

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

ARES TRADING SA,
Patent Owner.

Case IPR2023-00482
Patent 10,849,919

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

The Board should not institute *inter partes* review of claims 1-6, 8-9, 11-12, 14-16, 18-20, 23-27, 30, and 33-34 (“challenged claims”) of U.S. Patent No. 10,849,919 (the “’919 patent”) because Petitioner fails to show any reasonable likelihood of prevailing.

Before the ’919 patent’s invention, there were only two disease-modifying treatments (“DMTs”) that had been approved for progressive multiple sclerosis (“MS”)—mitoxantrone and ocrelizumab—but mitoxantrone was “rarely used in MS anymore” (Ex. 1019, 790) and ocrelizumab gained only “moderate interest.” Ex. 1001, 2:52-55. No other MS drugs had been approved by the FDA for a progressive MS indication, although DMTs had been approved for relapsing remitting multiple sclerosis (“RRMS”). Ex. 1019, 785, 790. While several clinical studies had investigated the use of DMTs glatiramer acetate, rituximab, and fingolimod to treat primary progressive multiple sclerosis (“PPMS”) (*id.*, 790 (Table 5-4)), these trials “did not reach meaningful clinical endpoints.” Ex. 1001, 2:55-60. Likewise, numerous clinical studies had investigated the use of ten different immune-modulating therapies, including cladribine, to treat secondary progressive multiple sclerosis (“SPMS”), but these studies were also referred to in the art as “uniformly disappointing.” Ex. 1019, 790. Further, smaller studies that evaluated other immunosuppressive agents “did not show an impact on disease

course.” *Id.* Thus, before the ’919 patent’s invention, there was a high unmet medical need for therapeutics that are effective in the field of progressive forms of MS. The ’919 patent addresses this unmet need and claims an MS dosing regimen using cladribine for treating a progressive form of MS not including early SPMS. Ex. 1001, 3:25-35.

Notably, in 2016, a year before the ’919 patent’s priority date, Petitioner’s own cited review article referred to planned or ongoing trials in progressive MS involving **twenty** different treatments across **eighteen** trials, but **none** of these included cladribine. *See* Ex. 1019, 795 (Table 5-6). Nevertheless, Petitioner asks the Board to find that the ’919 patent invention of using cladribine to treat a progressive form of MS that does not include early SPMS would have been obvious. As outlined below, Petitioner’s arguments are insufficient to warrant institution, and the Petition should be denied for at least the following reasons.

Ground I must fail because Petitioner fails to establish that a POSA would have been motivated to treat PPMS by modifying Alvarez-Gonzalez’s flat, subcutaneous cladribine dosing method in view of Giovannoni’s weight-based oral cladribine dosing method, especially when neither reference discloses clinical efficacy of cladribine for treating PPMS, or any progressive form of MS. Petitioner praises Alvarez-Gonzalez’s alleged “successful treatment” (Pet. 37), but offers no adequate rationale for why a POSA would have been motivated to

modify Alvarez-Gonzalez's method that only treated inflammation arising from rebound disease due to cessation of fingolimod to arrive at the claimed oral, weight-based dosing method to treat a progressive form of MS. Nor does Petitioner show that a POSA would have had a reasonable expectation of success in doing so.

Ground II adds Montalban, and challenges dependent claims reciting a cladribine-free period, but suffers from the same deficiencies as Ground I and thus must also fail. The addition of Montalban, an abstract referring to a Phase II study of oral cladribine in patients suffering from RRMS or SPMS with ongoing relapses, does not cure the fundamental defects in the combination of Alvarez-Gonzalez and Giovannoni, including that it does not teach treatment of a progressive form of MS that is not early SPMS, as recited in the claims.

Finally, Ground III also fails because Petitioner does not establish that the combination of Clinicaltrials.gov, Schreiber, and Montalban would have motivated a POSA to modify the prior art to arrive at a method of using cladribine to treat a progressive form of MS not including early SPMS as claimed, or that a POSA would have had a reasonable expectation of success in doing so. Clinicaltrials.gov, Schreiber, and Montalban do not disclose clinical efficacy of cladribine for treating a progressive form of MS that is not early SPMS as recited in the claims. Further, Petitioner's reliance on Montalban to allegedly teach treating SPMS patients that

do not include early SPMS patients is based on an erroneous claim construction of “early SPMS” that is at odds with the ’919 patent claims, specification, and prosecution history, as well as the state of the art as reflected in Petitioner’s exhibits.

Accordingly, institution of *inter partes* review should be denied.

II. BACKGROUND

Multiple sclerosis is a chronic inflammatory demyelination disease of the central nervous system. Ex. 1001, 1:25-27. MS is considered to be multi-phasic with sporadic episodes of remissions between exacerbations or disease progression. *Id.*, 1:43-46. Clinically defined MS types include relapsing remitting MS, secondary progressive MS, primary progressive MS, and progressive relapsing MS (“PRMS”). *Id.*, 1:47-50. The latter three types are referred to as progressive forms of MS or progressive MS.

Cladribine is a synthetic chlorinated purine analog, which is a nucleoside metabolic inhibitor that interferes with DNA repair and synthesis. *Id.*, 4:1-4, 50:31-32. Cladribine had been tested for treatment of PPMS and SPMS. Montalban (Ex. 1006), discussed below, referred to one study, reporting reduced relapse rate in a combined group of primarily RRMS and some SPMS patients, and stating that “the study was not powered for” an EDSS endpoint. Ex. 1006, 1. Another study reported that “clinical efficacy was not shown” for cladribine in

progressive MS patient populations. Ex. 1036, 1153; *see also* Ex. 1008, 319; Ex. 1019, 790.

The efficacy and safety of cladribine oral tablets for treating RRMS were investigated in a 96-week, Phase 3, double-blind, placebo-controlled clinical trial (CLARITY) in a large patient population. Ex. 1007, 416; Ex. 1001, 4:66-5:2. MAVENCLAD® (cladribine tablets) was approved in Europe in August 2017 for the treatment of RRMS in patients with high disease activity. Ex. 1001, 2:41-44.

By 2017, several clinical studies investigated approved RRMS drugs glatiramer acetate, rituximab, and fingolimod for treating PPMS (Ex. 1019, 790 (Table 5-4)) but “did not reach meaningful clinical endpoints.” Ex. 1001, 2:55-60. Numerous clinical studies had investigated the use of other immune-modulating therapies, including cladribine, to treat secondary progressive multiple sclerosis, but Petitioner’s cited review article described these studies as “uniformly disappointing.” Ex. 1019, 790.

In 2017, “none of the MS medications approved by the [FDA] carrie[d] an indication for progressive MS,” with the exceptions of mitoxantrone, which was “rarely used in MS anymore” (*id.*), and ocrelizumab, which gained only “moderate interest.” Ex. 1001, 2:52-55.

III. PERSON OF ORDINARY SKILL IN THE ART

Patent Owner reserves the right to challenge Petitioner's definition at a later stage in this proceeding, should the Board institute trial.

IV. CLAIM CONSTRUCTION

Petitioner contends that the claim term "early secondary progressive Multiple Sclerosis" ("ESPMS") should be construed as "a progressive form of MS that is distinct from the other claimed progressive forms (specifically, SPMS)."

Pet. 34. The Board should reject Petitioner's construction because it disregards the plain and ordinary meaning of the term "early secondary progressive Multiple Sclerosis," as informed by the '919 patent claims, the teachings of the '919 patent specification, the '919 patent prosecution history, and the common knowledge by a POSA in the art as reflected in peer-reviewed journal publications.

It has long been held that the "words of a [patent] claim are generally given their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*) (internal citations and quotations omitted). The Federal Circuit has

made clear ... the ordinary and customary meaning of a claim term is the meaning that the term would have to a [POSA] in question at the time of the invention ... Importantly, the [POSA] is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.

Id. at 1313.

Here, a POSA considering the '919 patent claims, teachings of the specification, and prosecution history would have understood that the plain and ordinary meaning of the term “early secondary progressive Multiple Sclerosis” is “an initial, transitional stage of secondary progressive multiple sclerosis” that is encompassed by SPMS.

First, the term “early secondary progressive multiple sclerosis” includes “secondary progressive multiple sclerosis,” which is *modified* by “early.” Thus, a POSA would have understood that early SPMS is a *sub-type* of SPMS and thus is encompassed by SPMS.

Second, the '919 patent claims and specification make clear that ESPMS is encompassed by SPMS. Claim 1 recites “[a] method of treating a progressive form of [MS] ... selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and

Progressive Relapsing Multiple Sclerosis (PRMS), and *wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).*” Ex. 1001, 64:45-57.¹ If early SPMS were a progressive form of MS that is “distinct from the other claimed progressive forms” as Petitioner contends, then there would have been no need to distinguish early SPMS by expressly excluding it from the claims. Under Petitioner’s construction, the claim limitation “wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS)” is superfluous; thus, Petitioner’s construction should be rejected. *See Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 809-10 (Fed. Cir. 2021) (“It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous.” (quoting *Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017))); *TMI Prod., Inc. v. Rosen Entm’t Sys., L.P.*, 610 F. App’x 968, 972-73 (Fed. Cir. 2015) (rejecting proposed construction that “create[d] redundancies in the claim language”).

The ’919 patent specification also supports Patent Owner’s construction of early SPMS. The ’919 patent specification explains that “[e]arly Secondary Progressive Multiple Sclerosis (ESPMS) is some form of Multiple Sclerosis that

¹ Hereinafter, all emphasis is added unless otherwise noted.

marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS.” Ex. 1001, 2:63-67. A POSA would have understood from this language that early SPMS is the initial, transitional period of SPMS, and is thus *encompassed* by SPMS.

Further, the ’919 patent specification discloses a *preferred embodiment* in which “Secondary Progressive Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis.” *Id.*, 7:62-64 (“Preferably, Secondary Progressive Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis.”). A POSA would have understood that the identification of such an embodiment—which is claimed in the ’919 patent—reflects an understanding that SPMS is broad and includes early SPMS unless it is expressly excluded. Thus, consistent with Patent Owner’s construction of early SPMS, the ’919 patent specification identifies a particular embodiment recognizing early SPMS as a *sub-type* of SPMS falling within SPMS.

Third, the prosecution history of the ’919 patent directly supports Patent Owner’s proposed construction. During prosecution, Patent Owner argued that the claimed “Secondary Progressive Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis,” citing to the ’919 patent specification describing the corresponding, preferred embodiment. Ex. 1004, 328 (citing to specification as filed describing a preferred embodiment in which SPMS does not

include ESPMS). However, the Examiner rejected this argument and “advised that SPMS *encompasses* ‘early’ SPMS.” *Id.*, 326. The Examiner further stated that in the ’919 patent specification, “‘early’ SPMS was only excluded from SPMS as a preferable embodiment.” *Id.* In response, Patent Owner amended then-pending claim 1 to expressly exclude early SPMS from the claimed method, as suggested by the Examiner, leading to allowance of the claims. *Id.*, 17-25, 302-314. Thus, the prosecution history of the ’919 patent also makes clear that early SPMS is encompassed by SPMS and not “distinct from the other claimed progressive forms” as Petitioner contends.

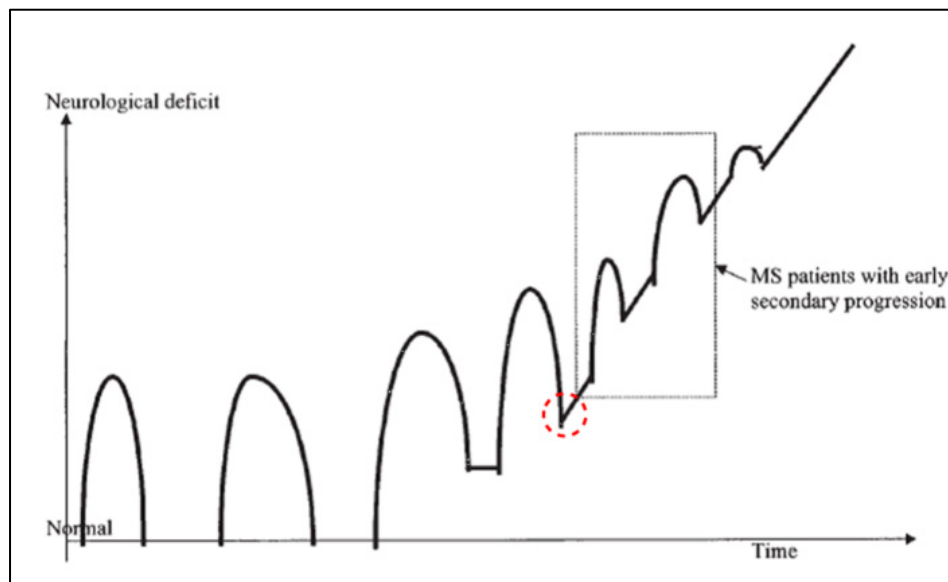
While Petitioner argues that Patent Owner admitted that SPMS does not include early SPMS (Pet. 35), as discussed above, the Examiner clearly and expressly rejected this because “SPMS *encompasses* ‘early’ SPMS.” Ex. 1004, 326. Further, the Examiner suggested that Patent Owner “amend claim 1 to expressly exclude ‘early’ SPMS from the claimed method,” a suggestion that Patent Owner followed. *Id.*, 302-314, 326. “While clear and limiting statements made by the patent owner can give rise to disclaimer, they do not in ... case[s] where those statements were clearly and expressly rejected by the Patent Office.” *Galderma Lab’ys, L.P. v. Amneal Pharms. LLC*, 806 F. App’x 1007, 1010-11 (Fed. Cir. 2020). Here, the record makes clear to a POSA that Patent Owner’s rejected

arguments do not impact the scope of “early SPMS,” which had to be expressly carved out to be excluded from SPMS. *See* Ex. 1004, 326.

Fourth, even the references cited by Petitioner to support its proposed construction of early SPMS contradict Petitioner’s construction and show that SPMS encompasses early SPMS.

Petitioner cites to Ex. 1014 (“Lublin 1996”) for the definition of SPMS. Pet. 13, 15. Lublin 1996 (titled “Defining the clinical course of multiple sclerosis: Results of an international survey”) explains that SPMS is defined as “progression with or without occasional relapses, minor remissions, and plateaus” after an “initial RR disease course.” Ex. 1014, 908. Petitioner cites to Ex. 1017 (“Skurkovich”) at Figure 1 to show the disease course for SPMS patients. *See* Pet. 16-17. But Ex. 1017 actually shows that SPMS patients ***include*** early SPMS patients. *See* Ex. 1017, 278. Skurkovich reported that the “positive clinical results ... may be related to the patient selection criteria, whereby only active early secondary progressive patients were included ... [which] means that within the group of secondary progressive MS patients, a ***subgroup*** of patients sensitive to ... immunomodulative treatment are still present.” *Id.*, 282. And while Skurkovich identifies early SPMS with the box shown in Figure 1, Lublin 1996 explains that “once the baseline between relapses begins to progressively worsen, the patient ***has switched*** from RR-MS to SP-MS.” Ex. 1014, 908. Here, as shown below in

the annotated version of Skurkovich Figure 1, a POSA considering Skurkovich and Lublin 1996 would have understood that in the time prior to reaching the early SPMS box, “the baseline between relapses [had] beg[un] to progressively worsen” (as indicated by the upward trajectory of the line and annotated by the dashed red circle), and thus the patient *already* transitioned to SPMS. *See id.* Accordingly, early SPMS, indicated by the box, corresponds to an initial, transitional stage of SPMS. Thus, a POSA in view of Lublin 1996 and Skurkovich would have understood that early SPMS is encompassed by SPMS.



Ex. 1017, 278 (annotated).

Other exhibits relied on by Petitioner to define SPMS and early SPMS also plainly show that early SPMS is part of SPMS. For example, Ex. 1016 (“Casanova”) states that “the SPMS group (‘Early SPMS’ and ‘Late SPMS’) had increased to 26 patients[.]” Ex. 1016, 60-61. Likewise, Ex. 1018 (“Sand”) states

that “patients with SPMS represent a difficult population to study; the identification of a larger patient group with early SPMS could improve recruitment for clinical trials.” Ex. 1018, 1655.

Thus, based on the plain meaning of the term in the context of the claims, specification, and prosecution history of the ’919 patent, and reinforced by the knowledge of a POSA as reflected in peer-reviewed publications, a POSA would have understood that early SPMS is an initial, transitional stage of SPMS that is encompassed by SPMS and not “distinct from the other claimed progressive forms.”

Patent Owner does not believe additional terms require construction at this stage but reserves the right to challenge Petitioner’s proposed constructions or address construction of additional claim terms at a later stage in this proceeding, should the Board institute trial.

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

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

A. Ground I – Petitioner Has Not Established That Claims 1-6, 8-9, 12, 14-16, 18-20, 24-27, And 34 Would Have Been Obvious Over Alvarez-Gonzalez And Giovannoni

In Ground I, Petitioner challenges claims 1-6, 8-9, 12, 14-16, 18-20, 24-27, and 34 as being obvious over Alvarez-Gonzalez (Ex. 1009) and Giovannoni (Ex. 1007). Pet. 36-49. Petitioner fails to show that a POSA would have been motivated to modify the prior art as alleged to arrive at a method of using cladribine to treat a progressive form of MS as claimed, or that a POSA would have had a reasonable expectation of success in doing so. For each reason, Ground I should not be instituted.

1. Claim 1 Would Not Have Been Obvious Over Alvarez-Gonzalez And Giovannoni

a) Petitioner Has Not Established Any Motivation To Combine Alvarez-Gonzalez And Giovannoni To Arrive At Challenged Claim 1

Petitioner fails to establish a motivation to modify Alvarez-Gonzalez's flat, subcutaneous cladribine dosing method in view of Giovannoni's weight-based oral cladribine dosing method to arrive at the weight-based, oral dosing method of claim 1 to treat a progressive form of MS as claimed.

First, Petitioner argues a POSA would have been motivated to treat PPMS based on Alvarez-Gonzalez. Pet. 36-37. However, a POSA would not have been motivated to treat PPMS as claimed because Alvarez-Gonzalez does not disclose clinical efficacy of cladribine for treating PPMS. Petitioner relies on Alvarez-

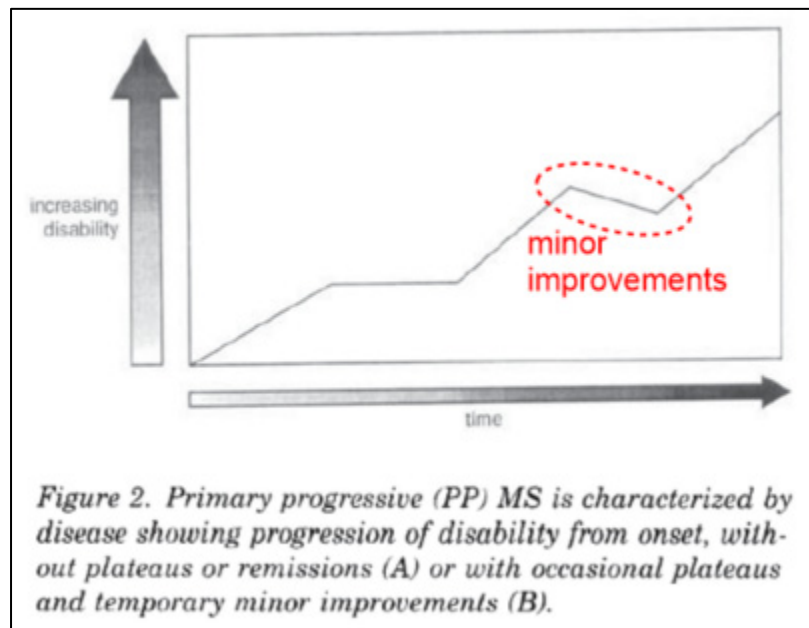
Gonzalez to disclose “a ‘successful treatment’ of a PP-active, i.e., primary progressive, patient with ‘significant clinical and MRI-disease activity’ with cladribine.” Pet. 37 (quoting Ex. 1009, 507, 509). However, Alvarez-Gonzalez only discloses the use of cladribine to “rescue” *a single patient* suffering from “[r]ebound disease following cessation of disease modifying treatment (DMT) [i.e., fingolimod.]” Ex. 1009, 506. While the patient in Alvarez-Gonzalez had been diagnosed with PPMS prior to treatment with fingolimod (*id.*), Alvarez-Gonzalez does not characterize her subsequent treatment with cladribine as “successful treatment” of a progressive form of MS, as Petitioner contends. Instead, Alvarez-Gonzalez characterizes the patient as “a case of *rebound disease* after fingolimod cessation in a pwPMS [i.e., “person with progressive MS”], who was successfully treated with Cladribine as an off-label ‘*rescue*’ therapy.” *Id.*, 506, 509 (“[W]e report the case of a pwPMS who developed rebound disease after fingolimod cessation and partially recovered following Cladribine administration.”). Rebound disease is not PPMS, but a “clinical relapse” caused by the release of lymphocytes (originally suppressed by fingolimod) back into the blood circulation after fingolimod treatment is stopped. *See id.*, 506 (“When [fingolimod] treatment is stopped lymphocyte levels usually return to normal within 4–8 weeks. The resulting release of lymphocytes back into the blood circulation may cause ‘*rebound*’ disease, defined as a degree of disease activity

significantly *exceeding pre-DMT activity.*”), 507 (“MRI taken 6 months after suspending Fingolimod and during the *clinical relapse*”). Notably, rebound disease can happen “[i]rrespective of the [MS] disease course[.]” *Id.*, 507.

Alvarez-Gonzalez clearly distinguishes between the use of a drug for treatment of MS versus its use for “rescue” therapy. As the title indicates, Alvarez-Gonzalez reports that “cladribine” was used “to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis,” not treat the underlying PPMS. *Id.*, 506. Specifically, Alvarez-Gonzalez states that cladribine was used “as an off-label ‘rescue’ therapy” and that “[t]reatment with a short course of subcutaneous cladribine 60 mg led to effective suppression of inflammatory activity and partial recovery with no short-term safety issues or adverse events.” *Id.* This disclosure of cladribine’s effect on a single patient’s inflammation associated with rebound disease would not have motivated a POSA to treat PPMS as claimed. While Petitioner’s Declarant opines that the patient in Alvarez-Gonzalez had an improved EDSS score (from 8 to 7) after cladribine treatment (Ex. 1002, ¶91; Ex. 1009, 507), Figure 2A of Alvarez-Gonzalez shows no improvement in the patient’s EDSS score 3 months after cladribine treatment. Ex. 1009, 508. Instead, Figure 2A shows that the patient’s EDSS score after cladribine treatment remained at 8, the same as before treatment. Notably, the change in EDSS score did not even return the patient to her condition at the end of

the fingolimod study, during which her EDSS score was 6.5. *Id.*, 507 (“Over the course of INFORMS, ... her EDSS deteriorated from 5.5 to 6.5[.]”), 508 (Figure 2A).

Furthermore, even if the patient’s EDSS score did improve from 8 to 7, minor improvements can occur in the normal course even absent treatment, as indicated in the definition of PPMS. *See* Ex. 1014, 908 (“Primary-progressive (PP) MS. The consensus definition is as follows: disease progression from onset with occasional plateaus and temporary minor improvements allowed (figure 2, a and b).”), 909 (Fig. 2B; “Figure 2. Primary progressive (PP) MS is characterized by disease showing progression of disability from onset, without plateaus or remissions (A) or with occasional plateaus and temporary minor improvements (B).”); Pet. 14; Ex. 1002, ¶28; *see also* Ex. 1014, 909 (Figure 2B) (as annotated below in red, where the dashed oval indicates minor recovery in a PPMS patient without treatment). Petitioner does not show, nor does Alvarez-Gonzalez indicate, that the change in EDSS score was not just a result of the natural course in PPMS.



Ex. 1014, 909 (Figure 2B) (annotated).

Given Alvarez-Gonzalez’s limited results—reducing inflammation to “rescue” one PPMS patient from rebound disease rather than treat PPMS—Petitioner offers no adequate rationale for why a POSA would have been motivated to modify Alvarez-Gonzalez’s method to arrive at the claimed method for treating a progressive form of MS including PPMS.

Giovannoni does not remedy these deficiencies of Alvarez-Gonzalez. Giovannoni discloses a 96-week phase 3 trial of a short-course oral cladribine tablet therapy in patients with RRMS, also known as the “CLARITY” study. Ex. 1007, 416-17. Giovannoni does not disclose any treatment of a progressive form of MS, and thus does not provide any motivation to combine its disclosure with

Alvarez-Gonzalez to treat patients with a progressive form of MS, e.g., PPMS, as claimed.

Second, Petitioner has not established that a POSA would have been motivated to modify Alvarez-Gonzalez's teaching of flat subcutaneous dosing to instead adopt oral, weight-based dosing as claimed. Petitioner argues that a POSA would have been "motivated to substitute Alvarez-Gonzalez's fixed yearly dose of subcutaneous cladribine with oral cladribine" because "[o]ral delivery of drugs is often preferred to parenteral delivery." Pet. 37 (quoting Ex. 1026). But Alvarez-Gonzalez identified and specifically considered the oral, weight-based dosing used in the CLARITY study and nevertheless chose to administer cladribine via **subcutaneous, flat** dosing. Ex. 1009, 509 ("Based on 100% bioavailability of Cladribine s.c. (versus 42% or the oral prodrug) 60 mg Cladribine/year in an individual weighing less than 90 kg resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study. Cladribine 10 mg s.c. was given on days 1, 2 and 3 in week one ... we administered further doses Cladribine of 10 mg s.c. on days 1, 2 and 3 in week 5."). Further, Alvarez-Gonzalez does not suggest switching to a weight-based dosage. Instead, Alvarez-Gonzalez teaches that for anyone weighing <90 kg, a flat dosing of 60 mg is recommended. *See id.* Alvarez-Gonzalez also expressly teaches the benefits and preference of parenteral routes, which include subcutaneous administration. For example, Alvarez-

Gonzalez explains that “parenteral cladribine may have some practical and clinical advantages over currently licensed DMT and offers additional value via cost-effectiveness[.]” *Id.*

Particularly in view of Petitioner’s praise of Alvarez-Gonzalez’s “successful treatment” (Pet. 37), Petitioner offers no adequate rationale for why a POSA would have been motivated to modify Alvarez-Gonzalez’s subcutaneous, flat dosing method to arrive at the claimed oral, weight-based dosing method to treat a progressive form of MS. Thus, Petitioner has not established that a POSA would have had any motivation to modify or combine the teachings of the cited prior art to arrive at the method of using cladribine to treat a progressive form of MS, e.g., PPMS, as recited in claim 1.

b) Petitioner Has Not Established Any Reasonable Expectation Of Success In Combining Alvarez-Gonzalez’s Method With Giovannoni To Arrive At Challenged Claim 1

Petitioner argues that a POSA would have reasonably expected an oral, fixed dose of cladribine at 1.75 mg/kg/year to successfully treat PPMS based on Alvarez-Gonzalez (Pet. 39), which discloses a fixed subcutaneous cladribine dose that “resembles bio-equivalence with the oral 3.5 mg/kg dose used in the pivotal CLARITY MS study.” Ex. 1009, 509. However, as discussed above, Alvarez-Gonzalez merely discloses subcutaneous, flat dosing of cladribine in a single

patient for “rescue” from inflammation associated with “[r]ebound disease following cessation of disease modifying treatment (DMT) [i.e., fingolimod.]” *Id.*, 506. Alvarez-Gonzalez fails to show clinical efficacy in treating a progressive form of MS and thus would not have led a POSA to reasonably expect the use of cladribine orally administered as claimed to treat a progressive form of MS.

While Petitioner argues that “Alvarez-Gonzalez reported that ‘no disease activity’ was detected on MRI following cladribine treatment” (Pet. 39 (quoting Ex. 1009, 506)), the patient also did not have any “disease activity” after fingolimod treatment. *Compare* Ex. 1009, 508 (Fig. 2B), *with* Ex. 1009, 508 (Fig. 2D). Thus, any disease activity that cladribine may have addressed was inflammation arising from the ***rebound disease*** following cessation of fingolimod. *See id.*, 506. As such, there is nothing in Alvarez-Gonzalez to suggest that its subcutaneous, flat dosing method—let alone an oral, weight-based dosing method—would have been effective in treating a progressive form of MS.

Giovannoni does not remedy the deficiencies of Alvarez-Gonzalez. Giovannoni discloses a weight-based use of oral cladribine to treat patients with ***RRMS***. Ex. 1007, 417. However, Giovannoni does not disclose treating any progressive form of MS, and thus would not have led a POSA to reasonably expect the use of cladribine to treat a progressive form of MS, e.g., PPMS, as claimed in the method of claim 1.

For at least these reasons, Petitioner fails to establish that a POSA would have had any reasonable expectation of success in modifying Alvarez-Gonzalez's method based on Giovannoni's study to arrive at the method of claim 1.

2. Claims 2-6, 8-9, And 12 Would Not Have Been Obvious Over Alvarez-Gonzalez And Giovannoni

Claims 2-6, 8-9, and 12 depend directly or indirectly from claim 1 and would not have been obvious over Alvarez-Gonzalez and Giovannoni for at least the same reasons as claim 1.

3. Claims 14-16 And 18-20 Would Not Have Been Obvious Over Alvarez-Gonzalez And Giovannoni

Claim 14 recites, in pertinent part: “[a] method of treating a patient diagnosed as suffering from *a progressive form of Multiple Sclerosis* ... wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” Ex. 1001, 65:59-66:12. Claim 14 requires oral, weight-based dosing according to a particular recited regimen for cladribine administration. *Id.*

As described above for claim 1, a POSA would not have been motivated to treat PPMS as claimed because Alvarez-Gonzalez teaches flat, subcutaneous dosing of cladribine as “rescue therapy” *for a single patient* experiencing rebound disease after withdrawal of fingolimod and does not disclose clinical efficacy of cladribine for treating PPMS. Furthermore, as described above for claim 1,

Alvarez-Gonzalez acknowledged oral, weight-based dosing but instead adopted flat, subcutaneous dosing and touted “parenteral” administration. Accordingly, a POSA (particularly if they viewed Alvarez-Gonzalez as a “success” as asserted by Petitioner) would not have been motivated to modify Alvarez-Gonzalez’s method to adopt oral, weight-based dosing as claimed. In addition, Giovannoni does not disclose treatment of progressive MS, nor provide a reason to modify Alvarez-Gonzalez to use oral, weight-based dosing, which Alvarez-Gonzalez already acknowledged but did not adopt. *Supra*, Section V.A.1.

Thus, for the same reasons discussed above for claim 1, a POSA would not have been motivated to modify or combine the teachings of Alvarez-Gonzalez and Giovannoni to arrive at a method of treating a progressive form of MS as recited in claim 14, nor would a POSA have had any reasonable expectation of success in doing so. For at least these same reasons, claim 14 also would not have been obvious over Alvarez-Gonzalez and Giovannoni.

Claims 15-16 and 18-20 depend directly or indirectly from claim 14 and would not have been obvious over Alvarez-Gonzalez and Giovannoni for at least the same reasons as claim 14.

4. Claims 24-26 Would Not Have Been Obvious Over Alvarez-Gonzalez And Giovannoni

Claim 24 recites, in pertinent part, “[a] method of treating a patient suffering from a progressive form of Multiple Sclerosis[.]” Ex. 1001, 66:51-67:39. Claim 24 requires oral, weight-based dosing according to a particular recited regimen for cladribine administration. *Id.*

As described above, a POSA would not have been motivated to treat PPMS as claimed because Alvarez-Gonzalez teaches flat, subcutaneous dosing of cladribine as “rescue therapy” for a single patient experiencing rebound disease after withdrawal of fingolimod and does not disclose clinical efficacy of cladribine for treating PPMS. Furthermore, as described above for claim 1, Alvarez-Gonzalez acknowledged oral, weight-based dosing but instead adopted flat, subcutaneous dosing and touted “parenteral” administration. Accordingly, a POSA (particularly if they viewed Alvarez-Gonzalez as a “success” as asserted by Petitioner) would not have been motivated to modify Alvarez-Gonzalez’s method to adopt oral, weight-based dosing as claimed. In addition, Giovannoni does not disclose treatment of progressive MS, nor provide a reason to modify Alvarez-Gonzalez to use oral, weight-based dosing, which Alvarez-Gonzalez already acknowledged but did not adopt. *Supra*, Section V.A.1.

Thus, for the same reasons discussed above for claim 1, a POSA would not have been motivated to modify or combine the teachings of Alvarez-Gonzalez and Giovannoni to arrive at a method of treating a progressive form of MS as recited in claim 24, nor would a POSA have had any reasonable expectation of success in doing so. For at least these same reasons, claim 24 also would not have been obvious over Alvarez-Gonzalez and Giovannoni.

Claims 25-26 depend directly or indirectly from claim 24 and would not have been obvious over Alvarez-Gonzalez and Giovannoni for at least the same reasons as claim 24.

5. Claims 27 And 34 Would Not Have Been Obvious Over Alvarez-Gonzalez And Giovannoni

Claim 27 recites, in pertinent part: “[a] method of treating a patient suffering from *a progressive form of Multiple Sclerosis*, ... wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS)[.]” Ex. 1001, 67:48-68:64. Claim 27 requires oral, weight-based dosing according to a particular recited regimen for cladribine administration. *Id.*

As described above, a POSA would not have been motivated to treat PPMS as claimed because Alvarez-Gonzalez teaches flat, subcutaneous dosing of cladribine as “rescue therapy” for a single patient experiencing rebound disease

after withdrawal of fingolimod and does not disclose clinical efficacy of cladribine for treating PPMS. Furthermore, as described above for claims 1, 14, and 24, Alvarez-Gonzalez acknowledged oral, weight-based dosing but instead adopted flat, subcutaneous dosing and touted “parenteral” administration. Accordingly, a POSA (particularly if they viewed Alvarez-Gonzalez as a “success” as asserted by Petitioner) would not have been motivated to modify Alvarez-Gonzalez’s method to adopt oral, weight-based dosing as claimed. In addition, Giovannoni does not disclose treatment of progressive MS, nor provide a reason to modify Alvarez-Gonzalez to use oral, weight-based dosing, which Alvarez-Gonzalez already acknowledged but did not adopt. *Supra*, Sections V.A.1., V.A.3, and V.A.4.

Thus, for the same reasons discussed above for claim 1, a POSA would not have been motivated to modify or combine the teachings of Alvarez-Gonzalez and Giovannoni to arrive at a method of treating a progressive form of MS as recited in claim 27, nor would a POSA have had any reasonable expectation of success in doing so. For at least these same reasons, claim 27 also would not have been obvious over Alvarez-Gonzalez and Giovannoni.

Claim 34 depends from claim 27 and would not have been obvious over Alvarez-Gonzalez and Giovannoni for at least the same reasons as claim 27.

Thus, Petitioner fails to show that a POSA would have been motivated to use oral, weight-based administration of cladribine to treat a progressive form of

MS according to the methods of any of claims 1-6, 8-9, 12, 14-16, 18-20, 24-27, and 34, or that a POSA would have had a reasonable expectation of success in doing so. Accordingly, Ground I should not be instituted.

B. Ground II – Petitioner Has Not Established That Claims 11, 23, And 33 Would Have Been Obvious Over Alvarez-Gonzalez, Giovannoni, And Montalban

Ground II challenges claims 11, 23, and 33 as allegedly being obvious over Alvarez-Gonzalez, Giovannoni, and Montalban. Petitioner fails to show that Alvarez-Gonzalez, Giovannoni, and Montalban would have motivated a POSA to modify or combine the teachings of the prior art to arrive at the methods of using cladribine to treat a progressive form of MS as recited in claims 11, 23, or 33, or that a POSA would have had a reasonable expectation of success in doing so. For each reason, Ground II should not be instituted.

Claim 11 depends from claim 1, and further requires that “orally administering Cladribine is in one or two treatment years ... followed by at least one year in which no Cladribine is administered.” Ex. 1001, 65:44-48.

Claim 23 depends from claim 14, which recites cladribine administration over two years, and further requires that “after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years[.]” *Id.*, 65:59-66:12, 66:46-50.

Claim 33 depends from claim 27, which recites administration of cladribine treatment courses during two treatment years, and further requires that “wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.” *Id.*, 67:48-68:64, 69:20-23.

As discussed above in Sections V.A.1, V.A.3, and V.A.5, claims 1, 14, and 27 would not have been obvious over the combination of Alvarez-Gonzalez and Giovannoni at least because a POSA would not have been motivated to treat PPMS as claimed because Alvarez-Gonzalez teaches flat, subcutaneous dosing of cladribine as “rescue therapy” for a single patient experiencing rebound disease after withdrawal of fingolimod, and does not disclose clinical efficacy of cladribine for treating PPMS. Furthermore, as described above for claims 1, 14, and 27, Alvarez-Gonzalez acknowledged oral, weight-based dosing but instead adopted flat, subcutaneous dosing and touted “parenteral” administration. Accordingly, a POSA (particularly if they viewed Alvarez-Gonzalez as a “success” as asserted by Petitioner) would not have been motivated to modify Alvarez-Gonzalez’s method to adopt oral, weight-based dosing as claimed. In addition, Giovannoni does not disclose treatment of progressive MS, nor provide a reason to modify Alvarez-Gonzalez to use oral, weight-based dosing, which Alvarez-Gonzalez already acknowledged but did not adopt. *Supra*, Sections V.A.1, V.A.3, and V.A.5. Thus,

claims 1, 14, and 27 would not have been obvious over the combination of Alvarez-Gonzalez and Giovannoni. For at least the same reasons, claims 11, 23, and 33 would not have been obvious over the combination of Alvarez-Gonzalez and Giovannoni. Montalban does not remedy these deficiencies.

Like Ground I, Petitioner's Ground II is based on "substitut[ing] Alvarez-Gonzalez's subcutaneous cladribine with Giovannoni's oral cladribine ... administered in two treatment years ... to treat PPMS." Pet. 50. However, Montalban does not teach treatment of PPMS. Montalban discloses results from a two-year, randomized, double-blind Phase IIb study in patients suffering from RRMS or SPMS with ongoing relapses. Ex. 1006, 1. Ground II relies on Montalban simply as "report[ing] that 'the clinical benefits of' oral cladribine 'were maintained ... for 4 years or more without further active treatment,' and thus allegedly motivating a POSA to use an "extended cladribine-free period." Pet. 50-51 (quoting Ex. 1006, 1). Thus, Ground II's reliance on Montalban does not remedy the lack of motivation or reasonable expectation of success based on Alvarez-Gonzalez or Giovannoni described above. *See* Section V.A, *supra*.

Accordingly, for at least the same reasons set forth with respect to independent claims 1, 14, and 27 in Ground I, Ground II must fail for dependent claims 11, 23, and 33, respectively.

Claims 11, 23, and 33 would not have been obvious over Alvarez-Gonzalez, Giovannoni, and Montalban for the following additional reasons.

Claim 11 requires that “orally administering Cladribine is in one or two treatment years ... followed by at least one year in which no Cladribine is administered.” Ex. 1001, 65:44-48. Like claim 11, claims 23 and 33 also recite a period during which no cladribine is administered after a treatment course. Claim 23 recites, in pertinent part, “wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.” *Id.*, 66:46-50. Claim 33 recites, in pertinent part, “wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.” *Id.*, 69:20-23.

Petitioner argues that a POSA “would have been motivated to substitute Alvarez-Gonzalez’s subcutaneous cladribine with Giovannoni’s oral cladribine dose[] ... administered in two treatment years ... to treat PPMS.” Pet. 50. Petitioner relies on Montalban to provide “motivation” to “follow the two-year-long cladribine treatment [of Giovannoni] with one or two cladribine-free years” to treat PPMS as allegedly disclosed by Alvarez-Gonzalez, and a “reasonable expectation of success” in doing so, because “‘the clinical benefits’ of

Giovannoni's ... regimen 'were maintained ... for 4 years or more without further active treatment.'" *Id.*, 50-51 (quoting Ex. 1006, 1) (last alteration in original).

But neither Giovannoni nor Montalban reported results for PPMS patients.² And as discussed above, Alvarez-Gonzalez only used flat, subcutaneous dosing of cladribine to "rescue" one PPMS patient from rebound disease. *See* Section V.A.1, *supra*. With no established efficacy against PPMS in Alvarez-Gonzalez to begin with, it is not clear what clinical benefits would be "maintained" in additional cladribine-free years. Thus, Alvarez-Gonzalez, Giovannoni, and Montalban would not have motivated a POSA to adopt the method of claims 11, 23, or 33 with reasonable expectation of success.

For at least these additional reasons, claims 11, 23, and 33 would not have been obvious over Alvarez-Gonzalez, Giovannoni, and Montalban.

² Giovannoni was focused on RRMS patients and, as described in more detail below in Section V.C, Montalban does not disclose treating patients with a progressive form of MS that does not include early SPMS, as required by claims 11, 23, and 33.

C. Ground III – Petitioner Has Not Established That Claims 1-6, 8-9, 11-12, 14-16, 18-20, 23-27, 30, And 33-34 Would Have Been Obvious Over Clinicaltrials.gov, Schreiber, and Montalban

Ground III challenges claims 1-6, 8-9, 11-12, 14-16, 18-20, 23-27, 30, and 33-34 as allegedly being obvious over Clinicaltrials.gov (Ex. 1005), Schreiber (Ex. 1008), and Montalban. Petitioner fails to show that the combination of Clinicaltrials.gov, Schreiber, and Montalban would have motivated a POSA to modify the prior art as alleged to arrive at a method of using cladribine to treat a progressive form of MS as claimed with a reasonable expectation of success in doing so. For each reason, Ground III should not be instituted.

1. Claim 1 Would Not Have Been Obvious Over Clinicaltrials.gov, Schreiber, And Montalban

a) Petitioner Has Not Established Any Motivation To Combine Clinicaltrials.gov, Schreiber, And Montalban To Arrive At Challenged Claim 1

Petitioner fails to establish why a POSA would have been motivated to combine the study of Montalban based on the protocol of Clinicaltrials.gov and the cladribine tablets of Schreiber—none of which discloses treating a progressive form of MS as claimed—to treat SPMS or any progressive form of MS that does not include early SPMS, as recited in the method of claim 1.

As an initial matter, Montalban is an abstract that refers to RRMS and SPMS patients with “ongoing relapses,” but Montalban does not disclose—nor does Petitioner show—treatment of SPMS or any progressive form of MS excluding

early SPMS, as required by claim 1. While Petitioner asserts that the “SPMS [patients] with ongoing relapses” are “SPMS-active” patients (Pet. 53), this does not exclude early SPMS patients. Even Petitioner argues—and Dr. Miller opines—that patients in “each of RRMS, ESPMS, and SPMS could exhibit disease activity (relapses).” *Id.*, 17; Ex. 1002, ¶34. Thus, the presence of relapsing “activity” and the identification of “SPMS-active” patients would not exclude early SPMS patients experiencing relapses. Indeed, as described above, early SPMS is part of SPMS. *See* Section IV, *supra*.

Petitioner also argues that a POSA would have been motivated to treat “a fully transitioned SPMS patient with disease activity” (Pet. 52), but Montalban does not identify any such “fully transitioned SPMS” patients—Montalban only generally refers to “SPMS [patients] with ongoing relapses[.]” *See* Ex. 1006, 1. Indeed, Montalban’s “Conclusions” are focused on RRMS, stating that “[t]hese results support the demonstrated efficacy of cladribine tablets in RRMS shown in CLARITY.” *Id.* Montalban’s study included RRMS and SPMS patients but only “14.5 [percent] of patients (N=172) had SPMS at baseline.” *Id.* Montalban does not specify what the results were for SPMS patients as opposed to the total patient population, the vast majority of which was RRMS. Montalban also states that “the study was not powered for” an EDSS endpoint and “[t]he proportion of patients with confirmed EDSS progression over 2 years was not significantly different for

cladribine 3.5mg/kg plus IFN- β vs. placebo plus IFN- β ,” before concluding that the “results support the demonstrated efficacy of cladribine tablets in RRMS.” *Id.* As such, Montalban does not motivate a POSA to treat progressive MS excluding early SPMS according to the claimed methods.

Neither Clinicaltrials.gov nor Schreiber remedies Montalban’s deficiencies. Clinicaltrials.gov provides an overview of the proposed protocol of the ONWARD study, which included RRMS patients and SPMS patients having relapses, but does not disclose excluding early SPMS patients or provide any results. Ex. 1005, 7. Petitioner also admits that “neither Clinicaltrials.gov nor Montalban taught a specific dosage form,” but argues that “POSAs would have used Schreiber’s 10-mg cladribine tablets because the tablets ‘allow for a very convenient short-course annual dosing regimen.’” Pet. 53 (quoting Ex. 1008, 324). However, with respect to progressive MS, Petitioner relies on Schreiber’s alleged disclosure of studies, e.g., by Sipe (Ex. 1025) and Rice (Ex. 1036), in which “cladribine treated disease activity in progressive MS.” Pet. 53-54. These studies did not use 10 mg oral tablets. *See* Ex. 1008, 319; Ex. 1025, 9 (patients received cladribine “given through a surgically implanted central line.”), 10; Ex. 1036, 1146 (cladribine was “administered by subcutaneous (SC) injection in patients with progressive MS”); *see also* Ex. 1058, 1716 (“Cladribine or placebo was administered monthly on an outpatient basis by 7-day i.v. infusions through a central venous catheter[.]”).

Further, most of the progressive MS studies referenced in Schreiber used significantly higher doses of cladribine than the claimed oral dosing of 1.5 mg/kg to 4.0 mg/kg, as recited in claim 1. *See* Ex. 1008, 319, 325. Sipe discloses “four monthly courses of 0.7 mg/kg cladribine,” i.e., 2.8 mg/kg, administered via a “surgically implanted central line” (Ex. 1025, 9) and Beutler discloses the same 2.8 mg/kg intravenous dose of cladribine (Ex. 1058, 1716 (“patients were given cladribine 0.10 mg/kg per day for 7 days as four monthly courses for a total of 2.8 mg/kg or placebo.”)). And while Rice discloses subcutaneous cladribine doses of 0.7 and 2.1 mg/kg, Rice reported that “clinical efficacy was not shown” for these doses. Ex. 1008, 1146 (“Patients received six courses of cladribine 0.07 mg/kg/day SC for 5 consecutive days (total dose, 2.1 mg/kg), followed by two courses of placebo or two courses of cladribine 0.07 mg/kg/day SC for 5 consecutive days (total dose, 0.7 mg/kg), followed by six courses of placebo”), 1153 (“clinical efficacy was not shown in this trial”). Thus, Petitioner fails to show that Schreiber teaches studying 10 mg oral cladribine tablets in progressive MS. Instead, Petitioner simply combines selected elements of the prior art in hindsight. Additionally, the majority of the cladribine doses used in the progressive MS studies identified in Schreiber (intravenous or subcutaneous 2.1 or 2.8 mg/kg, administered over four or six months), in view of the 42% bioavailability for oral cladribine disclosed by Alvarez-Gonzalez, would

correspond to at least 5.0 mg/kg oral dose ($2.1 \text{ mg/kg} / 42\% = 5.0 \text{ mg/kg}$), which is greater than an oral dose of 1.5-4 mg/kg per treatment year as claimed. Further, like Montalban and Clinicaltrials.gov, Schreiber does not disclose treating SPMS that excludes early SPMS. Thus, Clinicaltrials.gov and Schreiber do not establish motivation to treat a progressive form of MS according to the claimed methods.

Petitioner thus offers no adequate rationale for why a POSA considering Montalban, Clinicaltrials.gov, and Schreiber would have been motivated to arrive at the method of using cladribine to treat a progressive form of MS that does not include early SPMS, as recited in claim 1.

b) Petitioner Has Not Established Any Reasonable Expectation Of Success In Combining Clinicaltrials.gov, Schreiber, And Montalban To Arrive At Challenged Claim 1

Petitioner argues that a POSA would have reasonably expected that the dosing protocol of Clinicaltrials.gov (i.e., 1.75 mg/kg/year) “would successfully treat SPMS because Montalban ... ‘demonstrated significant efficacy benefits’” in SPMS patients with ongoing relapses using the same dosing protocol, and that such “success was confirmed” by Schreiber. Pet. 53 (quoting Ex. 1006, 1). But as discussed above (Section V.C.1.a), Montalban focuses its conclusions on RRMS and does not teach treating a progressive form of MS that does not include early SPMS. *See* Ex. 1006, 1 (referring only generally to SPMS patients; “[t]he

proportion of patients with confirmed EDSS progression over 2 years was not significantly different for cladribine 3.5mg/kg plus IFN- β vs. placebo plus IFN- β ”; “results support the demonstrated efficacy of cladribine tablets in RRMS”).

Indeed, Montalban does not report results based on MS type, the vast majority of which was RRMS, and instead reports results in aggregate. *See id.* (“14.5 [percent] of patients (N=172) had SPMS at baseline.”). Further, Schreiber does not provide any reasonable expectation of success in using the dosing protocol of Clinicaltrials.gov with 10 mg oral cladribine tablets to treat a progressive form of MS as claimed because, as discussed above, the progressive MS studies disclosed in Schreiber (1) did not use 10 mg oral tablets and (2) administered significantly higher doses of cladribine via an entirely different dosing method (e.g., 2.8 mg/kg intravenous, which would correspond to over 5.0 mg/kg oral³) or otherwise reported “clinical efficacy was not shown[.]” *See* Section V.C.1.a, *supra*.

Clinicaltrials.gov does not disclose any results of clinical efficacy at all, and thus also does not provide reasonable expectation of success with the claimed methods.

³ Based on the 42% bioavailability for oral cladribine disclosed by Alvarez-Gonzalez: (2.8 mg/kg / 42%) = 6.7 mg/kg. *See* Ex. 1009, 509.

Thus, the combination of Clinicaltrials.gov, Schreiber, and Montalban does not provide a POSA with reasonable expectation of success in achieving the method recited in claim 1.

For at least these reasons, Petitioner fails to establish that claim 1 would have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

2. Claims 2-6, 8-9, And 11-12 Would Not Have Been Obvious Over Clinicaltrials.gov, Schreiber, And Montalban

Claims 2-6, 8-9, and 11-12 depend directly or indirectly from claim 1 and would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban for at least the same reasons as claim 1.

3. Claims 14-16, 18-20, And 23 Would Not Have Been Obvious Over Clinicaltrials.gov, Schreiber, And Montalban

Claim 14 recites, in pertinent part: “[a] method of treating a patient diagnosed as suffering from *a progressive form of Multiple Sclerosis* ... wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” Ex. 1001, 65:59-66:12. Claim 14 requires oral, weight-based dosing according to a particular recited regimen for cladribine administration. *Id.*

As described above for claim 1, Petitioner’s Ground III does not establish that a POSA would have been motivated to treat a progressive form of MS as claimed or have a reasonable expectation of success in doing so, including because

Montalban focuses its conclusions on RRMS and does not teach treating a progressive form of MS that does not include early SPMS. Montalban does not specify what the results were for SPMS patients as opposed to the total patient population, the vast majority of which was RRMS. Montalban also states that “the study was not powered for” an EDSS endpoint and “[t]he proportion of patients with confirmed EDSS progression over 2 years was not significantly different for cladribine 3.5mg/kg plus IFN- β vs. placebo plus IFN- β ,” before concluding that the “results support the demonstrated efficacy of cladribine tablets in RRMS.” Ex. 1006, 1. Accordingly, Montalban does not motivate a POSA to treat progressive MS excluding early SPMS according to the claimed methods. Furthermore, as described above for claim 1, the progressive MS studies disclosed in Schreiber (1) did not use 10 mg oral tablets and (2) administered significantly higher doses of cladribine via an entirely different dosing method (e.g., 2.8 mg/kg intravenous, which would correspond to over 5.0 mg/kg oral) or otherwise reported “clinical efficacy was not shown.” *See* Section V.C.1, *supra*. Schreiber also does not disclose treating SPMS that excludes early SPMS. In addition, Clinicaltrials.gov does not disclose excluding early SPMS patients or provide any results of clinical efficacy at all. As such, Clinicaltrials.gov and Schreiber do not provide a reason to combine the study of Montalban based on the protocol of Clinicaltrials.gov and the cladribine tablets of Schreiber. *See id.* Thus, for the same reasons as discussed

above for claim 1, a POSA would not have been motivated to modify or combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to arrive at a method of treating a progressive form of MS as recited in claim 14, nor would a POSA have had any reasonable expectation of success in doing so. For at least these same reasons, claim 14 also would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

Claims 15-16, 18-20, and 23 depend directly or indirectly from claim 14 and would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban for at least the same reasons as claim 14.

4. Claims 24-26 Would Not Have Been Obvious Over Clinicaltrials.gov, Schreiber, And Montalban

Claim 24 recites, in pertinent part, “[a] method of treating a patient suffering from *a progressive form of Multiple Sclerosis*[.]” Ex. 1001, 66:51-67:39. Claim 24 requires oral, weight-based dosing according to a particular recited regimen for cladribine administration. *Id.*

As described above for claims 1 and 14, Petitioner’s Ground III does not establish that a POSA would have been motivated to treat a progressive form of MS as claimed or have a reasonable expectation of success in doing so, including because Montalban focuses its conclusions on RRMS. Montalban does not specify what the results were for SPMS patients as opposed to the total patient population,

the vast majority of which was RRMS. Montalban also states that “the study was not powered for” an EDSS endpoint and “[t]he proportion of patients with confirmed EDSS progression over 2 years was not significantly different for cladribine 3.5mg/kg plus IFN- β vs. placebo plus IFN- β ,” before concluding that the “results support the demonstrated efficacy of cladribine tablets in RRMS.” Ex. 1006, 1. Accordingly, Montalban does not motivate a POSA to treat progressive MS according to the claimed methods. Furthermore, as described above for claims 1 and 14, the progressive MS studies disclosed in Schreiber (1) did not use 10 mg oral tablets and (2) administered significantly higher doses of cladribine via an entirely different dosing method (e.g., 2.8 mg/kg intravenous, which would correspond to over 5.0 mg/kg oral) or otherwise reported “clinical efficacy was not shown.” *See* Sections V.C.1 and V.C.3, *supra*. In addition, Clinicaltrials.gov does not provide any results of clinical efficacy at all. As such, Clinicaltrials.gov and Schreiber do not provide a reason to combine the study of Montalban based on the protocol of Clinicaltrials.gov and the cladribine tablets of Schreiber. *See id.* Thus, for the reasons as discussed above for claims 1 and 14, a POSA would not have been motivated to modify or combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to arrive at a method of treating a progressive form of MS as recited in claim 24, nor would a POSA have had any reasonable expectation of

success in doing so. For at least these same reasons, claim 24 also would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

Claims 25-26 depend directly or indirectly from claim 24 and would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban for at least the same reasons as claim 24.

5. Claims 27, 30, And 33-34 Would Not Have Been Obvious Over Clinicaltrials.gov, Schreiber, And Montalban

Claim 27 recites, in pertinent part: “[a] method of treating a patient suffering from *a progressive form of Multiple Sclerosis*, ... wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS)[.]” Ex. 1001, 67:48-68:64. Claim 27 requires oral, weight-based dosing according to a particular recited regimen for cladribine administration. *Id.*

As described above for claims 1, 14, and 24, Petitioner’s Ground III does not establish that a POSA would have been motivated to treat a progressive form of MS as claimed or have a reasonable expectation of success in doing so, including because Montalban focuses its conclusions on RRMS and does not teach treating a progressive form of MS that does not include early SPMS. Montalban does not specify what the results were for SPMS patients as opposed to the total patient population, the vast majority of which was RRMS. Montalban also states that “the

study was not powered for” an EDSS endpoint and “[t]he proportion of patients with confirmed EDSS progression over 2 years was not significantly different for cladribine 3.5mg/kg plus IFN- β vs. placebo plus IFN- β ,” before concluding that the “results support the demonstrated efficacy of cladribine tablets in RRMS.” Ex. 1006, 1. Accordingly, Montalban does not motivate a POSA to treat progressive MS excluding early SPMS according to the claimed methods. Furthermore, as described above for claims 1, 14, and 24, the progressive MS studies disclosed in Schreiber (1) did not use 10 mg oral tablets and (2) administered significantly higher doses of cladribine via an entirely different dosing method (e.g., 2.8 mg/kg intravenous, which would correspond to over 5.0 mg/kg oral) or otherwise reported “clinical efficacy was not shown.” See Sections V.C.1, V.C.3, and V.C.4, *supra*. Schreiber also does not disclose treating SPMS that excludes early SPMS. In addition, Clinicaltrials.gov does not disclose excluding early SPMS patients or provide any results of clinical efficacy at all. As such, Clinicaltrials.gov and Schreiber do not provide a reason to combine the study of Montalban based on the protocol of Clinicaltrials.gov and the cladribine tablets of Schreiber. See *id.* Thus, for the same reasons as discussed above for claims 1, 14, and 24, a POSA would not have been motivated to modify or combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to arrive at a method of treating a progressive form of MS as recited in claim 27, nor would a POSA have had any reasonable expectation

of success in doing so. For at least these same reasons, claim 27 also would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

Claims 30 and 33-34 depend from claim 27 and would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban for at least the same reasons as claim 27.

Claim 30 would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban for the following additional reasons. Claim 30 recites, “the progressive form of Multiple Sclerosis is ***Secondary Progressive Multiple Sclerosis***.” Ex. 1001, 69:9-11. Based on its dependency from claim 27, claim 30 also excludes patients with early SPMS. As described above, Montalban does not teach treating SPMS that does not include early SPMS. *See* Section V.C.1, *supra*. Petitioner’s arguments relating to PPMS studies referenced in Schreiber (Pet. 62 (citing Pet. Section X.A)) are inapplicable to claim 30, which is limited to SPMS that does not include early SPMS. Further, Schreiber does not teach or suggest using cladribine to treat SPMS that does not include early SPMS. As discussed above in Section V.C.1, Schreiber discloses studies on progressive MS patients; however, nothing in Schreiber suggests the exclusion of early SPMS patients.

In addition, Clinicaltrials.gov does not teach or suggest treating SPMS patients with exclusion of early SPMS patients, as required by claim 30. Thus, for at least these additional reasons, Clinicaltrials.gov, Schreiber, and Montalban, even

in combination, fail to teach all the limitations of claim 30 and thus Petitioner's Ground III regarding claim 30 must fail. Additionally, Clinicaltrials.gov, Schreiber, and Montalban, even in combination, would not have motivated a POSA to modify or combine their teachings to arrive at the method of treating SPMS patients with the exclusion of early SPMS patients, as required by claim 30, nor provided a reasonable expectation of success in doing so.

For at least these additional reasons, claim 30 would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

6. Claims 11, 23, And 33 Would Not Have Been Obvious Over Clinicaltrials.gov, Schreiber, And Montalban

Claims 11, 23, and 33 also would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban because Petitioner fails to show that a POSA would have been motivated by Montalban to include a cladribine-free period after one or two treatment years, to arrive at the dosing regimen recited in claims 11, 23, and 33, or have any reasonable expectation of success in doing so.

Claims 11, 23, and 33 recite a period during which no Cladribine is administered after a treatment course. Claim 11 depends from claim 1, and further requires that "orally administering Cladribine is in one or two treatment years ... followed by at least one year in which *no Cladribine is administered.*" Ex. 1001, 65:44-48. Claim 23 depends from claim 14, which recites cladribine

administration over two years, and further requires that “after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years[.]” *Id.*, 65:59-66:12, 66:46-50. Claim 33 depends from claim 27, which recites administration of cladribine treatment courses during two treatment years, and further requires that “wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.” *Id.*, 67:48-68:64, 69:20-23.

As described above in Sections V.C.1, V.C.3, and V.C.5, claims 1, 14, and 27 would not have been obvious over the combination of Clinicaltrials.gov, Schreiber, and Montalban because Petitioner’s Ground III does not establish that a POSA would have been motivated to treat a progressive form of MS as claimed, or have a reasonable expectation of success in doing so, including because Montalban focuses its conclusions on RRMS and does not teach treating a progressive form of MS that does not include early SPMS. Montalban does not specify what the results were for SPMS patients as opposed to the total patient population, the vast majority of which was RRMS. Montalban also states that “the study was not powered for” an EDSS endpoint and “[t]he proportion of patients with confirmed EDSS progression over 2 years was not significantly different for cladribine 3.5mg/kg plus IFN- β vs. placebo plus IFN- β ,” before concluding that the “results

support the demonstrated efficacy of cladribine tablets in RRMS.” Ex. 1006, 1.

Accordingly, Montalban does not motivate a POSA to treat progressive MS excluding early SPMS according to the claimed methods. Furthermore, as described above for claims 1, 14, and 27, the progressive MS studies disclosed in Schreiber (1) did not use 10 mg oral tablets and (2) administered significantly higher doses of cladribine via an entirely different dosing method (e.g., 2.8 mg/kg intravenous, which would correspond to over 5.0 mg/kg oral) or otherwise reported “clinical efficacy was not shown.” *See* Sections V.C.1, V.C.3, and V.C.5, *supra*. Schreiber also does not disclose treating SPMS that excludes early SPMS. In addition, Clinicaltrials.gov does not disclose excluding early SPMS patients or provide any results of clinical efficacy at all. As such, Clinicaltrials.gov and Schreiber do not provide a reason to combine the study of Montalban based on the protocol of Clinicaltrials.gov and the cladribine tablets of Schreiber. *See id.* Thus, for the reasons as discussed above, a POSA would not have been motivated to modify or combine the teachings of Clinicaltrials.gov, Schreiber, and Montalban to arrive at a method of treating a progressive form of MS as recited in claims 1, 14, and 27, nor would a POSA have had any reasonable expectation of success in doing so. For at least these same reasons, claims 11, 23, and 33 also would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

Claims 11, 23, and 33 would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban for the following additional reasons.

Petitioner argues that a POSA would have been motivated to include a cladribine-free period after cladribine treatment because Montalban discloses that “the clinical benefits” of Giovannoni’s regimen “were maintained ... for 4 years or more without further active treatment.” Pet. 57 (quoting Ex. 1006, 1). However, Giovannoni’s study was limited to RRMS patients, so any benefits “maintained” in Giovannoni’s study were for RRMS patients, not for progressive MS patients as claimed. Ex. 1007, 416. And Montalban does not teach any benefits that were “maintained” for its SPMS patients, or any progressive MS patients, in a cladribine-free period. Instead, Montalban discloses that benefits were maintained for the CLARITY extension study, which was limited to RRMS patients. Ex. 1006, 1. Thus, Montalban would not have motivated a POSA to include a cladribine-free period after one or two treatment years in treating progressive patients as recited by claims 11, 23, and 33, nor would Montalban have led a POSA to reasonably expect success in doing so.

Further, neither Clinicaltrials.gov nor Schreiber discloses any alleged “clinical benefits” of cladribine during non-treatment years. Petitioner cites to Clinicaltrials.gov to disclose “a two-year-long cladribine treatment” (Pet. 57) but Clinicaltrials.gov does not disclose any cladribine-free period. Instead,

Clinicaltrials.gov discloses that subjects will receive a “total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks” and that those “who will complete the DB period will to [sic] enter in open label (OL) extension period, [and] if they meet the eligibility criteria they will be *given total cladribine* dose of 3.5 mg/kg over 48 weeks.” Ex. 1005, 11 (“Assigned Interventions” for the “Cladribine 3.5 mg/kg, IFN-beta” arm). Thus, Clinicaltrials.gov discloses 96 weeks plus 48 weeks, or *three years*, of cladribine dosing without any cladribine-free period, and does not describe a cladribine-free period that is “at least one year,” during the “1 or 2 years” after treatment, or during “years 3 and 4” as claimed.

Schreiber identifies the CLARITY and CLARITY extension studies for “[t]reatment of RRMS[.]” Ex. 1008, 320. However, Schreiber does not disclose any “clinical benefits” of cladribine during the placebo (i.e., non-treatment) year after two years of treatment. Thus, Clinicaltrials.gov, Schreiber, and Montalban would not have motivated a POSA to modify or combine the prior art’s teachings to arrive at the method of claims 11, 23, or 33, nor would a POSA have had any reasonable expectation of success in doing so.

For at least these additional reasons, claims 11, 23, and 33 would not have been obvious over Clinicaltrials.gov, Schreiber, and Montalban.

VI. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

Patent Owner reserves the right to argue objective indicia at a later stage in this proceeding, should the Board institute trial.

VII. CONCLUSION

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

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

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response contains 10,554 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. §42.24(d), excluding the parts exempted from the word count by 37 C.F.R. §42.24(a)(1).

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

CERTIFICATE OF SERVICE

I hereby certify that on May 17, 2023, I caused a true and correct copy of the following materials:

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