, Dr. Miller identifies Figure 1 of Weiner (Ex. 1008), which is reproduced below.



Ex. 1008, 212, Fig. 1. Figure 1, above, is titled a "clinical course and treatment of multiple sclerosis" and shows a common MS disease course, with the horizontal axis representing time and the vertical axis the level of disability. *Id.* (capitalization omitted). The figure includes an early "attack" followed by multiple "relapses," shown by vertical bars of different heights on the left half of the figure; then, at the time represented by a vertical dashed line near the middle of the figure, the onset of a progressive phase of the disease with persistent disability steadily increasing as shown by the upwardly sloping line as one moves to the figure's right. *Id.* (including, below the horizontal axis, a treatment strategy (e.g., improve recovery from attack, etc.) for the disease stage). According to Dr. Miller, as reflected in the figure above, "different therapies are designed to treat acute attacks, prevent or decrease the number of relapses, and prevent onset of or halt the progressive phase." Ex. 1002 ¶ 53 (citing Ex. 1008, 212–213).

As Dr. Miller further explains, "[b]ecause of the role the immune system plays in the underlying pathophysiology of MS, [administering] immunosuppressive drugs was '[t]he most common therapeutic approach' for treating MS before December 2004." *Id.* ¶ 16 (citing Ex. 1013, 4; Ex. 1007, 131); *see also id.* ¶ 30 ("Because of the role autoantigen-specific T lymphocytes were known to play in MS, suppressing these lymphocytes was a target of [prior] MS therapies"); *but see* Ex. 2051 ¶¶ 49–52 (Dr. Lublin testifying MS therapies generally involved immunosuppressive and immunomodulatory therapies, and some, though not all, involved suppressing lymphocytes (citing, e.g., increased levels of white blood cells in natalizumab-treated patients (Ex. 2019, 2)).

"Because cladribine caused 'prolonged, profound suppression of lymphocyte counts,' researchers began studying it in MS." Ex. 1002 ¶ 16

(citing Ex. 1016, 420); Ex. 2051 ¶ 64 (testifying that cladribine, originally approved for treating hairy cell leukemia, "was known for its ability to selectively reduce lymphocyte count" and, by 2004, had been investigated in several MS clinical studies). Dr. Miller testifies that "[i]n early studies, cladribine was shown to 'modulat[e] autoimmune processes involving lymphocyte abnormalities such as MS' and 'impressively decrease[]' relapse rates" in MS patients. Ex. 1002 ¶ 16 (citing Ex. 1018, 1146; Ex. 1013, 5, 7). According to Dr. Miller, "[d]uring treatment, neurologists commonly assessed the therapeutic effect of cladribine by monitoring a patient's lymphocyte count, with a sustained reduction of lymphocytes, e.g., below 1000 [cells]/µL, being characteristic of a treatment response." *Id.* (citing Ex. 1018, 1146; Ex. 1013, 5; Ex. 1014, 1717).

The '947 patent describes, in an example, a treatment regimen for patients with MS. Ex. 1001, 14:19–16:23 (Example 1). In a study on sixty patients with relapsing forms of MS, the patients were sorted into three groups: for the first year, Group 1 patients received placebo for four months followed by 8 months of no treatment; Group 2 patients received daily oral administration of cladribine (10 mg tablets) for about 5 days a month for two months, followed by placebo for two months, and 8 months of no treatment ("total dose of about 1.75 mg/kg"); and Group 3 patients received daily oral administration of cladribine (10 mg tablets, as above) for about 5 days a month for 4 months followed by 8 months of no treatment ("total dose of about 3.5 mg/kg"). *Id.* In the second year (starting month 13), the patent discloses that all three groups received oral cladribine for about 5 days a month for 2 months at the lower dose (i.e., total of "about 1.75 mg/kg" over

the 2 months) followed by 10 months of no treatment.[4] *Id.* (disclosing, *inter alia*, that lymphocyte markers are monitored and that "[p]atients in Groups 2 and 3 have a decrease in brain lesions"); *see also id.* at 5:52–6:12 (disclosing that "[e]fficacy" of cladribine for MS treatment can be measured by, for example, relapse frequency, reduction of MRI-detectable lesions, or improvements in clinical assessments like the "Expanded Disability Status Scale (EDSS)" or "Scripps Neurologic Rating Scale (SNRS)" scores).

D. Illustrative Claims

Claim 36, reproduced below, is the only independent claim challenged in this proceeding. It reads:

> 36. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:
>
> (i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
>
> (ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;
>
> (iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg; [and]
>
> (iv) a cladribine-free period wherein no cladribine is administered.

Ex. 1001, 19:14–30. Illustrating some of the challenged dependent claims, claim 39 depends from claim 36 and adds "wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg,"

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[4] The '947 patent indicates that the course of treatment continues into a third year (starting at month 25) that essentially repeats the regimen given during the second year. Ex. 1001, 16:4–9.

claim 41 depends from claim 36 and adds "wherein the cladribine-free period (ii) lasts about 10 months," and claim 45 depends from claim 36 and adds "wherein the formulation is orally administered at a daily dose of 10 mg cladribine." *Id.* at 20:5–7, 20:11–12, 20:20–22.

E. Asserted Prior Art and Ground

Petitioner asserts that claims 36, 38, 39, and 41–46 are unpatentable based on the following ground:

Claims Challenged	35 U.S.C. §[5]	References/Basis
36, 38, 39, 41–46	103	Bodor,[6] Stelmasiak[7]

Petitioner submits testimony from Aaron E. Miller, M.D. and Rodolfo Pinal, Ph.D. to support its challenge. Ex. 1002 (Miller Decl.); Ex. 1084 (Miller Rebuttal Decl.); Ex. 1080 (Pinal Decl.). Patent Owner responds with testimony from Fred D. Lublin, M.D. and Dr. Bernd Meibohm. Ex. 2051 (Lublin Decl.); Ex. 2052 (Meibohm Decl.). The deposition testimony of Drs. Miller, Pinal, Lublin, and Meibohm is also of record. Exs. 2009 and 2079 (Miller transcripts); Ex. 2080 (Pinal transcript); Ex. 1061 (Lublin transcript); Ex. 1062 (Meibohm transcript).

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[5] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 285–88 (2011), revised 35 U.S.C. §§ 102, 103 effective March 16, 2013. The '947 patent issued from an application filed before March 16, 2013, so pre-AIA §§ 102 and 103 apply. Ex. 1001, code (22).

[6] Bodor et al., WO 2004/087101 A2, published Oct. 14, 2004 ("Bodor" (Ex. 1022)).

[7] Zbigniew Stelmasiak, *A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis*, 41:1 Med. Sci. Monit. (March 1, 1998) ("Stelmasiak" (Ex. 1013)).

In addition to the testimony from the parties' designated experts above, the record also includes testimony from three fact witnesses: Alain Munafo, Ph.D. (Ex. 2053 (Munafo Decl.); Ex. 1063 (Munafo transcript)); Nicholas Bodor, Ph.D. (Ex. 2054 (Bodor Decl.); Ex. 1059 (Bodor transcript)); and Yogesh Dandiker, Ph.D. (Ex. 2055 (Dandiker Decl.); Ex. 1060 (Dandiker transcript)).

III. ANALYSIS

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the relevant art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Moreover, "[a]n obviousness determination requires finding both that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so."

CRFD Research, Inc. v. Matal, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (internal quotation marks and citation omitted).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the problems encountered in the art, the art's solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner proposes that the person of ordinary skill in the art ("POSA") would have a "high" level of skill. Pet. 28. In more detail, Petitioner contends:

> A POSA here would have drawn upon the knowledge and experience of related disciplines of a multi-disciplinary team that might lie outside the POSA's primary training. . . . A POSA for the '947 patent would have knowledge of multiple disciplines, such as immunology, biochemistry, and human physiology and anatomy, and also typically [would] be a clinician with experience and/or training in neurology. . . . The POSA typically would be a medical doctor with a specialty in neurology, specifically in treating autoimmune disorders of the nervous system, such as multiple sclerosis, and typically at least 2 years of experience with administering treatments to patients and evaluating results of such treatments, as well as experience or knowledge in related research and development.

Id. at 28–29 (citing Ex. 1002 ¶¶ 20–21).

Patent Owner responds with its own definition, which Patent Owner argues is "more accurate." PO Resp. 8–9. According to Patent Owner:

> 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. . . . 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. (citing Ex. 2051 ¶ 29). Regardless, Patent Owner contends, the claims are nonobvious, and its declarant (Dr. Lublin) qualifies as a POSA, under either definition. *Id.* (citing Ex. 2051 ¶¶ 30–31).

Patent Owner's definition includes aspects of pharmacology that are not explicitly recited in Petitioner's definition. We find those added aspects are consistent with the art (e.g., Ex. 1022, 40–41 (analyzing PK parameters for cladribine formulations)). We apply Patent Owner's definition in this Decision as it is somewhat more specific. In any event, neither party's analysis hinges on whether their respective POSA definition is adopted and the ultimate result here would not change under either definition.

C. Claim Construction

In an IPR, we construe claims using the same standard used to construe claims in a civil action before the courts under 35 U.S.C. § 282(b), including construing claims in accordance with the ordinary and customary meaning as understood by the POSA and the patent's prosecution history. 37 C.F.R. § 42.100(b). We need only construe terms that are in controversy and only as needed to resolve the matters in controversy. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019).

Petitioner proposes constructions for the following terms: (a) "total dose of cladribine"; (b) "an induction period"; and (c) "maintenance period." Pet. 29–33. No dispute here turns on interpretation of a "total dose of cladribine," and, as noted by Petitioner, "total dose" is defined in the '947 patent. Ex. 1001, 4:19–26 (defining "total dose" as the "cumulative dose," i.e., "the total dose of Cladribine administered during the treatment,

i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses"). We need not further construe this term.

Regarding the term "maintenance period," Petitioner argues the maintenance period dose should be construed as being "lower" than the induction period dose. Pet. 30–33: Pet. Reply 11. And, as a corollary, Petitioner argues the induction period dose is "higher" than the maintenance period dose. Pet. 29–30. The premise of Petitioner's argument is that, during prosecution, the applicant sought to distinguish the claims over the prior art, including the asserted Bodor reference, and therein limited the claims. *Id.* at 29–33. Patent Owner disagrees and argues that, although the claims encompass regimens where the maintenance period dose is lower than the induction period dose, they also encompass a regimen where the induction and maintenance period doses are the same. PO Resp. 9 (citing the Board's Institution Decision (Paper 10, 12–17)); Inst. Dec. 17 (explaining that, based on the intrinsic evidence as a whole, the maintenance and induction doses could be the same ("about 1.7 mg/kg")).

We need not further construe and limit the claims in the manner argued by Petitioner. As Petitioner states, Patent Owner's argument and the Board's preliminary claim construction (in the Institution Decision) "encompass" Petitioner's construction and Petitioner's "arguments apply under either." Pet. Reply 10; Tr. 24:1–9 (agreeing construction of the maintenance dose is "not an issue that [the Board] ha[s] to resolve because these claims would have been rendered obvious under either . . . our construction or Patent Owner[']s construction"). We need only construe

claim terms to the extent necessary to resolve the controversy at hand. *Realtime Data*, 912 F.3d at 1375.[8]

Any remaining dispute about the meaning or application of the claims will be addressed below, where we analyze the asserted obviousness. *See infra* Section III.D.4.

D. Obviousness over Bodor and Stelmasiak

Petitioner contends that claims 36, 38, 39, and 41–46 would have been obvious over the combined teachings of Bodor and Stelmasiak. Pet. 33–61.

Petitioner argues that Bodor is prior art under 35 U.S.C. § 102(a) and § 102(e). Pet. 22. The parties provide more extensive argument on the prior-art status of Bodor, which we address in Section III.D.3 below. PO Resp. 9–18 (arguing certain disclosure in Bodor is not "by another" and, thus, not prior art); PO Sur-reply 2–7 (same); Pet. Reply 3–10 (arguing Bodor's disclosure is prior art in full). Petitioner argues that Stelmasiak is prior art under § 102(b), which Patent Owner does not dispute. Pet. 24.

We summarize the asserted prior art below before turning to the parties' further arguments and our analysis.

1. Bodor (Ex. 1022)

Bodor is an international patent application that was filed March 26, 2004, and published October 14, 2004. Ex. 1022, codes (22), (43). Bodor

[8] In the event Petitioner should contend that an express construction of "maintenance period" and "induction period" was necessary for this Final Written Decision, we maintain and adopt our prior analysis on the issue. Inst. Dec. 12–17 (agreeing with Patent Owner that the maintenance period dose of claim 36 could be lower than the induction period dose, but it could also be the same (i.e., about 1.7 mg/kg)).

relates to "compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine." *Id.* at Abstr.

Bodor teaches that "[o]ral delivery of drugs is often preferred to parenteral delivery for a variety of reasons." *Id.* at 2:9–10. "[F]oremost," among the reasons given by Bodor, is "patient compliance." *Id.* "Patient compliance is enhanced insofar as oral dosage forms alleviate repeated health care provider visits, or the discomfort of injections or prolonged infusion times associated with some active drugs." *Id.* at 2:11–13.

"However," Bodor teaches, "to date the oral delivery of cladribine has been plagued by low bioavailability . . . and suboptimal interpatient variation." *Id.* at 2:22–25. Bodor teaches that "[i]t has now been found that amorphous cyclodextrins can be combined to form a particularly advantageous product which can be incorporated into a solid oral dosage form." *Id.* at 5:2–4. "This product is a [] cladribine-cyclodextrin complex, and solid oral dosage form containing it improves oral bioavailability and/or achieves lower interpatient and/or intrapatient variation of the drug." *Id.* at 5:4–7; *see also id.* at 11:27–12:3 (describing a cladribine and cyclodextrin complex "associated with improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation").

Bodor teaches cladribine has "been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions including . . . multiple sclerosis." *Id.* at 2:1–5. Bodor discloses that "an effective amount of the complex cladribine-cyclodextrin . . . is used (e.g., an amount affective for the treatment of multiple sclerosis[)]." *Id.* at 22:11–15. Bodor further teaches that "[t]herapeutically effective dosages described in the literature include those for . . . multiple sclerosis (from about 0.04 to about 1.0 mg/kg/day (see U.S. Patent No. 5,506,214))." *Id.* at

22:17–22 (defining "therapeutically effective amount"); *see also id.* at 22:27–23:6 (noting "various dosage amounts and dosing regimens have been reported in the literature for use in the treatment of multiple sclerosis," and listing references).[9]

Bodor discloses that, "[a]t the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant [] cladribine-cyclodextrin complex in the instant solid dosage form" would be given. *Id.* at 23:15–17. Further, Bodor teaches, this 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." *Id.* at 23:17–20; *see also id.* at 23:20–24 (disclosing an alternative regimen where 10 mg of cladribine is given once per day for five to seven days per month over six months, followed by eighteen months of no treatment).

Bodor teaches that the dosing regimen can be tailored to suit the needs of the patient. Specifically, Bodor teaches that "one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning and/or by administering cladribine . . . with another active ingredient." *Id.* at 24:1–6 ("The invention . . . provides a method to tailor the administration/treatment to the particular exigencies specific to a given mammal."). Furthermore, Bodor teaches that

[9] Many of the references identified and incorporated-by-reference in Bodor are of record, including U.S. Patent No. 5,506,214 ("Beutler patent" (Ex. 1026)), Rice (Ex. 1018), Romine (Ex. 1031), Selby (Ex. 1047), and Tortorella (Ex. 1015). *See* Ex. 1022, 7:7–10 (incorporating-by-reference the patents, applications, and scientific literature identified in Bodor), 22:27–23:6 (incorporating Rice, Romine, etc. by reference "in their entireties").

"[t]herapeutically effective amounts may be easily determined for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect." *Id.* at 24:6–9.

2. Stelmasiak (Ex. 1013)

Stelmasiak is an article about a pilot trial describing cladribine's use in patients with remitting-relapsing multiple sclerosis (RRMS), which paper published in 1998. Ex. 1013, 4–5 ("In the present study we tested clinical efficacy of cladribine in remitting-relapsing form of MS in a two-year open-label pilot clinical trial.").

In its Introduction, Stelmasiak teaches that "multiple sclerosis (MS) is an autoimmune disease in which abnormalities in immune regulation lead to the lymphocyte-dependent demyelination process in the central nervous system." *Id.* at 4. Stelmasiak teaches that "[c]ladribine . . . is a purine analog with potent and clinically useful activity against some indolent leukemias and lymphomas" and "[t]he drug displays a highly selective toxicity toward malignant lymphocytes, and normal lymphocytes are also subject to the cytotoxic effect of the drug." *Id.*

Stelmasiak teaches that, in its study, cladribine was used in a solution form for both oral and subcutaneous administrations. *Id.* at 5. "The drug was prepared as a sterile solution in isotonic saline, 1 mg/ml for oral use and 2.5 mg/ml . . . for subcutaneous injections." *Id.* Stelmasiak discloses that its study group comprised "10 patients (eight females and two males)" with "body weight 52-75 kg (median: 66 [kg])." *Id.*

According to Stelmasiak, "[s]ix cladribine courses were given at monthly intervals, and two additional courses were given at 9 and 12 or 15 months," where "[e]ach course consisted of five doses of the drug taken once daily on consecutive days." *Id.* Six of the patients received the

subcutaneous dosing (5 mg per day), and four patients received oral dosing (10 mg per day). *Id.* The patients were monitored for 24 months from the start of treatment. *Id.* at Abstr., 5–7.

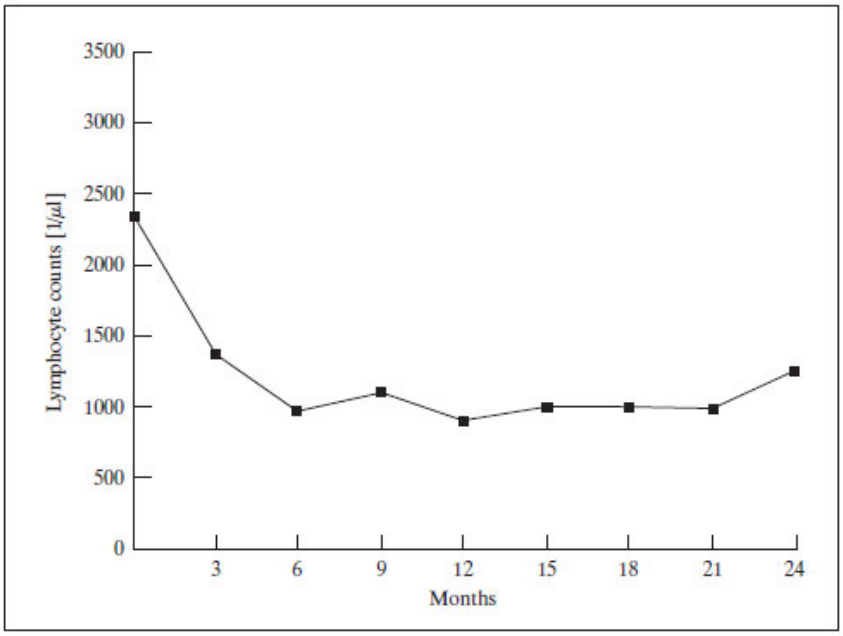
Stelmasiak reports that compliance and tolerance to the therapy were "good" and "side effects were mild." *Id.* at 5. Stelmasiak teaches that, in patients with RRMS, "treatment with cladribine decreases lymphocyte counts in peripheral blood, to 1/3 of the initial values on average." *Id.* at 7. Stelmasiak teaches that the "therapy appeared to be effective in seven patients who reported very marked (almost five-fold on average) reduction in the relapse rate during the 2 years." *Id.*; *see also id.* ("The relapse rate in some (but not all) patients is impressively decreased."). Stelmasiak discloses that, among a "responders" sub-group, the seven patients had "reported a total of 29 relapses during the two preceding years . . . and a total of 6 relapses during the two-year study period." *Id.* at 6. Stelmasiak further discloses that responding patients "showed also a somewhat more pronounced improvement in their neurological status as measured by EDSS scores." *Id.* at 7; *see also id.* at 6 ("Analysis of the data for the whole group revealed that EDSS scores were significantly reduced during the treatment compared to initial values . . . and that decreases observed at the third to fifteenth month were significant."). Stelmasiak teaches that "[a]long with clinical evaluation in MS, the detailed pattern of cladribine-induced immunosuppression in clinical conditions deserves further study." *Id.* at 7.

The therapy given in Stelmasiak's study appeared effective in seven of the patients, but Stelmasiak reports that it "seemed ineffective in the remaining three" patients. *Id.* The Stelmasiak authors report that they "were unable to identify any factor which would differentiate between the 'responders' and the 'non-responders.'" *Id.* (reporting, for example, that

"[t]here was no indication that a 'good response' is related to the actual cladribine dose per body weight").

Further, with respect to lymphocyte counts, Stelmasiak includes Figure 1, reproduced below.

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



Id. at 5. Figure 1, above, is a graph of average lymphocyte counts during the 2-year treatment course, with the number of lymphocytes (1/µl) plotted on the vertical axis versus time (months) on the horizonal axis. *Id.* Stelmasiak teaches that "[l]ymphocyte counts dropped from the initial count of 2336±595 per µl (mean±S.D.) to 968±229 per µl at 6 months, and remained at approximately 1000 per µl for the next 15 months." *Id.* at 5–6 ("A tendency toward normalization of lymphocyte count became evident only at the end of the 2-year observation period.").

3. Status of Bodor as Prior Art

a) Overview

Responding to the Petition's assertion that Bodor is prior art under § 102(a) or § 102(e), Patent Owner argues that a 6-line "dosing regimen" cited in Bodor against the challenged claims is the work of the '947 patent's inventors, not the named inventors on Bodor—Drs. Nicholas Bodor and Yogesh Dandiker. PO Resp. 9–18. Thus, according to Patent Owner, that "dosing regimen" of Bodor is not "by another" under § 102(e) and cannot be used against the '947 patent's claims as prior art.[10] *Id.*

In reply, Petitioner argues, *inter alia*, that Patent Owner has not met its burden of production to come forward with sufficient, corroborated evidence to support a determination that the "dosing regimen" from Bodor is the work of all four named inventors of the '947 patent—and their work alone. Pet. Reply 2–10. Moreover, even if the '947 patent's inventors were the source of Bodor's "dosing regimen," Petitioner argues that Patent Owner misapprehends the importance of the solid cladribine dosage form for oral administration, which was undisputedly the invention of Drs. Bodor and Dandiker. *Id.* at 4–5. Petitioner argues that, because that formulation is integral to the obviousness challenge and the cited "dosing regimen," Drs. Bodor and Dandiker should, at minimum, be deemed joint inventors of all applied portions of Bodor. *See, e.g.*, *id.* at 4–6, 10 ("Bodor and

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[10] Patent Owner notes, and we agree, that § 102(a)'s recitation of "by others" is equally addressed herein under the "by another" analysis. PO Resp. 10 n.5 (citing *In re Land*, 368 F.2d 866, 877–879 (CCPA 1966)). Assuming, on this record, that the priority date for the challenged claims is December 22, 2004, Bodor's publication on October 14, 2004, is not early enough to qualify Bodor as § 102(b) prior art.

Dandiker's tablets render them co-inventors of all relied-upon disclosures."). Hence, Petitioner contends Bodor's "dosing regimen" and the '947 patent do not share the same "inventive entity," so Bodor's disclosure is "by another" and prior art in full. *Id.* at 2–10; Pet. Suppl. Br. 1–2.

b) Factual Background

There is no overlap in the listed inventors or owners of the '947 patent and the Bodor reference. The latter names Drs. Bodor and Dandiker the inventors, and Ivax Corporation ("Ivax) as assignee. Ex. 1022, codes (71), (75). Conversely, the '947 patent lists Merck Serono S.A. as assignee, and names the following four inventors: Giampiero De Luca, Arnaud Ythier, Alain Munafo, and Maria Lopez-Bresnahan. Ex. 1001, codes (73), (75). Moving forward, we may refer to these individuals by their last name and omit any titles, unless needed for clarity (e.g., we may refer to Dr. Bodor to distinguish from the "Bodor" reference).

Although Bodor and the '947 patent share no facial overlap in their inventors or assignees, the trial record shows that there was a prior contractual relationship between Ivax and an affiliate of Patent Owner. Patent Owner presents evidence that, in October 2002, Ivax entered into a confidential product development and license agreement (the "Agreement" (Ex. 2048)) with Ares Trading S.A ("Ares"). PO Resp. 13. Patent Owner identifies Ares as a real party-in-interest in this proceeding (Paper 3, 1), and uses the name "Serono" to refer to itself and its affiliate, Ares, in its papers. *See, e.g.*, PO Resp. 2 n.1.

According to Patent Owner, Serono and Ivax entered into the Agreement to jointly develop oral cladribine for treating MS. *Id.* at 13. Patent Owner states that, 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,'" and "Serono agreed to 'conduct clinical trials' to determine 'the dose, safety, and/or efficacy' of IVAX's oral tablets or capsules" in furtherance of pursuing regulatory approvals and marketing the product. *Id.* at 13–14 (citing Ex. 2048, 2, 17–19). Patent Owner cites testimony from Munafo and Dandiker about the Agreement and discussing the delegation of responsibilities under it. Ex. 2053 ¶¶ 23–26; Ex. 2055 ¶¶ 14–15.[11]

Patent Owner submits testimony about the Serono and Ivax "teams" working under the Agreement. Munafo testifies that Serono's team included Munafo, Lopez-Bresnahan, Ythier, and De Luca, "along with many others." Ex. 2053 ¶ 18; *see also id.* ¶ 22 (testifying Serono's work led to the development of the drug Mavenclad, and the '947 and '903 patents, "which claim dosing regimens for treating MS"). The Ivax team included Bodor, Dandiker, "Dr. Stephen Marcus, and other team members." Ex. 2054 ¶ 14; Ex. 2055 ¶ 12.

Incident to Ivax's and Serono's collaboration, at least some of the members from each company met and communicated with each other about their work. Munafo testifies that "[c]onfidential communication between the Serono team and the IVAX team took place both at meetings (both in person and by telephone), where formal presentations were made, and by e-mail." Ex. 2053 ¶ 27; Ex. 2055 ¶ 15 (Dandiker testifying "the IVAX and Serono teams communicated frequently and confidentially" and "I sometimes emailed directly with Dr. Munafo"); *but see* Ex. 1059 (Bodor Tr.), 31:9–10 (testifying he had not heard of Munafo), 130:2–11 (testifying he did not

[11] Patent Owner also cites testimony from Dr. Bodor (PO Resp. 13 (citing Ex. 2054 ¶ 18)), but he admitted that he was not aware of, or familiar with, the Agreement at the relevant time. Ex. 1059, 132:19–135:3.

know, or recall meeting or communicating with, anyone from Serono; "I had no connection with Serono").

Patent Owner submits two documents related to communications and/or meetings between Ivax and Serono. First, is a document titled "Oral Cladribine for MS Project," which purports to be "Draft minutes" from a meeting on August 27, 2003, in Amsterdam. Ex. 2050 (the "Amsterdam Minutes"). The Amsterdam Minutes identify thirteen participants from Ivax and Serono as indicated in the screenshot below.

Serono Participants:
I. Emery, G. Francis, D. Frank, M. Lopez-Bresnahan, A. Munafo, A. Ythier, A. Jaber, by phone: N. Ammoury, J. Hillier
IVAX Participants:
S. Marcus, Y. Dandiker, D. Weiner, by phone: D. Emma
Serono International S.A.

Ex. 2050, 1 (annotated). As highlighted above, the Amsterdam Minutes list Lopez-Bresnahan, Munafo, and Ythier as among the Serono participants; and Dandiker is listed among the Ivax participants. *Id.*

The second document includes a December 17, 2003, cover email from Isabelle Emery at Serono to several other people at Ivax and Serono, attaching a draft "Briefing Document" titled "Cladribine." Ex. 2049, 1–3 (email), 5–9 (briefing document) (collectively the "Briefing Document"). The Briefing Document identifies Lopez-Bresnahan, Munafo, and Dandiker, among several others, as recipients and reviewers. *Id.* at 1–3, 5 (listing, e.g., Dandiker and Serono's A. Jaber as reviewers of the "CMC [(Chemistry, Manufacturing, and Controls)] section," Munafo and Ivax's Dr. Marcus as reviewers of "PK and PD [(Pharmacokinetic and Pharmacodynamic)] human info" in the Clinical Studies section, and Lopez-Bresnahan, Dr. Marcus, and seven others as reviewers of "All" sections).

Munafo testifies that the two documents illustrate the cladribine dosing regimen that Serono shared with Ivax. Ex. 2053 ¶¶ 29, 39–48.

Munafo testifies that, as reflected in the Amsterdam Minutes, Lopez-Bresnahan presented a Phase III design including two MS treatment regimens (or "arms") using oral cladribine. *Id.* In one arm, patients would receive total cumulative doses approximating 0.7 mg/kg, and in the other arm, patients would receive about 2.1 mg/kg. *Id.* ¶¶ 35–38 (citing Ex. 2050, 4–5). According to Munafo, the 0.7 mg/kg cumulative dose would be administered over 5 days and 2 months. *Id.*; Ex. 2050, 4 ("0.7 mg/kg (.35 mg/kg x 5 days x 2 months)").[12] Because the duration of treatment is recited as "24 months," Munafo testifies this means a cladribine-free period of "22-months." Ex. 2053 ¶ 38 (citing Ex. 2050, 4). Munafo testifies the Briefing Document describes a planned study to include three treatment groups: low dose (0.7 mg/kg), high dose (2.1 mg/kg), and placebo. *Id.* ¶ 41 (citing Ex. 2049, 47–48). According to Munafo, the low-dose group would receive 10 mg oral cladribine tablets daily for 5 consecutive days in each of the first 2 months, followed by placebo in months 3–6, then no pills in months 7–12. *Id.* ¶¶ 43–46 (testifying administration of placebo and no pills in months 3–12 "would result in a 10-month 'cladribine-free' period").[13]

Dandiker testifies that he attended the meeting in Amsterdam and gave a presentation on oral cladribine formulations that Ivax had developed and were investigating. Ex. 2055 ¶ 17 (citing Ex. 2050, 3–4). Dandiker also

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[12] According to Munafo, "this means 0.35 mg/kg per month for 2 months, delivered over 5 consecutive days each month." Ex. 2053 ¶ 37 n.4.

[13] Munafo explains that the administration of placebo in months 3–6 was required to maintain the "double-blind" protocol and, thus, conceal from the patients whether they were in the high, low, or placebo group. Ex. 2053 ¶¶ 42–44 (noting the high-dose (2.1 mg/kg) group received active drug in each of the first six months).

testifies that Lopez-Bresnahan presented on a Phase III study design consistent with the Amsterdam Minutes. *Id.* (citing Ex. 2050, 5–6). And, Dandiker recalls receiving a draft regulatory document in 2003, and believes the Briefing Document (Ex. 2049) is the document he received at that time. Ex. 2055 ¶ 18.

The asserted Bodor reference includes, *inter alia*, the following disclosure:

> 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.[14] Unlike several other disclosures in Bodor related to treating MS with cladribine, Bodor does not attribute this 6-line disclosure to any third-party source. *See, e.g.*, *id.* at 22:17–22 (disclosing "[t]herapeutically effective dosages . . . for multiple sclerosis" in Beutler (Ex. 1026), and "various dosage amounts and dosing regimens . . . for use in the treatment of multiple sclerosis" in, e.g., Romine (Ex. 1031) and Rice (Ex. 1018)).

Bodor includes three provisional patent applications in its priority chain. The first two provisionals were filed in 2003, and the third was filed in early 2004. Ex. 2044 ("March 2003 Provisional"); Ex. 2045 ("July 2003 Provisional"); Ex. 2046 ("February 2004 Provisional"). The 6-line

[14] The parties as shorthand refer to this passage as the "6-line disclosure" or the "6-line regimen." PO Resp. 6–7; Pet. Reply 3; PO Sur-reply 3–4. We may do likewise for consistency.

disclosure quoted above does not appear in the March 2003 Provisional or the July 2003 Provisional. *See generally* Exs. 2044 and 2045. The 6-line disclosure does appear in substantial part in the February 2004 Provisional—the only difference is that the provisional uses the phrase "for one week" instead of "for a period of five to seven days." Ex. 2046, 20:6–10.

Patent Owner submits testimony from Drs. Bodor and Dandiker related to the 6-line disclosure in Bodor. Ex. 2054 ¶¶ 25–26; Ex. 2055 ¶¶ 22–23. For example, in Dr. Bodor's declaration, there is a paragraph quoting the 6-line disclosure, after which Dr. Bodor testifies:

> Neither myself nor my team, including Dr. Dandiker, developed, researched, or invented the above dosing regimen. Indeed, no one on my team at IVAX developed, researched, or invented any cladribine dosing regimen for treating MS. I do not consider this regimen to be my invention, and it was not claimed in the BODOR PCT or the corresponding U.S. patents, Nos. 8,888,328 and 8,785,415. Ex. 2069; Ex. 2029.

Ex. 2054 ¶¶ 25–26; *see also* Ex. 2055 ¶¶ 22–23 (materially the same testimony from Dandiker). Drs. Bodor and Dandiker then declare their belief that, because Serono was working on "dosing regimens" for Phase III clinical trials as part of the collaboration with Ivax, "Serono communicated the dosing regimen" described in Bodor to Ivax. Ex. 2055 ¶¶ 24–26; Ex. 2054 ¶¶ 27–28 (testifying "it is highly likely that . . . Serono communicated the above dosing regimen" to Ivax).[15]

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[15] Other testimony from Dandiker and Bodor gives more context to what those witnesses mean by the phrase "dosing regimen." Dandiker testified that "dosing regimen" is "not my term," but he distinguishes a dosing regimen (how the formulation is clinically administered) from the formulation (how a dosage form is chemically designed to, e.g., give a desired release of drug). *See, e.g.*, Ex. 1060, 119:13–123:5. Dr. Bodor notes his studies used single doses of oral cladribine to compare pharmacokinetic

c) Analysis

Under 35 U.S.C. §§ 102(a) or (e), an inventor's own work is not prior art that may be used against the inventor. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 968 (Fed. Cir. 2014); *In re DeBaun*, 687 F.2d 459, 462 (CCPA 1982). Mere publication of an inventor's ideas in a reference patent or application of another person is not necessarily prior art "by another" against the inventor. *See In re Mathews*, 408 F.2d 1393, 1394–95 (CCPA 1969) (holding Dewey's publication of coworker Mathews's invention in Dewey patent (after Mathews had communicated that invention to Dewey) not usable as prior art against the Mathews patent).

In deciding whether a reference patent or published application is "by another" and qualifies as prior art under § 102(e), "[w]hat is significant is not merely the differences in the listed inventors, but whether the portions of the reference relied on as prior art, and the subject matter of the claims in question, represent the work of a common inventive entity." *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1356 (Fed. Cir. 2003). The "common inventive entity" inquiry, however, requires *identity* among the respective inventors. *Id.* Indeed, "a sole applicant or patentee and joint applicants or patentees are separate or different 'legal entities' and either is treated as 'another'" for purposes of determining whether a reference is prior art. *In re Land*, 368 F.2d at 878, 881 ("Land and Rogers individually [were] separate legal entities from Land and Rogers as joint inventors."). Thus, just

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properties and bioavailability. Ex. 2054 ¶ 17. Because he "never treated a patient using multiple doses of cladribine," Dr. Bodor testifies "we never used or studied anything that could be described as a 'dosing regimen.'" *Id.*

as a reference's disclosure of the invention of A and B[16] is usable as prior art against the invention of X, Y, and Z, a reference's disclosure of the invention of X and Y is usable as prior art against the invention of X, Y, and Z. *See, e.g.*, *MaxLinear Inc. v. Cresta Tech. Corp.*, IPR2015-00594, Paper 90 at 16–24 (PTAB Aug. 15, 2016) (reference to subset of inventors determined as § 102(e) art); *Dr. Reddy's Labs., Inc. v. Horizon Pharma. USA, Inc.*, IPR2018-00272, Paper 74 at 17 (PTAB Sept. 9, 2019) (same).

The three-part test set forth in *Duncan Parking* also guides the analysis here. *Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1358 (Fed. Cir. 2019); PO Resp. 10–18; Pet. Reply 3–10. According to that test, the 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 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, 914 F.3d at 1358. In *Google*, the Federal Circuit addressed the *Duncan Parking* test in the context of an obviousness challenge and explained that, "[t]o be a joint inventor of the [applied] reference . . . , [(co-author Moran)] must have made an inventive contribution to the portions of the reference relied on and relevant to establishing obviousness." *Google, LLC v. IPA Tech. Inc.*, 34 F.4th 1081, 1086 (Fed. Cir. 2022) (analyzing whether a reference co-authored by Martin, Cheyer, and Moran was § 102(a) art to the Martin and Cheyer patent); *see*

[16] The letters used here represent different individuals and the respective groupings (e.g., "A and B") reflect that those individuals are joint inventors of the hypothetical invention.

also id. at 1086 n.3 ("The portions of the reference being considered must be relied upon *and* relevant to establishing obviousness.").

Based on the parties' arguments, we see the issues as twofold. *First*, whether the evidence of record is sufficient to support a determination that the cited 6-line disclosure in the Bodor reference is the joint invention of Munafo, Lopez-Bresnahan, Ythier, and De Luca. If, for example, Bodor's 6-line disclosure did not reflect the invention of *all* the '947 patent's listed inventors, then there is no "common inventive entity" and Bodor's 6-line disclosure would be legally "by another" irrespective of whether Drs. Bodor or Dandiker contributed to it. *Second*, considering all Bodor's relied-upon teachings that are relevant to establishing the alleged obviousness of the claims (including portions that reflect the work of Drs. Bodor and Dandiker and not the '947 patent's named inventors), whether the contributions of Bodor and Dandiker are significant enough that they should be considered joint inventors of all applied portions of the reference.

(1) Whether Bodor's "Dosing Regimen" and the '947 Patent Share a Common Inventive Entity that Includes De Luca

Petitioner met its initial burden to show that Bodor is 102(a) and (e) art, "because nothing in Bodor facially 'represent[s] the work of a common inventive entity.'" Pet. Reply 2–3 (quoting *EmeraChem Holdings v. Volkswagen*, 859 F.3d 1341, 1345 (Fed. Cir. 2017)). As discussed above, there is no facial overlap in the named inventors or assignees of Bodor and the '947 patent. Nor could Petitioner have reasonably foreseen that Patent Owner would argue Bodor (or any portion of it) represented Patent Owner's own work. As Petitioner points out, "[n]either the patent nor its file history evince a joint research agreement." *Id.* at 3. Also, despite the Examiner

citing Bodor against the pending claims several times during prosecution of the '947 patent and related '903 patent (including reliance on the same 6-line disclosure discussed above), Patent Owner never argued that any of Bodor's teachings were disqualified as prior art. *See, e.g.*, Ex. 1004, 220–221 (Aug. 3, 2009, Office Action rejecting claims); Ex. 1025, 99–101 (Dec. 19, 2011, Office Action rejecting claims).

The burden thus shifted to Patent Owner to come forward with evidence sufficient to support the proposition that Bodor is not prior art. *Dr. Reddy's*, IPR2018-00272, Paper 74 at 14–19 (shifting burden to patentee to provide evidence the reference is not "by another"); *Google*, 34 F.4th at 1085–1086 (discussing shifting burdens of production in context of "by another" analysis). We agree with Patent Owner that the ultimate burden of persuasion in an IPR remains with Petitioner. PO Sur-reply 3. Yet missing from Patent Owner's produced documents and testimony is credible and corroborated evidence that named inventor De Luca provided an inventive contribution to the 6-line regimen that appears in Bodor. *Google*, 34 F.4th at 1087 (holding corroboration of alleged inventor testimony is required in the "by another" analysis).

The testimony of Drs. Bodor and Dandiker does not corroborate that De Luca made any inventive contribution to the 6-line disclosure. Dr. Bodor did not "know anybody from Serono" and "had no connection with Serono." Ex. 1059, 130:2–11. Dandiker never communicated with De Luca and could not say what, if anything, he did in relation to the collaboration between Ivax and Serono. Ex. 1060, 84:2–85:19 (Q: "Do you have an understanding of whether Dr. de Luca contributed to developing the dosing regimen for treating multiple sclerosis with oral cladribine," A: "I cannot say anything on that.").

None of the three documents produced by Patent Owner suggests that De Luca made any inventive contribution to the 6-line dosing regimen. Petitioner contends that "De Luca's name appears nowhere in" the Amsterdam Minutes or the Briefing Document, and Patent Owner provides no argument to the contrary.[17] Pet. Reply 6; PO Sur-reply 5 (citing, in response, only Munafo's uncorroborated testimony that De Luca was part of the team that developed the regimen).

Patent Owner produced no testimony from three of the four named inventors on the '947 patent. The only testifying inventor, Munafo, could not recall any specific contribution made by De Luca (Serono's chief IP attorney)—declaring generically that De Luca was one of several "team" members and, in some unspecified way, helped design the subject dosing regimen. Ex. 2053 ¶¶ 18, 21, 34, 40. When pressed at deposition on what De Luca "contribute[d] intellectually to the development of the cladribine regimen in Bodor," Munafo had nothing material to add. Quite the opposite, Munafo responded simply that De Luca had worked for Serono "for a very long time," but "in a department which was remote" to Munafo's, and so Munafo was "not aware of [De Luca's], how you call it, personal intellectual contribution." Ex. 1063, 94:4–95:8 ("I cannot give details on [(whether De Luca contributed to the cladribine regimen in Bodor)], besides the fact that [De Luca's] department was also represented in the project team.").

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[17] [redacted]

Munafo's vague, uninformative, and otherwise uncorroborated testimony about De Luca's contribution to the 6-line disclosure of Bodor does not help Patent Owner meet its production burden.

That essentially leaves us with the fact that De Luca is a listed inventor on the '947 patent. Here again, however, there is no evidence of record about what De Luca specifically contributed to any of the patent's claims (e.g., De Luca could be a joint inventor of all claimed subject matter, or perhaps only of certain subject matter appearing in a dependent claim). *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998) (explaining that a joint inventor "needs to perform only a part of the task which produces the invention" and "need not make a contribution to every claim of a patent"). And, although there are similarities between the claims compared to the 6-line disclosure of Bodor, there are also some differences. Claim 36, for example, comprises oral administration of cladribine, but it does not require use of 10 mg solid tablets comprising the cladribine-cyclodextrin complex like Bodor's disclosure. Bodor's 6-line disclosure also does not expressly describe a maintenance period dose and duration and secondary cladribine-free period as claimed.[18] Patent Owner does not

[18] There also appear to be differences in the dosing regimen described in the Amsterdam Minutes and Briefing Document versus what is claimed. For example, the Amsterdam Minutes refer to low and high "cumulative dose[s]" of 0.7 mg/kg (delivered over 2 months) and 2.1 mg/kg (delivered over 6 months). Ex. 2050, 4. Claim 36, however, requires a total induction dose of between about 1.7 mg/kg to 3.5 mg/kg given over about 2–4 months. Patent Owner does not explain if, and how, these regimens correspond to each other in such a way that it might suggest De Luca is necessarily a co-inventor on what is described in the minutes (and assuming De Luca is a joint inventor of claim 36). Also, if the recitation in the minutes of, for example, 0.7 mg/kg reflects an assumed total "effective" dose (meaning the dose to be delivered after reduced by a bioavailability coefficient), this

produce evidence that would show that De Luca must necessarily be a co-inventor of Bodor's 6-line disclosure simply because De Luca is named as a joint inventor on the '947 patent.

Patent Owner raises two counterarguments. Both are unavailing. First, Patent Owner contends that a reference's disclosure of the work of a "subset" of named inventors is not prior art against the invention of all named inventors. PO Suppl. Br. 1–2. Patent Owner cites *Applied Materials Inc. v. Gemini Rsch. Corp.*, 835 F.2d 279, 281 (Fed. Cir. 1988). But that case does not support Patent Owner's position. In *Applied Materials*, the Federal Circuit reversed the district court's determination that a "reference" patent naming McNeilly and Benzing was prior art to a related patent by McNeilly, Benzing, and Locke, which determination rested on the fact that the reference and patent *named* different inventors. *Id.* at 281 (explaining, "that an application has named a different inventive entity than a patent does not necessarily make that patent prior art").[19] Properly framed, the issue was whether the McNeilly/Benzing reference had disclosed the invention of McNeilly/Benzing/Locke, which the Federal Circuit answered in the affirmative. *Id.* at 280–281 (notably the reference and patent arose from a

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would seem to implicate further the importance of Dr. Bodor's formulation work, and not that of any named inventor of the '947 patent. *See, e.g.*, Ex. 1059, 34:11–40:8 (discussing Bodor's work on bioavailability).

[19] As the court further explained, "[w]hen the joint and sole inventions are related . . ., inventor A commonly discloses the invention of A & B in the course of describing his sole invention and when he so describes the *invention* of A & B he is not disclosing 'prior art' to the A & B invention, even if he has legal status as 'another.'" *Applied Materials*, 835 F.2d at 881 (quoting *In re Kaplan*, 789 F.2d 1574, 1576 (Fed. Cir. 1986)). Consistent with *Applied Materials's* result, this indicates the inventive entities must be identical.

single application filed by McNeilly & Benzing, which split into multiple applications due to the PTO's restriction requirement). McNeilly and Benzing's reference disclosure of the McNeilly/Benzing/Locke invention could, therefore, not be used to invalidate that same invention in the McNeilly/Benzing/Locke patent. The court thus required the inventive entities behind the reference's applied disclosure and the patent be identical.

Patent Owner also points to *Allergan* and MPEP § 2132.01. PO Suppl. Br. 1–2 (citing *Allergan*, 754 F.3d at 966). As noted by Petitioner, *Allergan* is of no avail because the Federal Circuit held that appellant had failed to prove that the cited art "represent[s] the work of the inventors *themselves*." *Allergan*, 754 F.3d at 968–69 (emphasis added); Pet. Suppl. Br. 2. *Allergan* did *not* hold that the work of a subset of inventors was disqualified as prior art.[20] The MPEP provision cited by Patent Owner states that "[a]n inventor's or at least one joint inventor's disclosure of his or her own work within the year before the application filing date cannot be used against the application as prior art" under § 102(a). Manual of Patent Examining Procedure (MPEP) § 2132.01 (9th ed. 2022). The authority behind this MPEP provision, however, does not support a conclusion that the "common inventive entity" inquiry requires something less than identity. To the contrary, the MPEP relies on *In re Katz*, which explained that a paper authored by Katz, Chiorazzi, and Eshar would only be excluded as prior art

[20] Patent Owner reads too much into *Allergan*, which focused on one co-inventor's (VanDenburgh's) authorship and alleged contribution to an applied reference (finding that contribution insufficient). *Allergan*, 754 F.3d at 968–70. We are unpersuaded that *Allergan* stands for the proposition that appellant would have prevailed and excluded the asserted art irrespective to whether co-inventor (Woodward) contributed to it, which the court did not substantively discuss, much less decide.

against the Katz patent if Katz *alone* invented the relied-upon disclosures in the paper. *In re Katz*, 687 F.2d 450, 455 (CCPA 1982) (explaining "co-authors may not be presumed to be coinventors merely from the fact of co-authorship").

In short, Patent Owner cites no authority holding that a reference's disclosure of the invention of a *subset* of inventors is disqualified as prior art against the invention of *all* the inventors. Patent Owner cites no case where a reference was disqualified as §§ 102(a) or (e) prior art absent the reference (or its applied teachings) and the claims sharing the same "inventive entity."

Second, Patent Owner argues that, under a "rule of reason," its evidence is sufficiently corroborated. PO Sur-reply 5–6; PO Suppl. Br. 2. It is true that whether an inventor's testimony is corroborated is evaluated under a "rule of reason" analysis, and that "[c]orroborating evidence may take many forms." *Ethicon*, 135 F.3d at 1461. But, as it concerns De Luca's alleged contribution to the 6-line disclosure, the testimonies of Bodor and Dandiker and the few internal documents produced by Patent Owner are silent. Munafo's vague assertion that De Luca had "discussions" with "various team members" that helped to develop the proposed regimen (Ex. 2053 ¶ 21) are undermined by Munafo's concession that he was "not aware of" and "cannot give details" about any contribution from De Luca (Ex. 1063, 95:3–8). And, this record is especially wanting for independent corroboration about De Luca's role vis-à-vis the Bodor regimen because the events in question took place over twenty-years ago.[21] Even considering the

[21] As noted above, Patent Owner never sought to disqualify Bodor during prosecution of the '947 and '903 patents when rejections based on Bodor were raised much closer in time to Ivax's and Serono's collaboration.

’947 patent, there is no sufficient evidence here from which we can conclude that a specific contribution from De Luca to the claimed subject matter found its way into Bodor’s 6-line disclosure.

Altogether, we conclude that Patent Owner cannot exclude Bodor’s 6-line disclosure as prior art unless that disclosure was invented by the *same* “inventive entity” as the ’947 patent’s challenged claims. And, on this record, we determine that Patent Owner has not provided sufficient evidence to support the conclusion that De Luca is an inventor of the subject matter in Bodor being applied against the ’947 patent. Bodor is, thus, “by another” and available as prior art.

(2) Bodor’s and Dandiker’s Contribution to the “Dosing Regimen”

Even if the four named inventors of the ’947 patent made an inventive contribution to Bodor’s 6-line disclosure, Petitioner argues that those contributors were not alone and that Patent Owner is ignoring the importance of Bodor’s and Dandiker’s cladribine tablet formulation. Pet. Reply 3–10.

According to Petitioner, under *Duncan Parking* step 1, Petitioner relies on additional Bodor disclosures relevant to establishing obviousness. *Id.* at 3–4. Petitioner cites Bodor’s stated benefits of its oral cladribine formulation (e.g., bioavailability), MS cladribine dosages achieving therapeutic results, fine-tuning cladribine’s dose and treatment duration, and Bodor’s examples (e.g., making of Bodor’s 3 mg and 10 mg tablets, and testing of tablets in patients with MS). *Id.* (citing Ex. 1022, 2, 22:17–19, 24:1–9, Examples 1–4). Patent Owner neither argues nor presents evidence that the ’947 patent’s named inventors are responsible for these other disclosures in Bodor, and we agree with Petitioner that at least some of these

additional disclosures are highly relevant to Petitioner's obviousness challenge. For example, Petitioner's citation to Bodor's teaching of lower interpatient variation with Bodor's solid tablets provides a reason to use that dosage form (Pet. 33–34); and Petitioner's citation to Bodor's disclosure about "fine tuning" the cladribine dose and length of treatment is relevant to Petitioner's position that a POSA would have regarded those variables as "result-effective" and optimizable to arrive at an obvious maintenance period dose and duration (Pet. 40–41). Those disclosures are thus, under *Google*, both relied-upon by Petitioner and relevant to establishing the alleged obviousness of the claims. *Google*, 34 F.4th at 1086. Although we agree that Bodor's 6-line disclosure plays a central role in Petitioner's obviousness challenge, we disagree with Patent Owner's suggestion that it is the only disclosure that counts in the *Duncan Parking* analysis. PO Sur-reply 3–4.

Petitioner also argues, under *Duncan Parking* step 2, that Bodor and Dandiker undisputedly invented the solid cladribine dosage form that is described and used in the so-called 6-line regimen. Pet. Reply 4–5 (citing, e.g., Ex. 1059, 25:13–26:2 ("That's my invention and Dr. Dandiker's invention"), Ex. 1060, 48:15–49:13 ("What we were trying to do was to make the first oral tablet . . . for cladribine so that it would help people, it would help patients. Multiple Sclerosis is a devastating disease. . . . And oral, I think, is just better for the patient."). Petitioner argues Drs. Bodor and Dandiker recognized the tablets' importance to MS treatments, as they are the sole inventors of MS treatment methods using those tablets, as claimed in two patents with priority to Bodor. *Id.* (citing Ex. 1022, claims 22, 27, 28; Ex. 2029, claims 54, 56, 61, and 75). And, even as it pertains to the disclosure of "10 mg" tablets in Bodor's 6-line regimen, Munafo could not

say that the '947 patent's inventors alone were responsible for that dose. Ex. 1063, 135:4–14 (testifying "it was a joint team effort"). Indeed, evidence suggests they were not alone. Ex. 2050 (Amsterdam Minutes), 3–4 [redacted] The teaching of the 10 mg cladribine tablets in Bodor's 6-line disclosure is not only relevant to the obviousness challenge, it is key to Petitioner's showing about how the claimed induction period's total dose limitation is met. *See* Pet. 49 (Ex. 1002 ¶ 83 (calculating (10 mg x 14 days = 140 mg; 140 mg ÷ 70 kg (average-weight patient) = 2 mg/kg (within range of 1.7–3.5 mg/kg)).

Patent Owner argues that Petitioner does not explain how Bodor's and Dandiker's involvement in a formulation renders them co-inventors of the regimen. PO Sur-reply 6–7 (arguing, *inter alia*, that Bodor also describes using the formulation to treat diseases in addition to MS, and never claimed the regimen involving administration for a specific number of days/months). That, however, is not accurate. As Petitioner points out, Bodor and Dandiker testified that their tablets exhibited properties important to Bodor's regimen, including improved absorption, reduced interpatient variation, and increased patient convenience/compliance. Pet. Reply 5 (citing, e.g., Ex. 1059, 34:11–40:8; Ex. 1060, 121:21–123:7, 124:11–125:6). Patent Owner's clinical pharmacology expert, Dr. Meibohm, agrees that such properties would have been considered when developing a dosing regimen. Ex. 2052 ¶ 2; Ex. 1062, 42:1–47:16, 48:7–57:21 (testifying interpatient variability, dosage form/route, patient compliance/adherence, and stability

would "all have been considerations in developing a dosing regimen as of the 2004 time frame").

Even Munafo agreed that "the formulation is part of the elements that you consider in designing a dosing regimen . . . and it [(Ivax's formulation)] became an element that we were considering when designing this dosing regimen." Ex. 1063, 79:8–14. Patent Owner argues that Munafo was only referring to "hypothetical" effects a formulation could have on the regimen; and, according to Patent Owner, there is no evidence the regimen actually changed based on the formulation. PO Sur-reply 7 (citing Ex. 1063, 78:5–80:4). Thus, according to Patent Owner, the formulation bears only an "incidental relation" to the regimen. We disagree. If we somehow excised the recitation of "10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form" from the remainder of the 6-line disclosure, it is unclear what dosage form is used or even how much of the drug would be given. *See* Pet. Reply 4 (annotating Bodor's 6-line disclosure; green highlighting reflecting subject matter not attributable only to named inventors on the '947 patent). The disclosure is intertwined and, on this record, we find that the tablets bear more than an incidental relation to the frequency and duration of administering those tablets.

Accordingly, upon considering all Bodor's relied-upon disclosures as discussed above and the significance of those disclosures to the obviousness challenge presented here, along with the contributions of Drs. Bodor and Dandiker to the cladribine tablets underlying those disclosures, we conclude that *Duncan Parking* step 3 is met. On the record here, the 6-line disclosure is not solely the invention of the '947 patent's named inventors, Drs. Bodor and Dandiker are at least co-inventors of all applied portions, and the Bodor reference is "by another" and available in full as prior art.

4. Obviousness of Claim 36

a) Overview

Petitioner contends that claim 36 would have been obvious over the teachings of Bodor and Stelmasiak. Pet. 33–54; Ex. 1002 ¶¶ 77–119. Petitioner contends that Bodor and Stelmasiak teach methods of treating multiple sclerosis comprising administering oral formulations of cladribine and that both treatments include induction and cladribine-free periods. Pet. 45–50 (citing, e.g., Ex. 1022, Abstr., 23:15–20; Ex. 1013, Abstr.). Indeed, Petitioner contends the induction period dosing in Bodor overlaps with the claimed induction period dosing, and is followed by a 10-month, cladribine-free period. *Id.* at 49–50 (arguing, e.g., that an average-weight patient would receive about 1.4 mg/kg to about 2.0 mg/kg, overlapping with claim 36's range of about 1.7–3.5 mg/kg).

According to Petitioner, Bodor at least suggests a retreatment period after the cladribine-free period, especially in view of the fact that MS is a chronic disease and many MS patients do require retreatment. *Id.* at 50–52 (citing Ex. 1022, 23:15–24; Ex. 1002 ¶¶ 86–87; Ex. 1009, 263). Petitioner notes that Stelmasiak teaches a cyclical treatment regimen that includes cladribine retreatments and intermittent cladribine-free periods. *Id.* (citing Ex. 1013, Abstr., 5; Ex. 1002 ¶¶ 88–89). Further, Petitioner contends, it would have been routine to optimize the total dose and length of cladribine administration in a maintenance phase. *Id.* at 40–43 (citing, e.g., Ex. 1022, 2, 11–12, 23, 24:6–9 (teaching therapeutically effective amounts can be "easily determined [] empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of benefits"), 53–54; Ex. 1002 ¶¶ 102–104 (testifying it would be logical and within the POSA's

ordinary skill to use Bodor's two-month treatment period as a starting point for optimization in a maintenance phase)).

Petitioner argues it would have been obvious to optimize the total dose and duration of Bodor's regimen as appropriate for treating MS. *Id.* at 40–42. Petitioner contends the POSA would have, as was standard practice in the field, regularly measured patients' lymphocyte counts while assessing therapeutic efficacy. *Id.* (citing, e.g., Exs. 1013, 5; Ex. 1014, 1717; Ex. 1018, 1146); *see also id.* at 36 (citing Ex. 1002 ¶¶ 103–104 (testifying that a POSA would have been motivated to intersperse drug-treatment periods with drug-free periods to manage hematological toxicity)). And, Petitioner contends, a POSA would have reasonably expected success in view of various clinical studies reporting on the efficacy of cladribine in MS patients. *Id.* at 43–44 (citing, e.g., Ex. 1014, 1719–1720; Ex. 1013, 7; Ex. 1023, Abstr.; Ex. 1002 ¶¶ 35–49).

In response, Patent Owner argues that claim 36 would not have been obvious for three principal reasons. *First*, Patent Owner contends that neither Bodor nor Stelmasiak teaches the claimed induction and maintenance period dosing. PO Resp. 19–33. According to Patent Owner, Bodor and Stelmasiak do not disclose "weight-based" dosing, and neither reference discloses the same maintenance period as claimed. *Id.* at 19–24. *Second*, Patent Owner contends there is no reason to combine Bodor's and Stelmasiak's teachings or reasonable expectation of success in doing so to arrive at the claimed method. *Id.* at 35–57 (arguing, *inter alia*, Petitioner's optimization arguments should fail because of alleged dissociation between suppressed lymphocyte counts and therapeutic efficacy). *Third*, Patent Owner argues that objective indicia support a conclusion of nonobviousness. *Id.* at 58–65 (asserting, e.g., alleged skepticism).

We address the parties' arguments and evidence in more detail below in the analysis that follows.

b) Whether the Prior Art Teaches or Suggests All Limitations, Including the Claimed Induction and Maintenance Periods

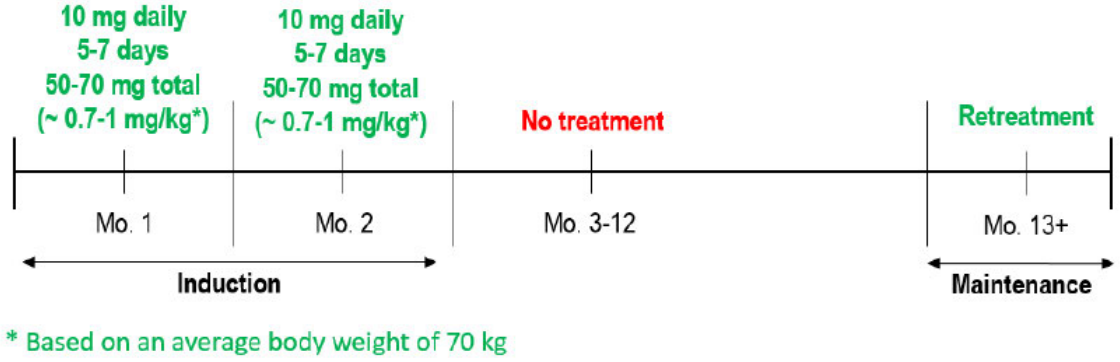
According to Petitioner, Bodor teaches treating MS by orally administering cladribine as recited in claim 36's preamble. Pet. 45, 47 (citing, e.g., Ex. 1022, 23:15–20). Petitioner contends that Stelmasiak similarly teaches treating MS, specifically patients with RRMS, using an oral formulation of cladribine. *Id.* at 47–48 (citing Ex. 1013, Abstr.). For the reasons given by Petitioner, we find that Bodor and Stelmasiak disclose claim 36's preamble language, whether that language is limiting or not. Patent Owner provides no argument to the contrary.

Petitioner argues that Bodor and Stelmasiak teach induction periods, and that Bodor teaches an induction period dosage and duration that overlaps with claim 36's recitation in step (i) that the total cladribine dose reached at the end of the induction period is about 1.7 mg/kg to about 3.5 mg/kg. *Id.* at 48–49 (citing Ex. 1022, 23; Ex. 1013, Abstr., 5). Specifically, Petitioner contends, Bodor teaches an induction period spanning two months wherein 10 mg of cladribine is administered once daily for five to seven days in the first month and repeated for five to seven days in the second month. Ex. 1022, 23. As Dr. Miller explains, that regimen would provide a total cladribine dose of 100–140 mg (e.g., 7 days x 10 mg x 2 months = 140 mg) at the end of the induction period and, for a patient of average weight, mathematically corresponds to a range of about 1.4 mg/kg to 2 mg/kg (e.g., 140 mg ÷ 70 kg = 2 mg/kg). Pet. 49; Ex. 1002 ¶ 83 (citing Exhibit 1050 for an average adult weight and showing the respective calculations).

Petitioner contends that Bodor further teaches a cladribine-free period that satisfies claim 36's step (ii). Pet. 49–50. Petitioner cites Bodor's teaching that the induction period discussed above is "followed by ten months of no treatment." *Id.* (citing Ex. 1022, 23:15–20). According to Petitioner, Bodor's cladribine-free period is within the scope of the claimed "cladribine-free period lasting from about 8 months to about 10 months." *Id.*; Ex. 1002 ¶ 85.

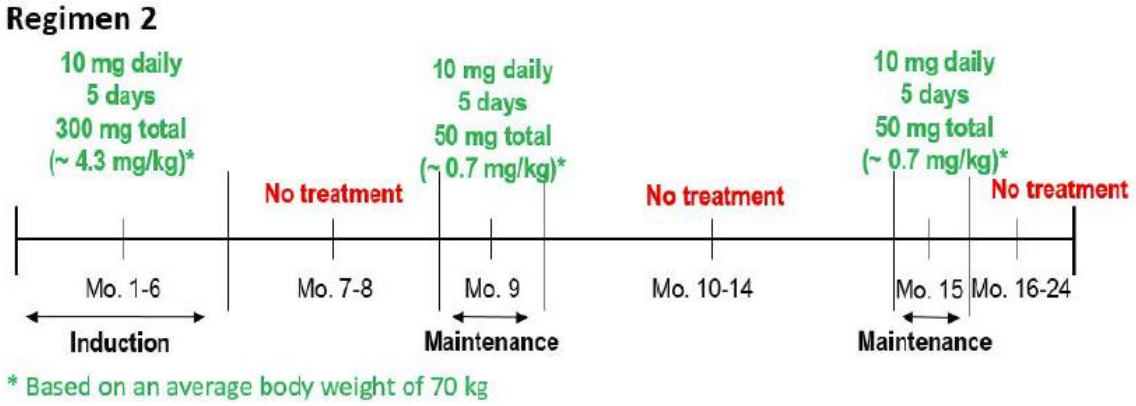
Furthermore, Dr. Miller opines that a POSA would have understood that Bodor suggests a retreatment period after the cladribine-free period. Ex. 1002 ¶ 86 (discussing Bodor's alternative regimen with a 6-month induction period, and an 18-month cladribine-free period (Ex. 1022, 23:15–24) and testifying that a POSA would understand Bodor to suggest a subsequent retreatment phase "otherwise, the specified length of time of the cladribine-free period is meaningless"). Dr. Miller testifies that a POSA would have known that MS is a disease without a cure that typically needs ongoing treatment and, reading Bodor in that context, would have "thought to re-administer cladribine again after the specified cladribine-free period." *Id.* ¶ 87 (testifying that "MS patients typically receive more than one course of drug therapy to treat active relapses, prevent relapses, and/or prevent or slow further progression of the disease"); *see also id.* ¶¶ 53–59.

Accordingly, Petitioner contends that a POSA would have understood Bodor as teaching a cladribine dosing regimen for the treatment of MS as shown in the schematic below.



Pet. 49–51 (citing Ex. 1002 ¶ 84). The image above is a schematic/timeline that shows an induction period (months one and two), a subsequent "No treatment" period of ten months, and then a "Retreatment" or "Maintenance" phase starting in the thirteenth month. Ex. 1002 ¶ 84. The schematic also shows daily and monthly cladribine doses in each of the first two months (~ 0.7–1 mg/kg for each month based on the average-weight patient). *Id.*

Petitioner argues that Stelmasiak teaches a cyclical cladribine regimen with "induction" and retreatment or "maintenance" periods. Pet. 52–53. Petitioner contends that Stelmasiak teaches a regimen ("Regimen 2") involving administration of oral cladribine for the first six months, a no-treatment period in months seven and eight, a retreatment at month nine, followed by another no-treatment period between months ten to fourteen, then another cladribine retreatment at month fifteen, which is again followed by a no-treatment period that spans months sixteen to twenty-four. *Id.*; Ex. 1013, Abstr., 5. Dr. Miller's schematic illustrating this dosing regimen from Stelmasiak is reproduced below.



Ex. 1002 ¶ 89. The schematic above shows the periods in which cladribine is administered (with dosing amounts in green font) occurring in months one through six, and at months nine and fifteen; following each of the periods in which cladribine is administered are "No treatment" periods (red font) lasting a certain number of months. Dr. Miller opines that a POSA would have understood the first six months as being an induction period and that the retreatments at month nine and fifteen would be understood as "Maintenance" treatments. *Id.* ¶¶ 88–89.

We find that Petitioner has shown by a preponderance of the evidence that Bodor teaches or suggests the induction period recited in claim 36's step (i) and subsequent cladribine-free period recited in claim 36's step (ii). We credit Dr. Miller's testimony, discussed above, explaining how those claim limitations would have been obvious from at least Bodor's teachings. Patent Owner's counterargument, discussed below, is unavailing.

Patent Owner contends that "flat and weight-based dosing are fundamentally different." PO Resp. 19 (asserting "in flat dosing all patients, regardless of weight, receive the same amount of a drug") (citing Ex. 2051 ¶¶ 91–93; Ex. 2052 ¶ 35). According to Patent Owner, Bodor considered "weight-based dosing in the art but still chose flat dosing" for its 2-months on, 10-months off regimen. *Id.* at 20; *see also* PO Sur-reply 8–10 ("In

contrast to the challenged claims' weight-based dosing, Bodor and Stelmasiak only disclose ***flat*** dosing.").

Insofar as Patent Owner is urging that claim 36 should be interpreted to *exclude* administering so-called "flat" doses (i.e., 100–140 mg) to patients of average weight where the total cladribine dose would fall within claim 36's recited range of about 1.7 mg/kg to 3.5 mg/kg, we reject that interpretation. Patent Owner did not propose any express "weight-based" claim construction in its Patent Owner Response and, in its Sur-reply, the only support cited by Patent Owner for its apparent limiting interpretation is an example in the patent (where patients receive a different number of tablets depending on their weight), and the prescribing information/label for the approved drug MAVENCLAD (and testimony about that drug's label). PO Sur-reply 8–9 (citing Ex. 1001, 14:41–44, Tables 3 & 4 (disclosing, e.g., that patients weighing between 60–69.9 kg receive ten 10 mg pills over the first two months; patients weighing 70–89.9 kg receive twelve to fourteen 10 mg pills over the first two months); Ex. 2001, 5).[22]

We see no adequate basis for limiting the claims in the manner suggested by Patent Owner based on the cited example and the extrinsic evidence about MAVENCLAD. We decline to import into the claims any express patient-weighing step or to construe the claims to require preexisting knowledge of a patient's weight. As we noted at institution, the claims include no active steps of determining a patient's weight or performing *a*

[22] Patent Owner also cites the Specification's disclosure that dosage administered to an individual "will vary depending on a variety of factors," listing pharmacokinetic properties, patient sex, age, weight, health, symptoms, frequency of treatments, and effect desired, among other factors. Ex. 1001, 5:30–35. We do not agree that this non-specific disclosure justifies limiting the claims as written in the manner urged by Patent Owner.

priori calculations to arrive at any alleged "weight-based" dosing before cladribine is taken or administered. Inst. Dec. 35–36 n.17. Indeed, the total dose in claim 36 is only recited passively in a wherein clause—"wherein the total dose of cladribine *reached at* the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg." Ex. 1001, 19:17–21 (emphasis added). We, thus, agree with Petitioner; Patent Owner "does not identify any term justifying limiting the claims to weight-based dosing." Pet. Reply 12; Ex. 1084 ¶ 32 (testifying "none of [the] claims . . . require an active step of determining a patient's weight before administering cladribine," and "the claims do not recite administering specific amounts of cladribine to patients of a specific weight").

In any event, the evidence points to the obviousness of converting so-called flat and weight-based expressions of the dose. And, in this field, those expressions are often used interchangeably to describe cladribine doses for treating MS. Bodor, for example, describes a regimen using 10 mg tablets administered over 5–7 days per month for 2 months, which Patent Owner argues is "flat." Ex. 1022, 23:15–20. Elsewhere, however, Bodor defines the "therapeutically effective amount" for treating MS with cladribine in view of the technical literature's reporting of values between "about 0.04 to about 1.0 mg/kg/day." *Id.* at 22:17–22 (citing Beutler (Ex. 1026)). Consistent with Dr. Miller's calculations of the total amount of cladribine given (on a mg/kg basis) with Bodor's regimen using 10 mg tablets, that total amount is well within Bodor's broader definition of known therapeutic amounts. Ex. 1002 ¶ 83. Contrary to Patent Owner's argument, Bodor does not suggest it was going in any new or nonobvious direction by expressing "flat" dosages in its regimen. PO Resp. 20.

Even the '947 patent makes the obvious conversion between flat and by-weight dose expressions when describing the *background* prior art. The patent describes a study by "Grieb" wherein "Cladribine has been orally administered during 6 monthly courses of 5 days at a total dose of about 4–5.7 mg/kg (patients of about 52 and about 75 kilos, respectively)." Ex. 1001, 3:3–21 (describing Grieb and citing Stelmasiak). Nowhere, however, does Grieb explicitly report a total dosage of 4–5.7 mg/kg. *See generally* Ex. 1023. The patent simply makes the basic mathematical conversion from Grieb's express disclosure (much like Bodor's cited regimen) of giving a certain dosing (e.g., 10 mg/day) over a specified timeframe. Ex. 1023, 324. Patent Owner suggests this description of Grieb should be discounted because the patent's inventors were more prescient than the ordinarily skilled artisan. PO Resp. 24. Yet that argument is undermined because that description appears in the "Background of the Invention," where the patent was plainly summarizing what was already known in the prior art. Ex. 1001, 1:23–3:21 (describing prior studies by Beutler, Grieb, and others). Moreover, although the alleged differences between "flat" and "by-weight" dosing has been a focus of Patent Owner's argument throughout this proceeding, the patent itself never highlights such distinctions, much less suggests any criticality to them.[23]

[23] Patent Owner does not identify any prosecution history that would support the alleged distinction between "flat" and "by-weight" dosing. We are aware of none. Indeed, the Examiner cited Bodor's alleged "flat" dose against the claims, which claims included similar "mg/kg" recitations. *See, e.g.*, Ex. 1004, 3, 221. And the applicant did not argue the alleged distinction Patent Owner raises now. *Id.* at 246–255.

Patent Owner argues that Bodor's dosing does not vary depending on the patient's weight. PO Resp. 20–21. We credit, however, Dr. Miller's testimony that, if Bodor's recited regimen using 10 mg cladribine tablets were given to patients of average weight, there would be material overlap with the induction period's total dose as claimed. *See, e.g.*, Ex. 1002 ¶¶ 83, 107; Ex. 1084 ¶¶ 9–10 (opining that it would have been obvious to administer Bodor's tablets to a patient of average weight (e.g., 70 kg), and in doing so, a POSA would have arrived at the claimed induction dose" and noting "Dr. Lublin did not disagree . . . that treating a MS patient of average weight would have been obvious")). *E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) ("The point of our overlapping range cases is that, in the absence of evidence indicating that there is something special or critical about the claimed range, an overlap suffices to show that the claimed range was disclosed in—and therefore obvious in light of—the prior art.").

Patent Owner argues that Dr. Miller arrives at the overlap in doses only through hindsight because Bodor does not expressly disclose patient weights. PO Resp. 21–23; Ex. 2051 ¶¶ 89–90 (agreeing with Dr. Miller's calculations but asserting it is hindsight to choose "one very particular-weight patient"). But reading Bodor's disclosure such that the regimen would not apply to at least average-weight patients is unsupported and illogical. *Fleming v. Cirrus Design Corp.*, 28 F.4th 1214, 1223 (Fed. Cir. 2022) ("Since *KSR*, we have explained that it is appropriate to consider the knowledge, creativity, and common sense of a skilled artisan in an obviousness determination."). The overlap also exists well beyond giving Bodor's regimen to a single patient weighing precisely 70 kg/154 pounds. Giving 140 mg to any patient weighing between about 50–80 kg (110–176

pounds) would result in an induction dosage within the bounds of claim 36's range.[24] And, as Petitioner points out, the art supports applying Bodor's dosing to average-weight patients. Pet. Reply 19 (citing Stelmasiak's cohort of patients weighing 52–75 kg (Ex. 1013, 5)); *see also* Ex. 1084 ¶¶ 64–65 (testifying it would have been obvious to treat patients of average weight and providing mg/kg calculations (n.3) for patients of various weights to further illustrate the overlap with the claims). Petitioner need not show that administering every dose to every hypothetical patient falls within the claim. *Hewlett-Packard Co. v. Mustek Sys.*, 340 F.3d 1314, 1326 (Fed. Cir. 2003) (explaining that prior art that "sometimes, but not always, embodies a claimed method nonetheless teaches that aspect of the invention").

Patent Owner argues that we should disregard Dr. Miller's opinions about the obviousness of the claimed induction period dosing because, outside of this IPR, he described MAVENCLAD's "weight-based" dosing as "rather unique." PO Resp. 21–22 (citing, e.g., 2007 (2019 video for National MS Society), 3:53–4:12; Ex. 2008 (transcript), 4:17–5:1). We credit Dr. Miller's responsive testimony, however, which explains that his comments were "made in the context of [FDA] *approved* MS drugs, not *all* drugs or dosing regimens being investigated in the prior art." Ex. 1084 ¶ 67. What may be "unique" in terms of FDA approval does not equate with being nonobvious over the relevant art. Considering the prior art and preexisting clinical studies generally, it is clear that administering "weight-based"

[24] Notably, the '947 patent also treats such bounds rather loosely. *See, e.g.*, Ex. 1001, 15 (Table 3 (target dose of "1.75 mg/kg"): suggesting, e.g., a patient receiving 14 tablets (each with 10 mg cladribine) and weighing between 85–89.9 kg would fit the criteria, which conversion produces a total dose range of about 1.56–1.65 mg/kg).

cladribine dosing is not unique. *See, e.g.*, Ex. 1018 (Rice), Abstr. (describing placebo-controlled clinical trials in MS patients receiving subcutaneous induction dose of 0.7 mg/kg (over 2 months) or 2.1 mg/kg (over 6 months)); Ex. 1002 ¶ 47 (discussing Rice's study).

Patent Owner argues that Stelmasiak does not remedy Bodor's deficiencies because it too allegedly teaches "flat" dosing, not "weight-based" dosing. PO Resp. 23. Also, Patent Owner contends, "Stelmasiak teaches away from" weight-based dosing. *Id.*; PO Sur-reply 10.

Bodor is not deficient for the reasons explained above. Pet. Reply 19 (noting Petitioner relies on Bodor's induction dosing, not Stelmasiak's). We also disagree that Stelmasiak teaches away from weight-based dosing.[25] Stelmasiak discloses that "there was no indication that a 'good response' is related to the actual cladribine dose per body weight." Ex. 1013, 6–7; Ex. 1084 ¶ 68 (testifying "a POSA would have understood that to simply mean that 'responders' in the study had different body weights"). This is not a teaching away. Stelmasiak sought to explain the variance in lymphocyte counts among its patients, and to identify "any factor" that might have differentiated between patients that were responders versus the non-responders. Ex. 1013, 6–7. Stelmasiak was "unable" to identify such a factor. But Stelmasiak nowhere teaches that expressing dosages in mg/kg and administering those dosages would result in an ineffective MS treatment. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (explaining the art's disclosure of alternatives is not a teaching away where the

[25] Because Patent Owner admits that Stelmasiak and Grieb have substantially the same disclosures (PO Resp. 24), the '947 patent's concession about what was known from Grieb undercuts Patent Owner's argument that Stelmasiak also discloses only "flat" dosing.

disclosure does not "criticize, discredit, or otherwise discourage the solution claimed"). To the contrary, at most, Stelmasiak suggests doing so would not have changed its results. Ex. 1084 ¶ 68 (testifying "Dr. Lublin provides no evidence that weight-based cladribine dosing was superior or not 'equivalent' to flat, fixed dosing").

Considering the totality of the record, we also find that it would have been obvious to follow Bodor's 2-month induction period and 10-month cladribine-free period with a retreatment or maintenance phase. Bodor teaches two "alternative" regimens—one noted immediately above, and another where the drug is administered for six months (giving a higher overall dose) with a longer 18-month drug free period. Ex. 1022, 23:15–24. We find persuasive Dr. Miller's testimony that Bodor's recitation of specific durations for the drug-free periods logically suggests a retreatment period. *See, e.g.*, Ex. 1002 ¶¶ 84–86 ("otherwise, the specified length of time of the cladribine-free period is meaningless"); *see also* Ex. 1084 ¶ 70 (noting Patent Owner's declarant "Dr. Lublin does not provide another explanation of why Bodor specifies the length of time of the cladribine-free period").[26] Indeed, Dr. Miller testifies, "[t]he most logical reading of Bodor would have included a re-treatment period, especially because such re-treatments were consistent with prior clinical studies where patients relapsed during or after

[26] At the hearing, when asked about why Bodor would specify the length of the cladribine-free period, Patent Owner's counsel stated that "it's a period in which the person should not be treated with cladribine" and is required for safety. Tr. 62:11–63:22. But this seems to reinforce Petitioner's point that, by specifying the number of months of the cladribine-free period, Bodor is suggesting one could safely retreat the patient as needed when that specified period elapsed—or at least the POSA would consider doing so.

cladribine therapy." Ex. 1084 ¶ 70 (citing Ex. 1013, Abstr.; Ex. 1031, 43); Pet. 36 (citing, e.g., Ex. 1002 ¶¶ 101–102; Ex. 1018, Abstr.).

We also find persuasive Petitioner's position and Dr. Miller's supporting testimony that it would have been logical and well within the POSA's skill to use Bodor's 2-month treatment period and cladribine dose as a "starting point" for optimization in a maintenance phase.[27] Pet. 40–42; Ex. 1002 ¶¶ 102–104; Ex. 1084 ¶ 88. Petitioner argues, it would have been routine and well within the ordinary capabilities of the POSA to "fine tune" the total dose and length of cladribine administration, including during a maintenance period. Pet. 42; Ex. 1002 ¶ 93. The prior art supports that POSAs regarded such variables as optimizable. Bodor teaches that:

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

Ex. 1022, 24:1–9; *see also* Ex. 1026, 5:20–25 (teaching that "one can tailor the dosage and duration" of cladribine administration "to the stage of the [MS] disease and the condition of the patient being treated").

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[27] For the same reasons discussed above, if the POSA repeated Bodor's dosage of 100–140 mg over two months in a maintenance phase for an average-weight patient (range of about 1.4–2.0 mg/kg), the dose and duration would overlap with the recitations in claim 36's step (iii) (total dose of about 1.7 mg/kg in a period lasting about 2–4 months).

Petitioner's position that it would have been obvious to use Bodor's induction dose/duration as a logical "starting point" in a maintenance phase is also more consistent with a concession made by Patent Owner during prosecution of the related '903 patent. There, it was argued that, if Bodor were understood to "imply" a retreatment (as the Examiner had found), "the teachings of the reference would suggest that the *same dosing regimen* be applied to the patient (10 mg of cladribine administered for 5-7 days each month for two consecutive months followed by another 10 month period of time in which the patient receives no treatment)." Ex. 1025, 100, 151 (arguing "[t]his would have resulted in the *same* total dose of cladribine being administered to the patient in *both* the induction phase and the maintenance phase") (emphasis added).

Petitioner also argues, and we agree, it would have been obvious to include a cladribine-free period after delivering treatment during a maintenance period. Pet. 54. As Dr. Miller explains, this is shown expressly in Stelmasiak, which followed the initial treatment and each retreatment period with cladribine-free periods. *Id.* (citing Ex. 1002 ¶¶ 94–95). Moreover, we credit Dr. Miller's testimony that a POSA would have incorporated cladribine-free periods to help control potential drug toxicity and side effects. *Id.* at 36–37 (citing Ex. 1002 ¶¶ 103–105 ("[A] POSA would have known that suppressing a patient's immune system would put them at increased risk of infection."); Ex. 1013, 5 (teaching "hematological toxicity of the drug (bone marrow suppression) raised some concern"); Ex. 1084 ¶ 87 (testifying "a POSA would have had the skill to monitor a patient's lymphocyte count and side effects associated with lymphocyte and myelosuppression and optimize the length of time of the second cladribine-

free period to mitigate side effects while maximizing lymphocyte suppression").

Patent Owner argues that Bodor and Stelmasiak do not disclose the maintenance period as claimed. PO Resp. 24–34 (citing, e.g., Ex. 2051 ¶¶ 98–122). Patent Owner contends that "safety concerns" stemming from prolonged immunosuppression would have suggested against retreating with cladribine. *Id.* at 25–27. Patent Owner contends that dosing of other FDA-approved MS disease-modifying agents (DMAs) were dosed continuously, not cyclically. *Id.* at 27–30 (arguing that Dr. Miller's citation to drugs like corticosteroids as evidence of cyclical retreatment is uninformative). And, Patent Owner contends, "most MS clinical trials studying cladribine" used only a single course of drug administration without any retreatment. *Id.* at 30–33. We address these arguments in turn below.

Because cladribine was known to be a strong immunosuppressive agent, there were some safety concerns with its use reflected in the art. *See, e.g.*, Ex. 1015, 1752 ("The primary toxicity caused by the drug is myelosuppression, which is a dose-limiting factor."); Ex. 1016, 430 ("[C]aution is recommended when the drug is administered before, after or with other drugs that may cause myelosuppression or immunosuppression.").

On the whole, however, the evidence shows that POSAs continued to use cladribine to treat MS patients in human clinical studies and considered cladribine to have an acceptable safety profile for such uses—especially balanced against the drug's promise. Stelmasiak reported no "clinically significant hematological side effects," and only "mild" side effects over its two-year study, even with an induction dose higher than Bodor's 2-month total dosing and giving multiple cladribine retreatments. Ex. 1013, 7.

Romine reported a mild infection in a few cladribine patients and one placebo patient but "[o]therwise, there were no side effects or adverse events." Ex. 1031, 35; *see also* Ex. 1018, 1153 (Rice reporting "no serious adverse events could be attributed to cladribine in this study."); Ex. 1047, Abstr. (Selby noting cladribine "was remarkably well tolerated"). Although Romine states that "[r]epeated treatment raises long-term toxicity issues . . . known to occur with *other* long-term immunosuppressive treatments," Romine, nevertheless, describes *retreating* twenty-four patients with cladribine. Ex. 1031, 43–44 (noting those patients were retreated for disease worsening, and reporting "no instances of marrow suppression or thrombocytopenia" but some increase (4% to 25%) in infection frequency versus the initial phase) (emphasis added); *see, e.g.*, Ex. 1084 ¶¶ 51–57 (reviewing cladribine's efficacy and safety profile as reported in the literature and testifying, "a POSA would have understood that cladribine continued to be administered to MS patients before 2004, despite the 'safety concerns' Dr. Lublin claims existed"). On balance, we disagree that a POSA would have considered a cladribine retreatment unacceptably unsafe following Bodor's 10-month cladribine-free period.

Patent Owner's argument about other FDA-approved MS drugs being dosed continuously without interruption fares no better in rebutting Petitioner's challenge. PO Resp. 27–30; Ex. 2051 ¶¶ 54–59, 102–103. The art's teachings are not limited to FDA-approved drugs. The prior art here *specific to cladribine* expressly teaches MS-treatment regimens that include cladribine-free periods and suggests retreating patients with cladribine as needed. Ex. 1022, 23:15–24; Ex. 1013, Abstr.; Ex. 1018, 1146; Ex. 1031, 43–44; Ex. 1002 ¶¶ 38–49; Ex. 1084 ¶¶ 69–70, 75. As persuasively argued by Petitioner, "[r]etreatment was recommended given cladribine's temporary

lymphocyte suppression and MS's chronic nature." Pet. Reply 21–22 (citing e.g., Ex. 1084 ¶¶ 71–73, 95–96). We credit Dr. Miller's literature-backed testimony that a POSA would have understood that, "[b]ecause lymphocytes rebound, the art recognized that the 'lengthy but impermanent duration of effect of cladribine means that retreatment will be necessary if cladribine is to become a practical long-term therapy for MS.'" Ex. 1084 ¶ 71 (quoting Ex. 1031, 43).

Patent Owner's argument that "most" clinical trials did not retreat with cladribine is equally unavailing. PO Resp. 30–33. The fact is, some studies did expressly retreat with cladribine—including at least Stelmasiak (retreatment at, e.g., months 9 and 15), Romine (retreatment if recurrence of disease worsening), and Rice (retreatment 12-months after last dose if evidence of disease progression). Ex. 1013, Abstr., 5; Ex. 1018, 1146; Ex. 1031, 43.

Patent Owner argues that the specific timing and dosing of Stelmasiak's retreatments are not the same as what is claimed. PO Resp. 33–34. That is true but inapposite because the challenge is obviousness based on the art's combined teachings. *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1050 (Fed. Cir. 2019) ("A finding of obviousness . . . cannot be overcome by attacking references individually where the rejection is based upon the teachings of a combination of references.") (internal quotation marks omitted). We find retreatment (and routine optimization thereof as necessary) at the end of Bodor's 10-month cladribine-free period would have resulted in the claimed maintenance period and dose. Patent Owner also dismisses the retreatments described in Rice and Romine because they were not "automatic" but depended on conditions like worsening of the

patient's disease or hematological criteria.[28] PO Resp. 31–32. But we fail to see how this undermines Petitioner's theory, which did not presuppose "automatic" retreatment either. *See, e.g.*, Ex. 1002 ¶¶ 100–101 (testifying that at least some patients would be expected to exhibit signs of disease relapse during or after Bodor's initial treatment, motivating retreatment for the relapsing patient after the 10-month cladribine-free period).

Patent Owner's arguments about a lack of "consensus" around *when* retreatment should occur and the possibility that drugs other than cladribine might be used in a retreatment phase are unpersuasive. PO Resp. 32–33. As discussed above, Stelmasiak teaches retreatment at about two and eight months after the 6-month induction dosing period ended; according to Dr. Miller, Bodor logically suggests a retreatment after a 10-month cladribine-free period lapses; and Rice and Romine teach a retreatment as needed by the patient and at twelve months after the initial treatment ended. Even if there was no "consensus" to give a maintenance dose after expiry of a cladribine-free period lasting about 8–10 months as claimed, where, as here, retreatment with cladribine following a drug-free period was well-known in the art, it is not inventive to discover optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Moreover, that some clinicians may have considered switching drugs in retreatment does not mean that a POSA would not have considered continuing treatment with cladribine. Ex. 1084 ¶ 73. Both scenarios could

[28] Rice, for example, teaches that the hematologic criteria were based on patient's complete blood count (CBC). Ex. 1018, 1146, 1154 (listing criteria including platelet, neutrophil, and hemoglobin counts above a threshold).

be true and, based on the record here, we find retreatments with cladribine were known and would have been considered.

For the above reasons, we are persuaded that claim 36's recited maintenance period and secondary cladribine-free period (in steps (iii) and (iv)) would have been obvious over the asserted art. We further address the parties' arguments about routine optimization of result-effective variables (e.g., cladribine dose and duration) in Section III.D.4.(c) below. *See, e.g.*, Pet. 40–43; PO Resp. 37–47 (addressing routine optimization in relation to argument about motivation and reasonable expectation of success).

c) Motivation to Combine and Reasonable Expectation of Success

According to Petitioner, a POSA would have been motivated to use Bodor's oral cladribine solid dosage form to treat MS. Pet. 33–34 (citing preference for oral drug delivery, increased bioavailability, and lowered interpatient variation with Bodor's oral dosage form as reasons to use Bodor's tablets to treat MS). *Id.* (citing, e.g., Ex. 1022, 2, 12, 23; Ex. 1002 ¶¶ 79, 97, 99). Further, Petitioner contends, a POSA would have expected at least some patients treated with Bodor's "two months on/ten months off" cycle to experience breakthrough disease or relapse that would require additional, maintenance treatment. *Id.* at 35 (citing Ex. 1002 ¶ 100 (testifying, with citation to supporting literature, that cladribine treatment is disease modifying but not permanent and that it was recognized that retreatment would be important)). As explained by Petitioner with Dr. Miller's supporting testimony, signs or symptoms of relapse may include, e.g., worsening neurologic function on physical examination of the patient or inflammatory demyelination (i.e., new lesion formation) on MRI scan. *Id.* (citing Ex. 1002 ¶ 100; Ex. 1016, 420; Ex. 1013, 6–7).

Because a POSA would have expected signs of relapse in at least some patients, Petitioner contends a POSA had reasons to retreat with cladribine, such as taught in Stelmasiak. *Id.* at 35–36 (citing Stelmasiak's reporting of a reduction in relapse rate, and improvements in patient EDSS scores). As discussed above, Petitioner contends that Bodor suggests retreatment too and that it would have been logical to use Bodor's induction dosing protocol in a retreatment phase. *Id.* at 42, 50; Ex. 1002 ¶¶ 86, 102. Petitioner contends a POSA, thus, would have had reasons to continue treating patients with cladribine after the induction and cladribine-free periods of Bodor. Pet. 36; Ex. 1002 ¶ 101. Indeed, Petitioner contends, retreatment, including with cladribine, was seen in various MS therapies described in the art. *Id.* (citing Ex. 1026, 11:5–7, Ex. 1022, 23; Ex. 1013, Abstr.; Ex. 1018, Abstr.; Ex. 1002 ¶¶ 101–102). Petitioner also contends a POSA had reasons to consider using lower maintenance-period doses or the same induction-period dose in the maintenance phase. *Id.* at 37–39; *id.* at 37 n.9; Ex. 1002 ¶¶ 89, 118.

Petitioner argues the claimed dose of cladribine reached at the end of the induction and maintenance periods would have been prima facie obvious over the prior art's teachings. Pet. 39–43. Petitioner cites an overlapping range with Bodor's 1.4 mg/kg to 2.0 mg/kg induction dosing compared to the range of "about 1.7 mg/kg to about 3.5 mg/kg" as claimed. *Id.* at 39 (citing Ex. 1002 ¶ 107). Petitioner contends that duration of treatment and dosage amount were known variables subject to routine optimization. *Id.* at 40–41 (citing Ex. 1002 ¶¶ 91–92, 99, 109–110; Ex. 1022, 2, 11–12, 23); *see also id.* (citing Bodor's definition (Ex. 1022, 22) for "therapeutically effective amount"). Petitioner cites the art's teaching that "one of skill will appreciate that the therapeutically effective amount of cladribine

administered . . . may be *lowered or increased* by fine tuning" and that "one can *tailor the dosage and duration* for which [cladribine] is administered to the stage of the disease and the condition of the patient being treated." *Id.* (quoting Ex. 1022, 24:1–3; Ex. 1026, 5:22–25) (emphasis added by Petitioner). Thus, Petitioner argues, cladribine's dose and length of administration are result-effective variables that can be modified to achieve a recognizable result (e.g., change in a patient's lymphocyte count). *Id.* at 41 ("Rice uses two different cladribine doses, 0.7 mg/kg and 2.1 mg/kg, with the higher dose having a higher suppression of lymphocyte counts.") (citing Ex. 1018, Fig. 4).

Accordingly, Petitioner argues, it would have been routine and within the POSA's capabilities to "fine tune" the total dose and length of cladribine administration. *Id.* at 42; Ex. 1002 ¶ 93. Dr. Miller opines that "it would have been logical for a POSA to have used Bodor's 2-month treatment period as a starting point, knowing that it could be routinely optimized." Ex. 1002 ¶ 102. Petitioner cites Bodor's teaching that "[t]herapeutically effective amounts may be easily determined, for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect." Ex. 1022, 24:6–9; Pet. 42. And, Petitioner contends, a POSA would have arrived at suitable doses and durations of cladribine administration by routinely measuring the patients' lymphocyte counts and monitoring for therapeutic efficacy. Pet. 42 (arguing "[t]his was standard practice in the field, as demonstrated by at least Stelmasiak, Rice, and Beutler") (citing Ex. 1013, 5, Ex. 1014, 1717; Ex. 1018, 1146; Ex. 1002 ¶¶ 16, 34, 102, 104)); *see also id.* at 42–43 (arguing no evidence of "criticality" to the dosage/duration for the maintenance period of claim 36).

Petitioner contends a POSA would have followed a retreatment period with another cladribine-free period. Pet. 36. According to Petitioner, a POSA would have been motivated to do so to manage possible adverse effects (e.g., hematological toxicity). *Id.*; Ex. 1013, 5; Ex. 1002 ¶¶ 103–105 (testifying the drug-free periods would have been seen as a desirable aspect of the regimen to mitigate toxicity and infections arising from the immuno-suppressive effects of cladribine).

Lastly, Petitioner contends a POSA would have had a reasonable expectation of success in arriving at the subject matter of claim 36. Pet. 43–45 (citing Ex. 1002 ¶¶ 111–119). Petitioner contends the POSA would have "followed the instructions in Bodor to orally administer the dosage forms following the dosage regimen" disclosed as suitable for treatment of MS. *Id.* at 44. Petitioner contends a POSA would have predictably included a maintenance and secondary cladribine-free period "because it was standard practice in the field to retreat MS patients over the course of the disease," and optimized the duration and dosing of such maintenance period as appropriate. *Id.* (citing Ex. 1013, Abstr.; Ex. 1002 ¶ 114). And, Petitioner contends, a POSA would have reasonably expected that the claimed cladribine regimen would be effective because it was known that cladribine can cause a "prolonged, profound suppression of lymphocyte counts," and "researchers published several clinical studies reporting on the efficacy of cladribine in MS patients." *Id.* at 44–45 (citing Ex. 1016, 420–421; Ex. 1013, 4, 7; Ex. 1022, 1–2, 23; Ex. 1014, 1719–20; Ex. 1023, Abstr.; Ex. 1002 ¶¶ 35–49, 115–116).

We find the POSA would have had sufficient motivation for modifying and optimizing Bodor's teachings to arrive at the subject matter of claim 36, and have had a reasonable expectation of success in doing so.

We explain our findings below and then turn to Patent Owner's arguments to explain why they are unavailing.

We find that Petitioner has proved by a preponderance of the evidence that a POSA would be motivated to use Bodor's solid oral 10 mg tablets and the recited 2-months on/10-months off regimen for treating MS patients. This requires little more than the POSA following Bodor's express guidance, and Bodor states that its dosage formulation has advantages (e.g., patient compliance with oral delivery; lower interpatient variability). Ex. 1022, 2, 12, 23; *see also* Ex. 1080 ¶ 16 (testimony of Dr. Pinal about the general preference for oral tablets and remarking on other attributes of Bodor's tablets making them desirable to use in an MS treatment regimen). Using Bodor's tablets and following the above-noted regimen would result in overlap with claim 36's induction period in step (i), as well as overlap with the claim's cladribine-free period recited in step (ii) as discussed above.

We find persuasive Dr. Miller's testimony that a POSA would have been motivated to retreat with cladribine at least those patients who showed signs of relapse—and done so after Bodor's 10-month cladribine-free period expires. Ex. 1002 ¶¶ 100–102 (citing, e.g., Ex. 1016, 420; Ex. 1013, 6–7; Ex. 1037, 908). We also agree that it would have been logical to use Bodor's initial treatment dose/duration as a starting point for optimization in a retreatment (maintenance) phase. *Id.* The prior art supports our finding that a POSA would have understood that cladribine dose and duration were known optimizable variables. *See, e.g.*, Ex. 1022, 24:1–9; Ex. 1026, 5:20–22; Ex. 1002 ¶¶ 18, 117–118 (testifying patient-specific dose optimization is a common practice in the clinic). Moreover, the known correlation between cladribine dose/duration (variables) and level of lymphocyte suppression (a result) supports our determination that the variables are "result-effective."

See, e.g., Ex. 1002 ¶¶ 91–92 (testifying "[i]t was also general knowledge in the art that a direct correlation exists between the dose and length of administration of cladribine and level of lymphocyte suppression"), 117–118; Ex. 1018 (Rice), 1152, Fig. 4 (describing "dose-dependent decreases" in lymphocyte levels at 0.7 mg/kg and 2.1 mg/kg); *see also id.* at 1151 (reporting a "small, dose-dependent, median percent decrease in T2 lesion volume"); Ex. 1047 (Selby), 297 (describing less rapid decrease and faster rebound in lymphocyte levels with cladribine at lower versus higher doses (2.1 mg/kg and 2.8 mg/kg)). Thus, we find that a POSA would have optimized Bodor's cladribine dose/duration in a maintenance phase as appropriate for the relapsing patient, and also included a secondary cladribine-free period (for safety and to mitigate toxicity) and, in doing so, would have predictably arrived at claim 36's steps (iii) and (iv).

We also find that a POSA would have reasonably expected success in arriving at the claimed subject matter. In addressing this issue, we conclude that "the claims are not limited to any efficacy degree or metric." Pet. Reply 10 (citing Ex. 1061 (Lublin Tr.), 136:3–8 (Q: "Do the claims . . . require any particular degree of efficacy in its methods of treating multiple sclerosis?" A. "No, not that I see")).[29] *C.f. Janssen Pharm., Inc. v. Teva Pharm. USA, Inc.*, 97 F.4th 915, 928–929 (Fed. Cir. 2024) (holding that, "[w]hatever role safety and efficacy data may play in assessing the strength of a motivation or lack of motivation to combine, . . . [the absence of safety and efficacy data in

[29] The patent also indicates that the "beneficial effect" of the invention, including any attenuation, decrease, reduction, or diminishing of pathological development of disease may be seen at *any stage* of the treatment course (e.g., after the induction treatment, during a cladribine-free period, etc.). Ex. 1001, 5:19–24.

certain art] cannot justify simply discarding that prior art particularly where, as here, the claims do not have any safety and efficacy requirement.”).

But even if the claims did require a specific treatment “efficacy,” the patent’s definition of the term is broad. It indicates that efficacy can be measured by, for example, “frequency of relapses” or “presence or absence of new lesions” as detected by MRI. Ex. 1001, 5:52–6:9 (describing reduction in MRI T_1 lesions as a “primary efficacy variable” and “secondary efficacy variables” as including, for example, lesion volume, frequency of exacerbations, and EDSS or SNRS scores); *see also id.* at 16:10–52 (example, using MRI-detected lesions as the efficacy metric; remarking that the treatment is “efficient in decreasing brain lesions and no severe adverse effect is observed”).

With that context about what the claims require (or rather, don’t) as to specific therapeutic efficacy, we consider the preexisting technical literature about cladribine’s positive effects when treating MS patients, which Petitioner has identified. *See, e.g.*, Pet. 19–21 (summarizing studies by Beutler, Stelmasiak, Romine, and Rice, which we highlight below in order of their publication (from roughly 1996 through 2000)).

> <u>Beutler</u>: in a 2-year, placebo-controlled, double-blind, crossover study, noted improvement in EDSS and SNRS scores in patients receiving cladribine, and “highly statistically significant changes” in brain lesions. Ex. 1014, 1717–1719 (“Our studies clearly show that cladribine retards the progression of neurologic impairment of patients with chronic progressive MS” and “[i]n our studies we observed marked improvement in the appearance and disappearance of lesions” in patients receiving both the high and low doses (2.8 mg/kg and 1.4 mg/kg).); *see also id.* at 1716 (“Analysis of the results revealed a favorable influence on neurological performance scores . . . and on MRI findings on patients treated with cladribine.”).

Stelmasiak: in a 2-year pilot study of cladribine's use in RRMS patients, reported "EDSS scores were significantly reduced [(a positive outcome)] during the treatment compared to the initial values" and the "number of relapses . . . was markedly reduced (almost five times on average)" in seven of the ten patients. Ex. 1013, 4, 6–7 ("The relapse rate in some (but not all) patients is impressively decreased" while side effects are "mild").

Romine: in an 18-month, placebo-controlled, double-blind study on patients with RRMS, reported "significant favorable effect of cladribine on the joint frequency and severity of relapses" and "MRI-enhancing lesions were completely suppressed in the cladribine patients." Ex. 1031, 35 (subcutaneous injection of total 2.1 mg/kg over six months). Romine, thus, "conclude[d] that cladribine shows promise as a treatment for relapsing-remitting multiple sclerosis." *Id.* (noting, with the exception of "mild" infection in a few patients, "there were no side effects or adverse events").

Rice: in a multi-year, placebo-controlled clinical trial[30] of progressive MS patients, concluded that, although "[n]o significant treatment effects were found for cladribine in terms of changes in EDSS or SNRS scores[,] [b]oth doses [(0.7 mg/kg and 2.1 mg/kg)] of cladribine produced and sustained significant reductions in the presence, number, and volume of gadolinium-enhanced T1 brain lesions on MRI." Ex. 1018, 1145 (describing the drug as "generally safe and well tolerated"), 1153 ("MRI findings . . . were more compelling" (compared to the results for clinical efficacy as measured by EDSS/SNRS scores), noting "T1 lesions represent areas of breakdown of the blood-brain barrier and are generally believed to be sites of new inflammation that probably precede symptoms and other MRI signs in MS," and those "lesions were virtually eliminated by treatment with cladribine").

[30] Rice included a 12-month double-blind phase, which was followed by a long-term extension phase for some patients. Ex. 1018, 1146.

These preexisting studies reasonably demonstrate cladribine's safety and efficacy—at least comparable to what is reported in the '947 patent and encompassed by the patent's definition of "efficacy." The expectation of success need be only reasonable, not absolute. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, the test for obviousness does not require "actual success" in the prior art. *See Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1379 (Fed. Cir. 2019) (Stoll, J., dissenting) (citing *PAR Pharm. Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014)). But here, the art does report actually significant and positive results in the treatment of MS as discussed above, including fewer lesions and a reduction in relapses. *See* Pet. 44–45 (citing studies); Pet. Reply 13–14 (citing studies); Ex. 1084 ¶ 89 (testifying a POSA would have reasonably expected Bodor's oral cladribine tablets and regimen of administering them "to effectively suppress lymphocytes and treat MS by reducing relapse rates and/or brain lesions as detected by MRI"). Bodor fully incorporates-by-reference many preexisting MS cladribine studies, including those from Romine and Rice (summarized above) immediately before disclosing its 2-months on, 10-months off regimen. Ex. 1022, 22:27–23:6. Even if Bodor did not itself report clinical results of that regimen, we find a POSA would have reasonably expected success in treating MS patients with it (optimized to include a suitable maintenance dose and secondary cladribine-free period, as discussed above).

Patent Owner argues that Petitioner fails to establish a motivation for changing Bodor's "flat" cladribine-dosing method to a "weight-based" method. PO Resp. 35–36 (arguing no overlap between Bodor's "flat" dosing and the claims), 48–49 (citing Ex. 2051 ¶¶ 85–97, 132, 164–166). Patent Owner presumes that the claims exclude giving allegedly "flat" dosing of

between 100–140 mg to a range of patients (including those of average weight, e.g., 70 kg) that would otherwise result in mg/kg dose expression that overlaps with the claims. We reject this argument for reasons already explained above. *See supra* Section III.D.4.(b). Bodor's method need not be *changed* in the manner urged by Patent Owner.

Patent Owner argues that a POSA would not have been motivated to retreat MS patients after Bodor's 10-month cladribine-free period, or done so with a reasonable expectation of success. PO Resp. 53–55. According to Patent Owner, there was no general, cyclical immunosuppression framework and FDA-approved MS drugs were dosed continuously. *Id.* at 53–54. Patent Owner contends Petitioner is citing Stelmasiak's cyclical regimen in hindsight because, even with its retreatments, EDSS scores eventually returned to baseline. *Id.* at 54–55. And, PO argues, if retreatment was needed, a POSA could have looked at other available MS drugs. *Id.* at 55.

We reject this argument for reasons already explained above, including our crediting of Dr. Miller's testimony that it would be logical to retreat relapsing patients following Bodor's 10-month cladribine-free period, and in view of multiple studies that did retreat with cladribine (e.g., Rice, Romine, and Stelmasiak). Patent Owner contends that, as to Rice and Romine, the art did not teach repeated treatment absent a pharmacological rationale and patient need. *Id.* at 54 (citing Ex. 2051 ¶¶ 180–181). This does not undermine Petitioner's showing because, as already explained, Dr. Miller testifies that retreatment would have been considered appropriate for patients showing signs of continued need (e.g., disease worsening, relapses during or after the cladribine-free period). Ex. 1002 ¶¶ 51, 52, 91, 99–102. Petitioner's theory also does not suggest that retreatment would have occurred without concomitant considerations of safety (e.g.,

lymphocyte counts). Ex. 1084 ¶¶ 11, 69–72 (noting, e.g., mean lymphocyte counts in Rice had rebounded to a level above 1.0 x 10^9/L by the tenth month following the last cladribine dose). Regarding Stelmasiak, it at least *maintained* EDSS scores during its full two-year study—a positive result showing the disease did not worsen. *Id.* ¶¶ 52 ("EDSS scores at 24 months were the same as they were at baseline indicates a lack of overall disability worsening."), 94–95; Ex. 1061 (Lublin Tr.), 57:3–4 (admitting "[t]here also could be decreased worsening of the EDSS," and "if your agent slows that worsening, then that's a therapeutic effect").

Patent Owner argues that a POSA would not have been motivated to combine Bodor and Stelmasiak to arrive at the claimed induction or maintenance doses. PO Resp. 49–53, 55–57. According to Patent Owner, the bioavailability of Stelmasiak's oral cladribine/saline solution is higher than Bodor's tablets, so a POSA would not have been motivated to "start" with Bodor over Stelmasiak. *Id.* at 50–53 (arguing "Bodor lacks efficacy data for its dosing regimen"). Patent Owner also contends a POSA would have expected Bodor's lower induction dose (total dose (140 mg) with less bioavailability) would have been less effective than Stelmasiak's induction dose (300 mg) and unable to suppress lymphocytes to the same degree as Stelmasiak. *Id.*; *see also id.* at 55–57 (arguing that Stelmasiak's lower maintenance doses are given earlier (after a 2- or 5-month drug-free period), following Stelmasiak's higher induction dose compared to Bodor, and thus provide no reason to lower a maintenance dose in Bodor or wait ten months to give it).

We disagree with Patent Owner's argument. Even assuming Stelmasiak's formulation has a higher bioavailability (allegedly 50% versus about 39% in Bodor), there are other reasons for the POSA to have selected

Bodor's regimen. Ex. 2009, 61:13–18 (Miller agreeing the reported bioavailability for Bodor's 10 mg tablets is 39.1–39.4%). Bodor describes other desirable features with its tablets, including lower interpatient variability and patient convenience. Pet. 33–34; Ex. 1022, 2, 11–12. The premise of Patent Owner's argument—that the POSA needs to have chosen to start with Bodor over Stelmasiak—is also flawed. The law "does not require that a particular combination must be the preferred, or the most desirable." *Novartis Pharma. Corp. v. West-Ward Pharma Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019); *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021) ("[It is] not necessary to show that a combination is the best option, only that it be a suitable option.") (internal quotation marks omitted). Bodor's induction dosing and duration need not be modified by Stelmasiak to arrive at the induction period as claimed. And adding a maintenance phase to Bodor is a logical extension of its disclosures, which would have been further obvious in view of cladribine retreatments already known in the art and routine optimization. Pet. Reply 22 (noting Petitioner cited Stelmasiak for suggesting a cyclical regimen, but "did not argue modifying Bodor's method to incorporate *Stelmasiak's* cladribine-free period and lower-dose maintenance periods").

Insofar as it concerns an expectation of efficacy with Bodor's regimen and Petitioner's reliance on Stelmasiak, we agree with Petitioner, "there is no fixed lymphocyte-reduction 'bright-line threshold'" that guarantees efficacy. Pet. Reply 22 (citing, e.g., Ex. 1084 ¶ 14 (testifying "lymphocytes do not need to be suppressed to below 1000 cells/µL to achieve a therapeutic effect—1000 cells/µL is merely exemplary")). Stelmasiak, for example, discloses that a "significant" improvement (i.e., reduction) in EDSS scores was seen within three months of the start of treatment when lymphocyte

counts were well above 1000/µL. Ex. 1013, 6; PO Resp. 52 (annotation to Stelmasiak's Figure 1 where, at three months, lymphocyte count was ~ 1350 cells/µL, and only about "150 mg" of cladribine was given at that stage).[31] Moreover, the reasonable expectation of success is shown by the record as a whole (see discussion of Rice, Romine, Beutler, and Stelmasiak above); *see, e.g.*, Pet. Reply 26 ("Rice reported that cladribine doses similar to Bodor's suppressed lymphocytes to ≤ about 1000 cells/µL" and "reported lowered brain lesions and volumes")); Ex. 1084 ¶¶ 16, 92–93; Ex. 1080 ¶¶ 78–83.

Patent Owner also argues that Petitioner's routine optimization arguments should fail for an additional six reasons. We address below.

Patent Owner argues that Petitioner provides no reason to optimize a cladribine dose/duration based on a patient's lymphocyte count, which is not an "efficacy" measure. PO Resp. 37–41; Ex. 2009, 121:8–18 (Dr. Miller testifying "lymphocyte suppression is a measure of cladribine's treatment response," but "is not a measure of efficacy"); Ex. 2079, 42:5–14 (same). According to Patent Owner, "the art consistently shows that lymphocyte count is a metric of safety, not therapeutic efficacy for cladribine treatment." PO Resp. 40–41 (citing, e.g., Ex. 2051 ¶ 142; Ex. 1013, 5; Ex. 1014, 1717; Ex. 1018, 1146); PO Sur-reply 12–13.

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[31] Stelmasiak's graph also reflects "average" lymphocyte counts across a group of patients, and Stelmasiak reports a mean reduction with a standard deviation that would suggest some patients were above 1000/µL and some below. Ex. 1013, 5 ("968±229"). Stelmasiak does not indicate that patients could be sorted into responders and non-responders based on whether lymphocyte counts were above or below 1000/µL. *Id.* at 7 ("We were unable to identify any factor that would differentiate between the 'responders' and the 'non-responders.'").

We are unpersuaded that this undermines Petitioner's challenge. As argued by Petitioner, "Merck wrongly posits routine-optimization must correlate with ***therapeutic efficacy***, but the doctrine applies to ***any*** property known to be affected by the optimized variable." Pet. Reply 2, 26–27; *E.I. DuPont De Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1009 (Fed. Cir. 2018) ("[A] recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective."). The evidence here shows a known correlation between, for example, cladribine dose and lymphocyte levels.[32] *See, e.g.*, Ex. 1018, 1152 (analysis showing cladribine treatment associated with "dose-dependent decreases" in lymphocytes); Ex. 1084 ¶¶ 12, 81, 82; Ex. 1061, 72:5–22 (Dr. Lublin admitting MS studies used lymphocyte counts to measure cladribine's pharmacological effect and that the count can vary in a dose-dependent manner). Thus, even if lymphocyte count was understood to be primarily a safety metric in prior studies, as argued by Patent Owner (*see, e.g.*, PO Resp. 39–40), it can be applied in a result-effective variable analysis. Pet. 40–43; Pet. Reply 26–27.

Patent Owner argues there is "no guidance" on threshold lymphocyte counts that would have been sufficient to show efficacy. PO Resp. 41–42 ("Stelmasiak's data shows that a reduction in lymphocyte counts does not

[32] At least Beutler also points to a dose-dependent relation to both efficacy and toxicity. Ex. 1014, 1716 ("Toxicity and therapeutic response were dose-related"), 1717–1720 (describing the higher dose's stabilization of disease as "quite durable" while the lower dose "provide[s] a larger margin of safety" but "appeared to be less durable than that observed at higher doses," and noting a "dosage-response relationship"); *see also id.* at 1717 (describing "peak improvement at [about] 8 mo after treatment initiation" in the lower dose regimen); Ex. 1018 (Rice), 1151 (noting "small dose-dependent, median percent decrease in T2 lesion volume").

correlate with cladribine efficacy."). Citing Stelmasiak, Patent Owner contends that a POSA would have believed that Bodor's dosage would be insufficient to reduce lymphocytes below 1000 cells/µL or produce any efficacy. *Id.* (citing Ex. 2051 ¶¶ 149–150); PO Sur-reply 14.

Patent Owner's argument does not undercut the asserted routine optimization on this record. What is routine in prior MS clinical studies with cladribine is that lymphocyte counts were tracked over time while therapeutic efficacy (e.g., relapse rate, brain lesions, EDSS scores, etc.) is monitored concurrently. *See, e.g.*, Ex. 1013; Ex. 1016; Ex. 1018; Ex. 1031; Pet. 42 (arguing this approach was "standard practice in the field"). Rice, for example, reported effects on lymphocyte levels at similar doses to Bodor's, and reported that "lesions were virtually eliminated by treatment with cladribine." Ex. 1018, 1153; Ex. 1080 ¶¶ 81–82 (showing relation between Bodor and Rice dosing); Ex. 1002 ¶¶ 47, 91; Ex. 1084 ¶ 16 ("A POSA would have thus expected to achieve a[t] least similar results with Bodor's cumulative dose."). Patent Owner cites a paper by Dr. Miller where he allegedly "disparaged" Rice's lack of treatment promise, and noted "an enigmatic dissociation between positive effects on MRI and unconvincing clinical benefit." PO Resp. 40 (citing Ex. 2004, 341, 350; Ex. 2009, 21:13–23:1). It is true that Rice did not observe a "clinical" benefit (i.e., improved EDSS scores) in its study with the more difficult-to-treat progressive MS patients, but Rice undisputedly did observe decreased lesions across all doses. Ex. 1061, 61:7–10 ("Progressive MS is more difficult to treat . . . [t]han relapsing-remitting MS"). Claim 36 encompasses treating any form of MS (including RRMS) and, even if efficacy is required, fewer lesions would suffice. Ex. 1001, 5:54–59. Dr. Miller testifies persuasively that

reduced lesions would have been reasonably expected with Bodor's regimen. Ex. 1084 ¶ 16.

Patent Owner contends that, even if lymphocyte count were a measure of efficacy, Petitioner's theory about adjusting the "daily dose" of cladribine is flawed because lymphocytes were not measured "daily" and "daily lymphocyte count" would not provide meaningful information. PO Resp. 43–44 (citing, e.g., Ex. 1014, 1717 (describing evaluation of lymphocyte count on a "monthly" basis)).

This argument is unpersuasive. Patent Owner misconstrues Petitioner's position, which was simply using "daily dose" in the same way it is used in the '947 patent. Ex. 1001, 4:18–21 (disclosing that the total dose is determined by adding the daily doses), 20:17–22. In other words, Petitioner is referring to the dose that's administered daily, not changing the dose on a daily basis or measuring lymphocytes each day. Pet. 42 (explaining that modifying the daily dose would allow for fine-tuning the "total dose" and length of administration); Ex. 1002 ¶ 93. So, for example, Bodor's dose (10 mg tablets given 5–7 days each month) could be increased or decreased, producing an overall higher or lower total dose in the induction or maintenance periods and lymphocytes could be monitored at a periodicity routine in the art (e.g., monthly).

Patent Owner argues that Petitioner identifies no recognizable result associated with cladribine's "therapeutic effect." PO Resp. 44 (arguing lymphocyte suppression is not an "efficacy" measure). According to Patent Owner, Rice would not have led a POSA to expect success through optimization based on lymphocyte counts or MRI results. *Id.*; PO Sur-reply 2, 5 (suggesting that "coherence" across multiple outcome measures, not just MRI lesion results, is needed to confirm treatment efficacy), 14–15 (arguing

no reasonable expectation of success via optimization and that MRI outcomes do not necessarily demonstrate a treatment effect).

As we determined above, however, even if lymphocyte count is a measure of patients' level of immunosuppression and primarily a safety consideration, it can still be the "result" in a result-effective variable analysis, given that it was recognized that cladribine dose and duration are correlated with lymphocyte count. Also, inasmuch as Rice's MS treatment regimen includes a similar induction period dose and duration[33] compared to Bodor's, we agree with Dr. Miller that a POSA would have reasonably expected Bodor's regimen to reduce brain lesions—as expressly reported by Rice. Ex. 1084 ¶ 16; Ex. 1002 ¶¶ 47–49, 91.

The notion that the POSA would not have wanted to decrease lesions in the MS patient's brain or considered the same an "efficacy" measure is refuted by the patent itself and inconsistent with other evidence of record. Ex. 1001, 2:56–58 (describing Rice's results as "positive on the significant reduction on MRI-measured brain lesions"), 3:22–26 (describing, as "background" and after noting prior studies by Rice and others, that "it would be desirable to have a method for treating [MS] comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity [of] adverse events"); Ex. 1061, 61:11–62:5 (testifying MRI results (reduction in number

[33] Rice's low-dose arm includes two courses of cladribine (0.07 mg/kg/day for five consecutive days each month (i.e., over 2-months), for a total dose of 0.7 mg/kg, which was followed by a cladribine-free period. Ex. 1018, 1146. As Dr. Pinal explains, Bodor's 1.4–2.0 mg/kg dosing, when corrected for bioavailability of Bodor's tablets (40%) is 0.6–0.8 mg/kg and, thus, is very similar to Rice's subcutaneous dose of 0.7 mg/kg. Ex. 1080 ¶¶ 81–82.

of new lesions over time) provides "proof-of-principle" for MS treatments); *see also* Ex. 1018, 1145 ("In patients with RRMS and SPMS, there is a correlation between the frequency and extent of lesion enhancement and short-term disease activity."); Ex. 1014, 1720 ("The usefulness of MRI as a measure of clinical activity and potentially as an objective means for assessing response to therapy has recently been documented.").

Patent Owner contends that Petitioner's reliance on Rice for the points noted above is new and untimely. PO Sur-reply 18–21. We disagree. The Petition relied on Rice (along with Romine, Beutler, etc.) throughout as informing the POSA's background knowledge, even if it was not expressly asserted in combination with Bodor. *See, e.g.*, Pet. 2, 7, 15–17, 20–21, 26, 36, 41–42. We also find that Petitioner's reliance on Rice in the Reply is fairly responsive to arguments raised by Patent Owner during trial, including that Dr. Miller allegedly disparaged Rice's MRI and other results and that Rice does not connect lymphocyte counts to efficacy or support a reasonable expectation of success. *See, e.g.*, PO Resp. 40–41, 44.[34]

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[34] Patent Owner also contends Petitioner has pivoted away from the significance of lymphocytes as a purported sign of "efficacy" and that, at institution, the Board understood lymphocyte count was *the* measure of "efficacy." *See, e.g.*, PO Sur-reply 12 (characterizing as a "revised theory"). This argument overstates the Board's preliminary decision. There we explained, for example, that it did not appear a bright-line lymphocyte level was necessary for a therapeutic effect (e.g., EDSS score reduction) to be seen. *See, e.g.*, Inst. Dec. 47–48 (citing, e.g., MRI and EDSS scores as distinct from lymphocyte counts), 49 (noting reports of "efficacy" in the literature, including Stelmasiak, Rice, and Romine, and citing lesion reduction and the patent's broad definition of "efficacy" (n.22)). We recognize, however, that some of the language used in our earlier decision (and the Petition as well (e.g., Pet. 42 (suggesting measuring efficacy "based on" changes in lymphocyte counts)) could have been more precise.

Patent Owner contends that MS is complex and involves slowly evolving disability, so it would require years to evaluate changes to a dosing regimen and corresponding "treatment benefits" and "clinical outcomes." PO Resp. 44–45. According to Patent Owner, even Dr. Miller admitted that clinical trials in even a few patients can take months to years to complete. *Id.* (citing Ex. 2009, 114:17–116:16). Thus, Patent Owner argues, routine optimization is precluded. *Id.*

The issue, however, is not whether any optimization of Bodor's dosing regimen could be completed rapidly, but whether it would have been done routinely through normal experimentation expected by skilled artisans in the field. The prior art evidences that POSAs would consider changes to dosing amount and duration as routine in this very field. *See, e.g.*, Ex. 1026, 5:20–25 (disclosing that "one can tailor the dosage and duration" of cladribine as needed for the patient being treated and MS stage); Ex. 1022, 24:1–9 (describing "fine tuning" of cladribine amounts and that "[t]herapeutically effective amounts may be easily determined," by starting lower and increasing in stepwise increments while evaluating beneficial effects). Moreover, as Petitioner explains, cladribine-dosing adjustments do not require years of clinical assessment. Pet. Reply 28; Ex. 1084 ¶ 84 (testifying "relapse rates and lesions can be assessed in as little as 6 to 12 months"). MRIs can show a treatment response within six months, changes in lymphocyte levels can be seen within a few months, and relapse rates are measured over a one-year period. *See, e.g.*, Ex. 1031, 40, Fig. 6; Ex. 1013, Fig. 1; Ex. 1061, 38:6–12 (Dr. Lublin admitting that relapse rates are measured by counting the number of relapses and dividing by time ("[t]ypically one year")).

Lastly, Patent Owner contends that there were "numerous possible combinations" for potential optimization. PO Resp. 45–48 (arguing Petitioner's position is tantamount to throwing metaphorical darts at a dartboard). But Patent Owner's contention elides the guidance already provided in the art, including Bodor's MS treatment regimen using 10 mg cladribine tablets in a 2-months on/10-months off sequence, the logic of using Bodor's induction dose/duration as a starting point for optimization in a maintenance phase, the undisputed inclusion of cladribine-free periods after dosing periods for safety reasons (as routinely seen in the art), and the positive results described in preexisting human clinical studies (decreased lesions, reduced relapses rates, improved clinical (e.g., EDSS) scores). Ex. 1002 ¶¶ 33–52; Ex. 1084 ¶¶ 51–52, 106, 122.

For all the reasons noted above, we find that Petitioner has proved by a preponderance of the evidence that a POSA would have been motivated to combine the teachings of Bodor and Stelmasiak to arrive at the subject matter of claim 36 and done so with a reasonable expectation of success.

d) Objective Indicia of Nonobviousness

Patent Owner argues that evidence of alleged skepticism, unexpected results, and a long-felt but unmet need are objective indicia that supports a determination that the claims are nonobvious. PO Resp. 58–65.

Objective indicia of nonobviousness are "only relevant to the obviousness inquiry 'if there is a nexus between the claimed invention and the [objective indicia].'" *In re Affinity Labs of Tex., LLC*, 856 F.3d 883, 901 (Fed. Cir. 2017) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006)). "The patentee bears the burden of showing that a nexus exists." *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999).

Patent Owner does not assert that it is entitled to a presumption of nexus. Instead, Patent Owner argues that its evidence of alleged skepticism, etc., "bear[s] a direct nexus to the claimed invention" because "the evidence is the 'direct result of the unique characteristics of the claimed invention.'" PO Resp. 63–64 (quoting *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373–74 (Fed. Cir. 2019) (explaining that, even if a presumption of nexus is inappropriate, the patentee may still prove nexus by showing that the evidence of secondary considerations is the direct result of the unique characteristics of the claimed invention). Patent Owner contends that it has shown a nexus between its evidence and at least claims 36 and 39—claims that Patent Owner contends encompass the FDA-approved method for administering MAVENCLAD and the method of cladribine administration studied in the CLARITY trial. *Id.* at 64–65 (citing, e.g., Ex. 2033 (CLARITY), 425–426; Ex. 2035 (CLARITY Extension), 1594, 1599, 1603).

We discuss nexus issues below as necessary when addressing the parties' arguments about the alleged skepticism, unexpected results, and long-felt, unmet need.

Patent Owner contends that, after reviewing the CLARITY study, the FDA "raised concerns over higher cancer risks associated with Mavenclad®." PO Resp. 59–60 (citing Ex. 2038, 1);[35] PO Sur-reply 23–24 (citing, e.g., Ex. 2079, 136:8–13 (agreeing regulators raised safety concerns about malignancies)). From this, Patent Owner contends "FDA's skepticism provides further evidence that the claimed dosing regimen was nonobvious." PO Resp. 59–60.

[35] Patent Owner also cites Exhibit 2039 in support of this argument, but there is no exhibit with that number submitted in this record.

Regardless of any nexus, Petitioner contends that Exhibit 2038 does not evidence skepticism. Pet. Reply 30 (citing Ex. 1084 ¶¶ 19, 99–100, 114–116). According to Petitioner, Patent Owner's evidence merely reflects the FDA's request for more information after reviewing the CLARITY study results to better understand the "safety risks and overall benefit-risk profile." *Id.* (quoting Ex. 2038, 1).

We find that Exhibit 2038 does not evidence skepticism that supports a determination of nonobviousness. Nothing in Exhibit 2038 reveals any skepticism about cladribine's "effectiveness" in treating MS, which the FDA concluded was shown through "substantial evidence" in the CLARITY study. Ex. 2038, 1. To the extent the FDA sought further information about safety, including any concerns over possible cancers, this was simply the agency attending to its normal duties. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (explaining that the FDA's request for clinical safety and efficacy data "reflects attention to the FDA's normal duties," not skepticism). Moreover, the FDA was, in all likelihood, merely responding to the data provided to the agency in relation to the CLARITY trial, which trial did report "neoplasms (including those that were found to be benign, malignant, or unspecified)" in about 1 % of patients. Ex. 2051 ¶ 228 (quoting Ex. 2033, 424). To the extent the data raised questions on the FDA's part, there is no evidence here to suggest such questions were unfounded at that time—the FDA just requested more information to appropriately weigh the risks versus the benefits.[36]

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[36] Not only did the CLARITY study include reports of neoplasms in a few patients, the MAVENCLAD label states that treatment "may increase the risk of malignancy." Ex. 2001, 8 (citing clinical studies showing increased incidence of malignancy in treated patients versus placebo). The fact that

Patent Owner also argues that certain writings of Dr. Miller and others evidence industry skepticism. PO Resp. 58–59 (Ex. 2051 ¶¶ 195–198). Patent Owner cites a book chapter co-authored by Dr. Miller in 2000, discussing recently-completed cladribine trials and writing "[a] trial of cladribine failed to show benefit in progressive disease." *Id.* (citing Ex. 2005, 45, 67). Patent Owner also cites a 2008 review co-authored by Dr. Miller, referencing earlier studies and 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." *Id.* (citing Ex. 2004, 341). Lastly, Patent Owner cites a 2005 book chapter from another specialist in this field, Dr. Noseworthy, stating: "We remain to be convinced that cladribine is useful, and do not recommend its use in the management of patients with multiple sclerosis." *Id.* (citing Ex. 2031, 753); PO Sur-reply 24–25 (arguing the authors questioned cladribine's safety and efficacy).

We find that these writings are entitled to minimal weight as evidence of skepticism. The nexus showing as to these writings is weak. The writings are principally focused on the treatment of progressive MS, yet the claims recite treating any form of MS and, thus, encompass the respectively easier-to-treat relapsing remitting form (RRMS).[37] Ex. 1061, 61:1–10, 123:6–13 (testifying Exhibit 2005 does not cite RRMS studies). Dr. Miller

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the FDA may have initially flagged an increased cancer risk was not, therefore, without apparent basis and Patent Owner has not shown that its FDA-approved method avoids all such risks.

[37] Exhibit 2031 references a paper by Grieb, but it appears to be a different publication by Grieb than discussed above and, thus, it is not apparent that it relates to RRMS. *Compare* Ex. 2031, 753, 855, *with* Ex. 1001, 3:2–6. Romine, cited in Exhibit 2031, studied RRMS patients. Ex. 2031, 753.

testified that he commented only on progressive MS in Exhibits 2004 and 2005. Ex. 1084 ¶¶ 103–106 ("I expressed no skepticism about cladribine's efficacy in treating RRMS" and "a POSA would have understood cladribine to have efficacy in treating RRMS, as demonstrated by Stelmasiak and Romine"). The claims also require no specific efficacy endpoint and, even if they did, the patent defines efficacy broadly as discussed above to include, for example, *any* of the following: improved EDSS scores, reduced relapse rates, or fewer lesions. *See supra* Section III.D.4.(c). Even if Drs. Miller and Noseworthy were not yet prepared at the time of those writings to recommend cladribine's use in their patients in actual clinical practice, they expressed no skepticism about cladribine's ability to, for example, reduce the number of MRI-detected brain lesions. To the contrary, Dr. Noseworthy expressly noted the reduced lesions reported in cladribine-treated patients in both Romine and Rice. Ex. 2031, 753; *see also* Ex. 2004, 341, 350 (Miller citing the "statistically significant" reduction in lesion "number and volume" per Rice's data).

Patent Owner argues that MAVENCLAD, as illustrated by the results of the CLARITY studies, provides unexpected results. PO Resp. 60–63. More specifically, Patent Owner contends the CLARITY trials showed that giving a total dose of 3.5 or 5.25 mg/kg over two years, followed by two years of placebo, resulted in "***durable*** clinical efficacy" comparable to continuing the dosing regimen over a four-year period, but with an improved safety profile. *Id.* at 60–61 (arguing that the extension phase of the study showed that the benefits of the two-year regimen were "***maintained***" in many patients who remained free from relapses or sustained disability progression. *Id.* (citing Ex. 2035, 1594, 1603; Ex. 2042, 3; Ex. 2051 ¶ 205).

Patent Owner also cites the follow-on "CLASSIC-MS study, finding 'sustained long-term mobility and disability benefits of cladribine tablets' during the median ***10.9 years'*** follow-up period." *Id.* at 61 (quoting Ex. 2036, 719). Thus, Patent Owner argues, the CLARITY and follow-up trials showed that the dosing method provides not only significantly reduced relapse rates, risk of disability progression, and MRI measures but also "unexpected durability" provided by a shorter-duration (two-year) dosing regimen that is more convenient for patients, especially compared to other approved MS drugs requiring continuous dosing. *Id.* at 62–63 (citing Ex. 2035, 1603; Ex. 2042, 4 (interview of clinical neurologist, stating "[t]hat convenience for them is really, really big").[38] Patent Owner also cites a paper hypothesizing that cladribine is an "immune reconstitution therapy," where reconstituted lymphocytes might become less autoreactive to CNS tissues, potentially explaining the prolonged efficacy beyond the first two treatment years. PO Resp. 62–63(citing Ex. 2032, 1923); PO Sur-reply 25–26.

Petitioner responds that Patent Owner's nexus showing is flawed concerning the alleged unexpected results. Pet. Reply 31–32. According to Petitioner, MAVENCLAD "treats ***RRMS*** patients for ***2 years*** with cladribine ***tablets***" but "the claims are broader, encompassing ***any*** type of MS, ***any oral*** cladribine dosage form, and ***any regimen of ≥ 2 years***." *Id.* (citing Ex. 1084 ¶¶ 124–125; Ex. 1061, 143:13–16). Petitioner contends the evidence also does not show unexpectedly superior results because Patent Owner did not compare its results with the closest prior art—Bodor. *Id.* at

[38] Patent Owner also cites Exhibit 2023 in support of this argument, but there is no exhibit with that number of record.

31. And, Petitioner contends that the asserted "durable" result is not unique to Patent Owner's method compared to the prior art methods and, instead, is just inherent to cladribine. Pet. 32 (citing Ex. 1084 ¶¶ 113, 126, 130).

We give moderate weight to Patent Owner's evidence of unexpected results. As to nexus, the claims are not coextensive with the MAVENCLAD or CLARITY method for the reasons given by Petitioner, but Patent Owner persuades us they are reasonably commensurate. PO Sur-reply 26–27 (citing *Rambus, Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013); *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (explaining that an applicant need not test every embodiment within the scope of the claims to show unexpected results). Dr. Lublin provides detailed claim charts showing the correspondence between MAVENCLAD/CLARITY and claims 36 and 39, which evidence Petitioner does not rebut beyond arguing that the claims are broader. Ex. 2051 ¶¶ 223–226 (opining, also, that MAVENCLAD's safety and durable efficacy is tied to the unique features of the claims, particularly the 3.5 mg/kg cumulative two-year dosing regimen).

The weight given to Patent Owner's unexpected-results evidence is, however, discounted somewhat because, as Petitioner argues, Patent Owner provides no comparison against the Bodor regimen, which we agree is the closest prior art. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (explaining, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art"). As we explained above, Bodor's regimen using 10 mg cladribine tablets for oral administration materially overlaps with claim 36 (and claim 39, as well) in at least the induction period's dosage and

duration, and the 10-month cladribine-free period.[39] Neither Stelmasiak nor Romine, for example, is closer than Bodor to the claims. Petitioner has, nevertheless, argued that Rice's induction dosage/duration is similar to Bodor's, yet Rice did not report favorable results to the same extent as seen in the CLARITY trials (e.g., Rice did not see significant improvement in EDSS scores, much less report durability lasting beyond 10 years in some patients as argued by Patent Owner).[40] *Compare* Ex. 1018, 1152–1153, *with* Ex. 1033, 420–423; Ex. 2035, 1594. Inasmuch as Rice's results are cited by Petitioner as informing effects that would have been expected with Bodor's regimen, we are unpersuaded on this record that the long-term durability cited by Patent Owner would have been expected. *C.f.* Ex. 1031 (Romine), 43 (citing "an estimate based on observations of cladribine in chronic progressive MS . . . would indicate that beneficial effect should eventually decline and would not be expected to last much beyond 2 years").[41]

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[39] At the hearing, Patent Owner also was unable to identify any data or other evidence showing criticality relative to the dosages or durations recited in the claims. Tr. 77:14–78:16 (arguing generally that the "inventors found a sweet spot").

[40] This is, however, an imperfect comparison because Rice's patients had the more difficult-to-treat progressive form of MS, as discussed above, whereas CLARITY tested patients with relapsing MS (RRMS). Ex. 2033, 416; Ex. 2035, 1594.

[41] Petitioner's contention that long-term durability may simply arise from an inherent property or mechanism of cladribine's use is not decisive here because, as explained by the Federal Circuit, "[w]hat is important regarding properties that may be inherent, but unknown, is whether they are unexpected." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017).

Lastly, Patent Owner argues that MAVENCLAD satisfies a long-felt and unmet need. PO Resp. 63. According to Patent Owner, MAVENCLAD offers MS patients a more convenient dosing regimen that requires a relatively short-term (2 year) commitment with the possibility of offering long-lasting relief. *Id.* (citing Ex. 2042, 1, 4; Ex. 2051 ¶¶ 209–216) (testifying that there was a long-felt need for a safe, effective, and convenient oral therapy for MS, compared to less convenient approved options requiring continuous injections).

Petitioner raises the same nexus counterargument as discussed above for the asserted unexpected results, and argues that Patent Owner's long-felt, unmet need contentions fail because Patent Owner relies on "irrelevant ***post-filing*** evidence." Pet. Reply 31 (citing Ex. 1084 ¶¶ 128–133).

We give moderate weight to Patent Owner's long-felt, unmet-need evidence. The evidence is reasonably commensurate in scope with claims 36 and 39 as noted above related to the asserted unexpected results. Petitioner criticizes Patent Owner's reliance on "post-filing" evidence, yet does not persuasively rebut Dr. Lublin's testimony to the effect that patients wanted a more convenient and less-frequent regimen for treating MS. Ex. 2051 ¶¶ 209–216. If nothing else, a desire for taking a drug intermittently and orally versus more frequent injections seems like common sense, whether today or in 2004, and the '947 patent suggests a desire for methods of treating MS involving the oral administration of cladribine. Ex. 1001, 3:22–30; *see also* Ex. 1022, 2:11–13 (disclosing oral forms enhance compliance and decrease the discomfort of injections). The evidence is discounted somewhat because more convenient oral forms of cladribine were already known in the art for use in treating MS patients, using intermittent dosing schedules, and had undergone clinical studies in

MS patients where favorable results and only "mild" side effects were reported. *See, e.g.*, Ex. 1013, 4, 7; Ex. 1022, 22–23; Ex. 1026, Abstr., 10:47–60; *In re Kao*, 639 F.3d at 1068 (explaining that objective indicia of nonobviousness must be tied to "*novel*" elements of the claim to be afforded substantial weight) (citations omitted). Moreover, even if MAVENCLAD is more convenient, Patent Owner cites no persuasive evidence to show that other approved DMTs that were available in 2004 did not already provide safe and efficacious treatments for MS.

Altogether, although we afford some weight to Patent Owner's evidence of objective indicia as discussed above, we do not find that evidence especially strong. Considering Petitioner's strong showing that Bodor's regimen teaches claim 36's steps (i) and (ii), with overlapping cladribine dosages and treatment durations, the suggestion and logic of adding a retreatment phase to Bodor's regimen given MS's chronic nature and the knowledge of cladribine retreatments in the art following cladribine-free periods, the art's teaching to "tailor" (i.e., optimize) the dose/duration according to the patients' needs, and the reporting of positive results in earlier clinical trials (e.g., reduced MS lesions, which qualifies as treatment "efficacy" per the patent), the record leans in Petitioner's favor. *Pfizer*, 480 F.3d at 1372 ("Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.").

5. Dependent claims

Petitioner contends that claims 38, 39, and 41–46 would also have been obvious over Bodor and Stelmasiak. Pet. 55–60. Petitioner persuades us the challenged dependent claims would have been obvious for the reasons discussed above for independent claim 36, and the further reasons given by Petitioner and Dr. Miller concerning the dependent claims, which reasons

are supported by the preponderance of the evidence of record and we adopt that reasoning as our own unless otherwise noted. *Id.*; Ex. 1002 ¶¶ 120–139; Ex. 1084 ¶¶ 97–98.

Patent Owner raises no separate argument for any of the dependent claims except for claim 39, which narrows claim 36's induction period total dose from "about 1.7 mg/kg to about 3.5 mg/kg" to "about 1.7 mg/kg." PO Resp. 57–58 (arguing that Stelmasiak disclosed use of a different dosage amounts in the induction and maintenance periods) (citing Ex. 2051 ¶¶ 189–192).

We disagree with Petitioner's contentions that the claims require an induction period dose that is higher than the maintenance period dose, as we discussed above. *See supra* Section III.C. The doses can be the same (both "about 1.7 mg/kg") as argued by Patent Owner. *Id.* And, as also discussed above, Bodor's induction dose/duration for an average weight MS patient is 1.4–2.0 mg/kg over two months, which overlaps with claim 36's range and encompasses claim 39's induction dose of about 1.7 mg/kg. *Supra* Section III.D.4.(b)-(c). We credit Dr. Miller's testimony that it would have been logical and obvious to use Bodor's induction period dose/duration as a starting point for optimization as necessary in the maintenance phase. *Id.* Patent Owner cites no evidence of criticality to the recited induction or maintenance dosage and duration and, for the reasons already discussed above, we conclude that claim 39 would have been obvious as well.

6. Conclusion

Up considering the totality of the argument and evidence of record, and for the reasons explained above, we determine that Petitioner has proved by a preponderance of the evidence that claims 36, 38, 39, and 41–46 are unpatentable for obviousness.

IV. MOTIONS

Four motions to seal remain pending (Papers 19, 42, 54, and 55). Patent Owner moves to seal Exhibits 2048, 2049, and 2050 as including alleged research, development, and commercial information that Patent Owner maintains is confidential, and further requests entry of the Board's Default Protective Order. Paper 19, 4–7. Petitioner moves to seal its Reply and Exhibits 1059, 1060, 1063, 1080, and 1084 as including information that Merck considers confidential. *See, e.g.*, Paper 42, 3–4. Petitioner and Patent Owner move to seal their demonstratives. Paper 54, 3–4 (noting, e.g., the demonstratives relate, at least in part, to Exhibits 2048–2050); Paper 55, 2–8 (explaining that the demonstratives include excerpts from, for example, Exhibits 1063, 2049, and 2050). None of the motions is opposed.

The Board recognizes "a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an *inter partes* review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Tech., LLC*, IPR2012-00001, Paper 34, 1–2 (PTAB Mar. 14, 2013). Except as otherwise ordered by the Board, the record of an *inter partes* review shall be made available to the public. 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14.

The standard for granting a motion to seal is "for good cause." 37 C.F.R. §§ 42.20(c), 42.54(a). In determining whether good cause has been shown, the Board considers, among other things, whether the information sought to be sealed is truly confidential and whether the expressed interest in maintaining confidentiality outweighs the strong public interest in an open record. *Argentum Pharm. LLC v. Alcon Rsch., Ltd.*, IPR2017-01053, Paper 27 at 2–3 (PTAB Jan. 19, 2018) (informative).

We grant Patent Owner's unopposed Motion to Seal Exhibits 2048, 2049, and 2050, and enter the Board's Default Protective Order. Patent Owner persuades us that Exhibits 2048, 2049, and 2050, include confidential research and development information.

Paper 42, Petitioner's Motion to Seal its Reply and Exhibits 1059, 1060, 1063, 1080, and 1084 is denied. Petitioner must provide minimally-redacted, public versions of its Reply and the exhibits in question (it appears that the only redacted version submitted by Petitioner is for Exhibit 1059, but the motion is denied in full to avoid piecemeal resolution). This denial is without prejudice and Petitioner may refile its motion within twenty days. If refiled, the aforementioned redacted version of the Reply and exhibits will be filed at the same time.

We grant the parties' motions (Papers 54 and 55) to seal their respective demonstratives. Although the parties did not provide redacted versions of their demonstratives, demonstratives are not evidence. Nor are the demonstratives substantively relied on herein and, thus, the absence of redacted versions does not impede the public's interest in an open and understandable record.

V. OBJECTIONS

Patent Owner also filed objections to a handful of Petitioner's demonstrative slides. Paper 57 (objecting to slides 41–44 and 47 in Petitioner's Demonstratives (Ex. 1092)). Patent Owner's objection is that those slides include "new argument" outside the trial record. *Id.* at 2–3.

Patent Owner's objections are overruled. Slide 41 quotes Federal Circuit precedents, with which the Board is already familiar. Slides 42 through 44 include appropriate cites to where the evidence/argument cited therein was raised in prior papers and evidence, illustrating a comparison

between what was argued throughout trial; and, to the extent Petitioner's headings constitute minimal attorney argument, they only generically relay that Petitioner disagrees with Patent Owner's Sur-reply characterizing Petitioner's argument as being "new." We similarly overrule the objection to slide 47. Although slide 47's chart includes more citations than a similar chart on page 4 of the Reply, Petitioner did rely on the other cited portions of Bodor in its papers, and the added citations are generally consistent with the argument raised by Petitioner in its analysis of whether Bodor is "by another." Pet. Reply 3–10 (arguing, e.g., that the named inventors on Bodor invented the solid cladribine dosage forms, and also described cladribine as useful for treating MS).

VI. CONCLUSION[42]

On this record, Petitioner has shown by a preponderance of the evidence that the challenged claims are unpatentable based on the ground advanced in the Petition.

In summary:

[42] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
36, 38, 39, 41–46	103	Bodor, Stelmasiak	36, 38, 39, 41–46	

VII. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has proved by a preponderance of the evidence that claims 36, 38, 39, and 41–46 are unpatentable;

FURTHER ORDERED that the Parties' Motions to Seal (Papers 19, 54, and 55) are *Granted* as provided above;

FURTHER ORDERED that Petitioner's Motion to Seal (Paper 42) is *Denied* without prejudice as provided above;

FURTHER ORDERED that the Board's Default Protective Order is entered and controls access to confidential information in this matter;

FURTHER ORDERED that within ten (10) business days, the parties will jointly provide a minimally redacted version of this decision that is available to the public; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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