

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

ARES TRADING S.A.,
Patent Owner.

Case IPR2023-00482
U.S. Patent No. 10,849,919

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,849,919**

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1007	Giovannoni, G., et al., “A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis,” <i>The New England Journal of Medicine</i> , 362 (5), (Feb. 4, 2010), with attached supplementary appendix. (“Giovannoni”)
1008	Schreiber, K., et al., “Cladribine in the Treatment of Multiple Sclerosis,” <i>Clinical Investigation</i> , 1 (2), (2011). (“Schreiber”)
1009	Alvarez-Gonzalez, C., et al., “Cladribine to Treat Disease Exacerbation after Fingolimod Discontinuation in Progressive Multiple Sclerosis,” <i>Annals of Clinical and Translational Neurology</i> , 4 (7), (March 17, 2017). (“Alvarez-Gonzalez”)
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1066	Archived Clinicaltrials.gov Pages for NCT00213135 “CLARITY - Safety and Efficacy of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (MS),” ClinicalTrials.gov, captured by Wayback Machine on Jul. 3, 2013 (pp. 6-8), with Affidavit of Nathaniel E. Frank-White (pp. 1-3, 9)
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TABLE OF ABBREVIATIONS

Abbreviation	Definition
MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
ESPMS	Early secondary progressive multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
CNS	Central nervous system

I. STATEMENT UNDER 37 C.F.R. § 42.22(A)

Hopewell Pharma Ventures, Inc. (“Hopewell”) petitions for *inter partes* review, seeking cancellation of claims 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, and 33-34 of U.S. Patent No. 10,849,919 (EX1001, “the ’919 patent”), originally assigned to Merck Patent GmbH. The patent is currently assigned to Ares Trading S.A., a wholly owned subsidiary of Merck KGaA (collectively, “Merck”). The challenged claims are unpatentable under 35 U.S.C. § 103. This Petition is supported by the declaration of Dr. Aaron Miller, M.D. (EX1002), an expert in multiple sclerosis.

II. INTRODUCTION

The claims encompass methods of treating a progressive form of multiple sclerosis (“MS”) comprising orally administering cladribine “at fixed dose per patient, per body weight and per treatment year,” wherein the fixed dose is “in a range of 1.5 mg/kg to 4.0 mg/kg,” and wherein the progressive form of MS “does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).” EX1001, 64:45-57. The prior art would have rendered such methods obvious.

MS is a chronic autoimmune disease with no known cure. EX1061, 263; EX1002, ¶15. Before 2017, the clinical course of MS was known to follow a variable pattern over time, and was characterized by either relapses (episodic acute periods of worsening), gradual progressive deterioration of neurologic function, or

both. EX1014, 907; EX1002, ¶15. These clinical courses were categorized into five different forms: relapsing-remitting (“RRMS”), “early secondary progressive” (“ESPMS”), secondary progressive (“SPMS”), primary progressive (“PPMS”), and progressive relapsing (“PRMS”). *Id.*, 908-910; EX1002, ¶¶15-16. While PPMS and PRMS were known to each be progressive “from onset,” SPMS was categorized as a stage of MS where an initial RRMS disease course is “followed by progression.” EX1014, 908; EX1002, ¶15. Because there were, and are, “no clear” criteria to determine when a patient transitioned between RRMS and SPMS, the field referred to the transitional period as a distinct form: ESPMS. EX1013, 280; EX1016, 62-63; EX1017, 278, FIG. 1; EX1002, ¶¶15, 34.

All five MS forms were known to involve immune cells called T- and B-lymphocytes that attack the nerves in the central nervous system (“CNS”), causing inflammation. EX1020, 1593-1594, 1597; EX1002, ¶¶16,37-42. It was also well-known that in all forms of MS, the inflammatory processes created areas of damage to the nerves, called lesions. EX1020, 1593; EX1002, ¶¶16,40. Newly created and actively inflamed lesions typically caused relapses or acute exacerbations of symptoms (“disease activity”), whereas the accumulation of damage and the slow expansion of existing lesions caused the insidious progression of clinical symptoms (“disease progression”). EX1013, 280; EX1020, 1593-1594; EX1002, ¶¶16,40-41. While disease activity was generally associated

with RRMS, and disease progression was generally associated with SPMS, PPMS, and PRMS, it was also well known that SPMS, PPMS, and PRMS also involve disease activity in some patients. EX1013, 280; EX1016, 63; EX1020, 1597; EX1002, ¶16. Patients with PPMS or SPMS with disease activity were referred to as “PP-active” or “SPMS-active.” EX1013, 280, 282; EX1002, ¶16.

Numerous prior art references taught that cladribine, including oral cladribine, was effective in treating disease activity in all forms of MS. EX1002, ¶¶43-45. For example, **Giovannoni** (EX1007) and **Schreiber** (EX1008) taught that orally administered cladribine, in a fixed dose of 1.75 mg/kg/year, was effective in treating disease activity in RRMS (the CLARITY trial). They also taught that oral cladribine was “convenient” and addressed issues stemming from prior parenteral cladribine dosage forms, such as treatment adherence. EX1008, 317, 324; EX1002, ¶17. The Clinicaltrials.gov website for the ONWARD trial (EX1005; “**Clinicaltrials.gov**”) and the inventor-authored **Montalban** (EX1006) taught the effective treatment of disease activity in RRMS and SPMS patients, using the same 1.75 mg/kg/year oral cladribine therapy disclosed in Giovannoni and Schreiber. EX1002, ¶17. **Alvarez-Gonzalez** (EX1009) reported successfully treating a PP-active patient using subcutaneous cladribine in a dosage that “resemble[d] bio-equivalence” with the oral one Giovannoni and Schreiber disclosed. EX1009, 509; EX1002, ¶17. Notably, during prosecution, Merck did not cite any of the art

teaching that disease activity may be present in each form of MS and that cladribine is effective in treating such activity, including in PP-active and SPMS-active, so the Examiner never considered it. EX1002, ¶73; *see generally* EX1004.

Given the state of the art, POSAs seeking to treat patients with a progressive form of MS with disease activity, including patients without ESPMS, would have chosen cladribine because of its demonstrated efficacy against such activity. EX1008, 319; EX1009, 509; EX1002, ¶49; *see also* EX1033; EX1036; EX1025; EX1058. POSAs would have further used oral cladribine, including the regimen at a fixed 1.75 mg/kg/year dose, because the prior art disclosed it was effective against disease activity and a preferred dosage form. EX1026, 2:9-13; EX1002, ¶52.

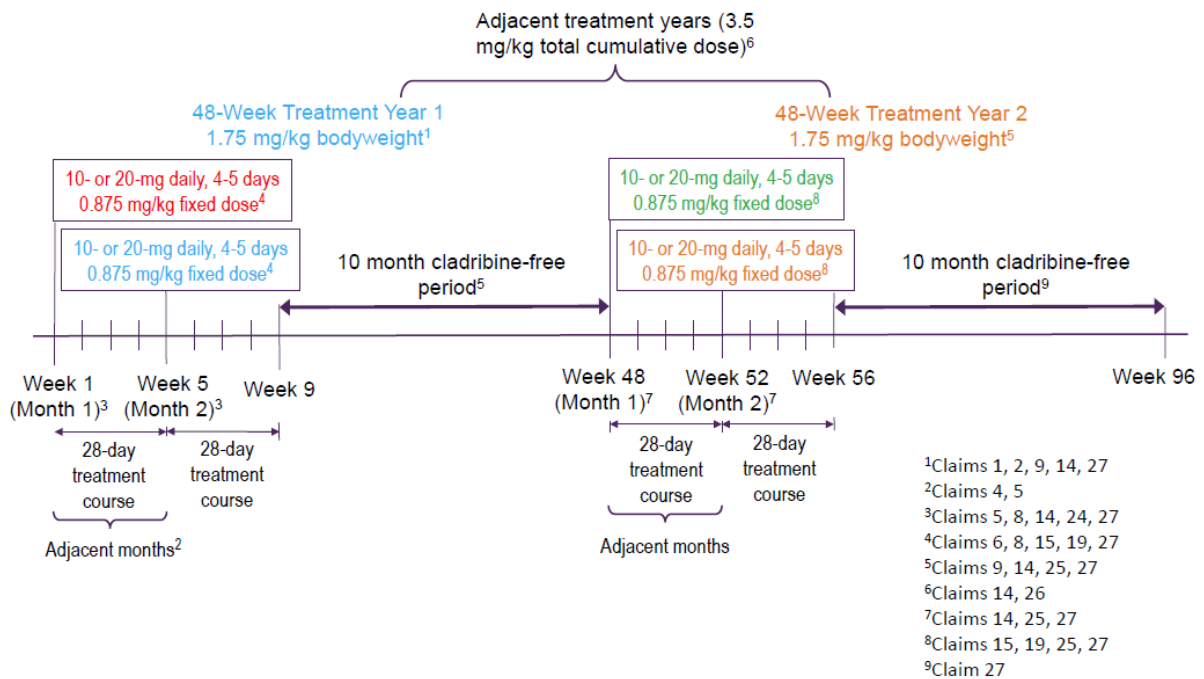
For example, POSAs would have been motivated to use cladribine to treat PPMS because Alvarez-Gonzalez disclosed successfully treating a PP-active patient with cladribine. EX1002, ¶18; EX1009, 506. POSAs would have also been motivated to substitute Alvarez-Gonzalez's subcutaneous cladribine with oral cladribine because it was well-known that oral dosage forms were preferred over subcutaneous ones. EX1007, Abstract; EX1002, ¶18. And POSAs would have selected Giovannoni's fixed 1.75 mg/kg/year oral dose and regimen—which was the same as the one later claimed in the '919 patent—because Alvarez-Gonzalez's subcutaneous dose “resemble[d] bioequivalence” with Giovannoni's oral dose,

arriving at claim 1. EX1009, 509; EX1002, ¶18. POSAs would have had a reasonable expectation that such oral cladribine would effectively treat PPMS because Alvarez-Gonzalez reported cladribine's efficacy in progressive MS. EX1009, 509; EX1002, ¶18.

Likewise, POSAs would have been motivated to use Clinicaltrials.gov's oral 1.75 mg/kg/year cladribine regimen to treat patients who had fully transitioned from RRMS to SPMS, and thus by definition did not have ESPMS, because Montalban reported "significant efficacy benefits" in SPMS-active patients with this very regimen. EX1005, 9-14; EX1006, 1; EX1002, ¶19. And, because Clinicaltrials.gov was silent regarding the specific strength of the oral cladribine tablets, POSAs would have been motivated to use Schreiber's 10-mg cladribine tablets because these tablets were "a very convenient" option. EX1008, 324; EX1002, ¶19. POSAs would have had a reasonable expectation that such oral cladribine would effectively treat SPMS because Montalban disclosed cladribine's efficacy in SPMS-active, thus arriving at claim 1. EX1006, 1; EX1002, ¶19.

The remaining challenged claims of the '919 patent add nothing more than aspects of the CLARITY dosing regimen disclosed in the prior art. EX1005, 11; EX1007, 417-418, Supplementary FIG. 1; EX1008, 320, 326; EX1002, ¶20. Dr. Miller prepared the following graphic summarizing how the claimed methods correspond to the 2-year-long dosing regimen disclosed in at least Giovannoni

(EX1002, ¶20):



Schematic 1.

Thus, the claimed methods would have been *prima facie* obvious to POSAs.

EX1002, ¶¶12-14.

Although the '919 patent alleges “new and surprisingly advantageous clinical results,” EX1001, 3:25-35, such assertions cannot overcome the strong *prima facie* obviousness showing here. EX1002, ¶21. The patent points to the results of Merck’s ONWARD study, stating that it “surprisingly” showed that the claimed method is “effective in the treatment of progressive forms of MS,” like PPMS and SPMS, “beyond” ESPMS. EX1001, 3:36-67. But Montalban already disclosed these very results and the prior art demonstrated there could have been

no surprise that the claimed methods would treat PPMS and SPMS with disease activity, “beyond” ESPMS. EX1002, ¶¶315-318. The claimed methods were not “unexpected” or inventive over the prior art. *Id.*

III. THE ’919 PATENT AND ITS PROSECUTION HISTORY

The ’919 patent issued on December 1, 2020, from U.S. Appl. No. 16/199,119, filed November 23, 2018, and claims priority to Provisional Application No. 62/590,442, filed November 24, 2017.¹

The ’919 patent provides a dosing regimen for using cladribine to treat progressive forms of MS, where the progressive forms of MS are SPMS, PPMS, and PRMS, but not ESPMS. EX1001, Abstract. EX1002, ¶¶69-70.

Claim 1 recites:

1. A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg, wherein the progressive form of Multiple Sclerosis is 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

¹ Petitioner does not concede that the ’919 patent is entitled to this date.

progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).

Id., 64:45-57; EX1002, ¶¶71,88,195. The remaining claims specify, e.g., the cumulative dose of cladribine, the number of tablets administered, the form of progressive MS treated, the patient's patient, etc. *Id.*, 64:58-65:8, 65:21-27, 65:44-51, 65:59-66:19, 66:28-40, 66:46-68:64, 69:9-11, 69:20-27; EX1002, ¶¶71-72.

Prosecution History: The Examiner initially rejected claims reciting “a progressive form of Multiple Sclerosis” using certain cladribine dosing regimens as anticipated by or obvious over De Luca (U.S. 8,377,903) (EX1010). EX1004, 333-338. Regarding claims 1 and 14 (and dependent claims), the Examiner found that De Luca “fairly taught” the claimed method of treating SPMS by orally administering 1.70 mg/kg cladribine in the first two months of a treatment year, followed by ten months without administering cladribine, followed by additional treatment years. *Id.*

Regarding independent claims 24 and 27 (and dependent claims), the Examiner correctly found that “these claims only distinguish over” claims 1 and 14, and dependent claims, “in that [they] set forth specific dosages of Cladribine to be administered in accordance with the specific body weight of a subject to be treated.” *Id.* However, because De Luca “fairly taught” that the cladribine dosage administered to an individual will vary depending upon a variety of factors, the

Examiner correctly concluded that “the therapeutic method of [] De Luca ... is clearly a result-effective variable that a practitioner of the art of neurobiology would find *prima facie* obvious to optimize.” *Id.*, 337-338.

Following this rejection, Merck “proposed avoiding De Luca [] by limiting the claims to the treatment of PPMS, SPMS and PRMS.” *Id.*, 326. The Examiner noted that “SPMS encompasses ‘early’ SPMS,” which was recited in claim 1 of De Luca, and thus “suggested that [Merck] ... exclude ‘early’ SPMS from the claimed method.” *Id.*

Merck then amended the claims corresponding to issued claims 1, 14, and 27 to recite that the progressive form of MS is selected from the group consisting of SPMS, PPMS, and PRMS, but does not include ESPMS. *Id.*, 301-314. Merck distinguished the different forms of MS and argued that: (a) SPMS “*does not include*” ESPMS (emphasis added) and (b) while De Luca referred to orally administering cladribine at amounts of 1.75 mg/kg and 3.5 mg/kg, “[t]he present application appears to be the only source of clinical data showing the efficacy of [clad]ribine on the progressive form of MS such as SPMS or PPMS patients.” *Id.*, 317-318.

But, Merck failed to disclose the prior art containing precisely such “clinical data.” EX1002, ¶74. For example, the inventor-authored Montalban provided the results of the ONWARD study showing the claimed cladribine regimen’s efficacy

in treatment of patients with “SPMS with ongoing relapses.” EX1006, 1; EX1002, ¶¶74, 215-216. And Alvarez-Gonzalez disclosed successfully treating a PPMS patient with activity using a subcutaneous cladribine dosing regimen that was modeled after and bioequivalent to the one later claimed in the ’919 patent. EX1009, 509; EX1002, ¶¶74, 92. Yet, Merck never disclosed these references during prosecution and the Examiner never considered them. *See generally* EX1004; EX1002, ¶74. Instead, the Examiner allowed the case without providing a specific reason for allowance. EX1004, 17-24.

IV. STATE OF THE ART BEFORE NOVEMBER 24, 2017

A. Multiple sclerosis is a chronic disease with a number of different forms that can each exhibit disease activity

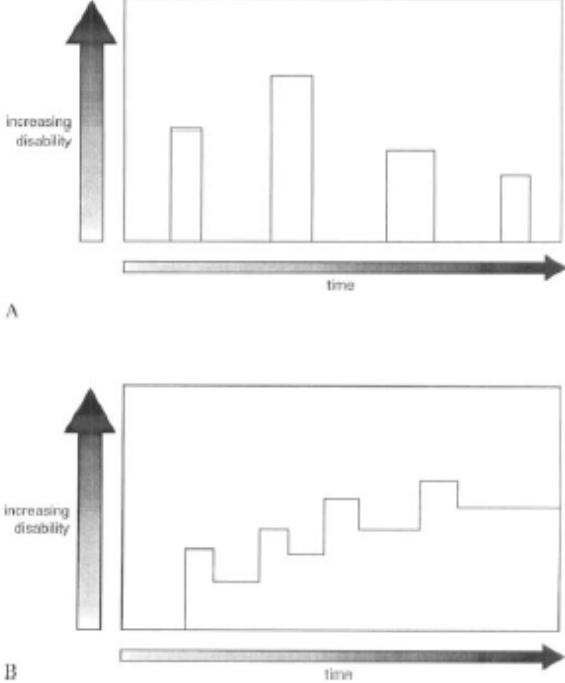
Multiple sclerosis (MS) is a chronic, inflammatory autoimmune disease of the CNS. EX1011, 115; EX1002, ¶25. MS is associated with certain cells in the immune system—e.g., T and B lymphocytes —damaging the myelin sheaths surrounding and protecting the axons² of the CNS nerve cells. EX1011, Abstract; EX1002, ¶25. This process creates lesions (areas where the myelin sheath is

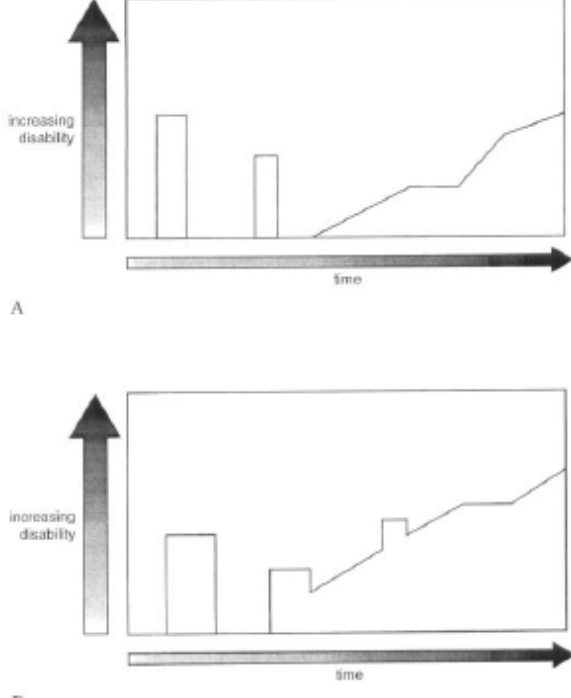
² An axon is a projection of a nerve cell that conducts electrical impulses to other nerve cells, and the myelin sheath is an insulating layer that surrounds the axon. EX1068, 75; EX1002, ¶25.

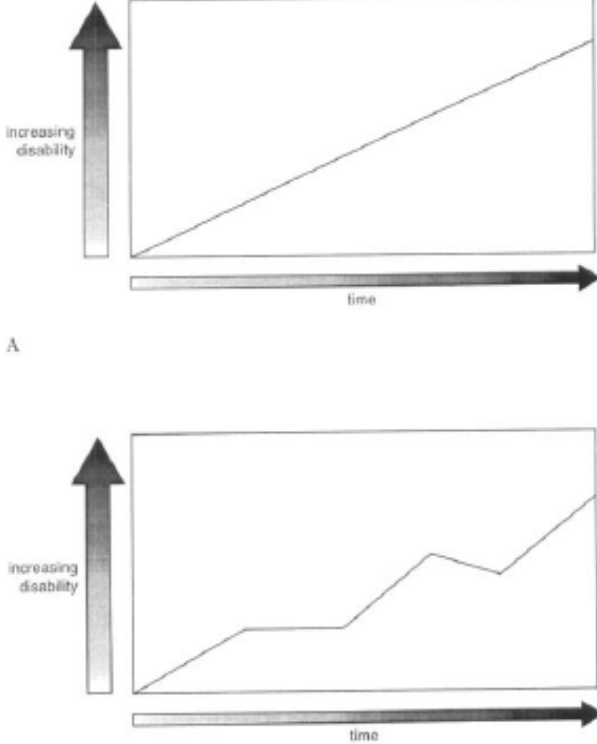
stripped off the nerves), which disrupt electrical conduction and cause clinical symptoms of MS. *Id.*

MS is diagnosed based on clinical symptoms (including muscle weakness, numbness, or pain or tingling in parts of the body) and objective “signs”, such as lesions detected on an MRI. EX1002, ¶26; EX1013, 279-280. The clinical course of MS follows a variable pattern over time, and is characterized by episodic acute periods of worsening (also called relapses or exacerbations), gradual progressive deterioration of neurologic function, or both. EX1014, 907; EX1002, ¶27.

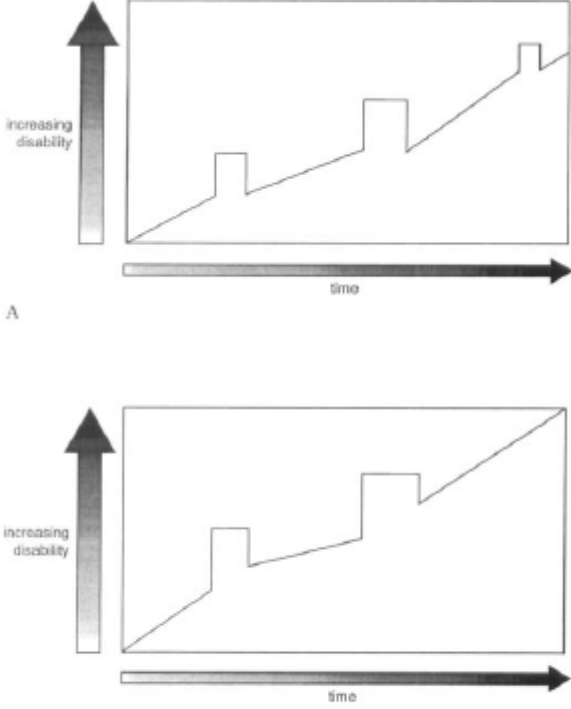
Historically, the field characterized clinical courses of MS into the forms summarized below:

MS Form and Definition	Illustration
Relapsing-Remitting (RRMS) “[C]learly defined disease relapses with full recovery or with sequelae and residual deficit... characterized by a lack of disease progression.”	 A B <i>Figure 1. Relapsing-remitting (RR) MS is characterized by clearly defined acute attacks with full recovery (A) or with sequelae and residual deficit upon recovery (B). Periods between disease relapses are characterized by lack of disease progression.</i>

MS Form and Definition	Illustration
Secondary Progressive (SPMS) “[I]nitial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus.”	 Figure 3. Secondary progressive (SP) MS begins with an initial RR course, followed by progression of variable rate (A) that may also include occasional relapses and minor remissions (B).

MS Form and Definition	Illustration
Primary Progressive (PPMS) “[D]isease progression from onset with occasional plateaus and temporary minor improvements allowed.”³	 A <i>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).</i>

³ PPMS and PRMS patients (unlike SPMS patients) do not initially exhibit an RRMS course because they show disease progression from “onset.” EX1014, 909; EX1002, ¶30.

MS Form and Definition	Illustration
Progressive Relapsing (PRMS) “[P]rogressive disease from onset, with clear acute relapses... characterized by continuing progression.”	 Figure 4 consists of two line graphs, A and B, illustrating the progression of disability over time in Progressive Relapsing Multiple Sclerosis (PRMS). Both graphs have a vertical axis labeled 'increasing disability' and a horizontal axis labeled 'time'. Graph A shows a line that starts at the origin and rises with a series of steps, representing acute relapses, followed by a continuous upward slope, indicating ongoing progression. Graph B shows a similar pattern of steps representing relapses, but the line returns to the baseline after each step, indicating full recovery after each relapse. The caption below the graphs states: 'Figure 4. Progressive-relapsing (PR) MS shows progression from onset but with clear acute relapses with (A) or without (B) full recovery.'

EX1014, 908-910, FIGs. 1-4; EX1002, ¶28.

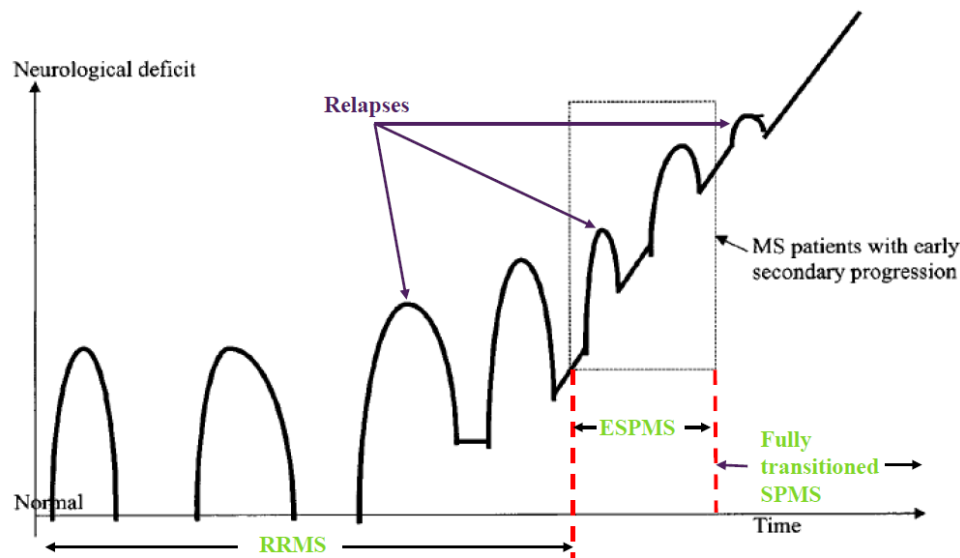
While RRMS is characterized by inflammation that gives rise to new active lesions, and SPMS and PPMS exhibit less acute, systemic inflammation and fewer “active lesions” than RRMS, SPMS and PPMS can also exhibit disease activity. EX1020, 1593, 1595; EX1002, ¶29; EX1014, 910; EX1009, 507; *see also* EX1013, 280; EX1019, Abstract. This is why, before 2017, the field added modifiers to indicate disease “activity” (i.e., “clinical assessment of relapse occurrence or lesion activity detected by CNS imaging,” associated with active or acute inflammation; modifier: “**active**”); and disease “progression” (i.e., “clinical evidence of disease

progression, independent of relapses, over a given period of time;” modifier:

“**progressive**”). EX1013, 280-281, 283, FIGs. 1-2; EX1019, Abstract, 785; EX1002, ¶¶31-32. Thus, it was known that each form of MS could exhibit disease activity, and PPMS or SPMS patients with activity were called “PP-active” or “SPMS-active”⁴. EX1013, 280-281; EX1002, ¶¶32-33.

There were “no clear” criteria for determining the exact point in time “when RRMS converts to SPMS.” EX1013, 280; EX1015, 77; EX1002, ¶34. Researchers in the field, including Merck, referred to this transition period as a distinct form of MS called “early secondary progressive” or “ESPMS.” *E.g.*, EX1016, 63; EX1018, 1655; EX1010, 1:19-22, 18:7-25; EX1002, ¶34. Dr. Miller annotated (in green and red) a figure published in Skurkovich to illustrate how POSAs understood the concept of ESPMS:

⁴ PRMS was eliminated and was re-classified as “PP-active.” EX1013, 280; EX1002, ¶32.



EX1017, 278; EX1002, ¶34.

The figure also illustrates, and POSAs would have understood, that each of RRMS, ESPMS, and SPMS could exhibit disease activity (relapses). EX1017, 278; EX1002, ¶34.

Before 2017, POSAs would have understood that an MS patient with PPMS, including PP-active, cannot by definition have ESPMS because ESPMS is the transition state between RRMS and SPMS, while a patient with PPMS never exhibited RRMS. EX1014, 908-910, FIG. 2; EX1002, ¶34. Similarly, an MS patient with SPMS, including SPMS-active, who has fully transitioned from RRMS to SPMS by definition cannot have the distinct transitional ESPMS form. EX1017, 278; EX1002, ¶34.

Thus, before the '919 patent was filed, POSAs knew that the different MS forms could be classified as RRMS, ESPMS, SPMS, PPMS, and PRMS, and that

each of these forms could exhibit disease activity. *See* EX1002, ¶34.

B. Cladribine was known to be effective against disease activity

Cladribine is an immunosuppressive drug that “caused prolonged, profound suppression of [T- and B-lymphocytes]” associated with the disease process in MS. EX1024, 420, 422; EX1002, ¶¶46-48. “Trials of parenteral cladribine for relapsing and progressive MS were conducted” as early as the 1990s. EX1008, 319; EX1002, ¶49. The results of pre-2017 parenteral cladribine trials “for relapsing and progressive MS” were published in, e.g., Romine, Rice, Sipe, and Beutler, concluding that cladribine: (a) “significantly reduced” “the frequency and severity of relapses” in RRMS; (b) “markedly reduced” gadolinium-enhancing lesions (a type of active lesion) detected on MRI in progressive MS; and (c) provided “evidence of efficacy” in patients with progressive MS. EX1008, 319; EX1009, 509; *see also* EX1033; EX1036; EX1025; EX1058; EX1002, ¶49.

In 2010, Giovannoni published results of Merck’s successful CLARITY trial evaluating oral cladribine tablets in RRMS. EX1007, 417; EX1002, ¶55. Giovannoni concluded that “treatment with cladribine resulted in reductions in the rates of clinical relapse and in the risk of disability progression and in the suppression of active inflammatory lesions, as visualized on MRI.” EX1007, 425; EX1002, ¶55. Thus, Giovannoni demonstrated that oral cladribine was effective against disease activity. EX1002, ¶¶35-36, 55. Following CLARITY, Merck

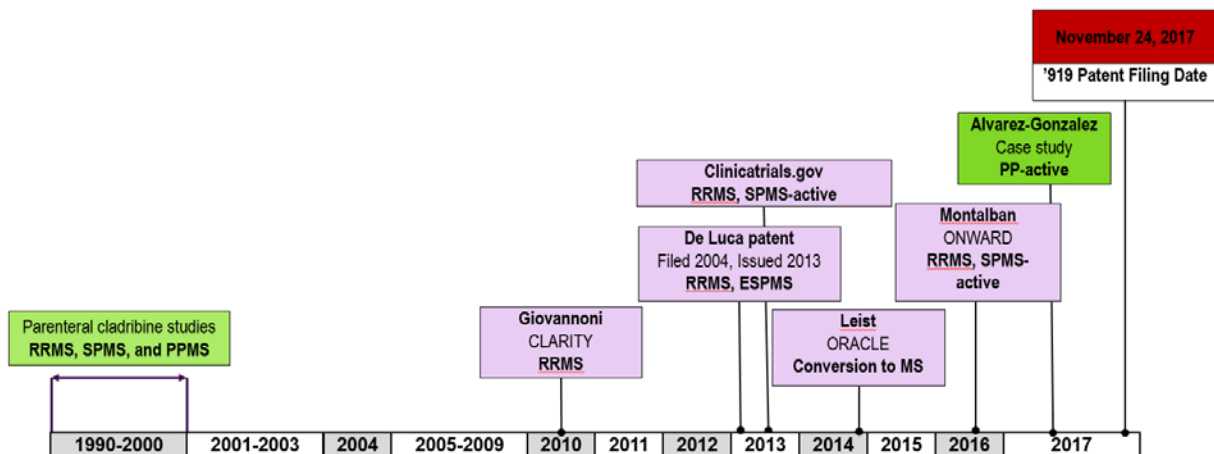
published the results of an extension study, reporting that the benefits of CLARITY's oral cladribine treatment "were maintained" in these patients "for 4 years or more without further active treatment." EX1006, 1; EX1002, ¶56.

Merck and others in the field published the results of additional oral cladribine studies following CLARITY, further showing oral cladribine's efficacy against disease activity in MS. EX1002, ¶54, 65. For example, Merck's 2013 De Luca patent reported the results of a clinical trial where administration of oral cladribine tablets to patients with "relapsing forms" of MS "decreas[ed] brain lesions." EX1010, 14:6-14, 16:45-49; EX1002, ¶54. De Luca further claimed a "method of treating [ESPMS] and [RRMS]" with cladribine. *E.g.*, EX1010, 16:51-57; EX1002, ¶54. In 2014, Leist published the results of the ORACLE trial evaluating the same cladribine treatment used in CLARITY in delaying conversion of initial presentation of MS symptoms to "clinically definite MS." EX1027, 257-258; EX1002, ¶57. Leist concluded that "[c]ladribine significantly reduced the number of" active lesions; i.e., treated disease activity. EX1027, 262, 265-266; EX1002, ¶57.

In 2013, Merck also published the methodology for the ONWARD trial in Clinicaltrials.gov, which evaluated the same oral cladribine regimen as in CLARITY to treat patients with, e.g., "[RRMS] or SPMS with superimposed relapses." EX1005, 12; EX1002, ¶62. In 2016, Montalban reported the results of

the ONWARD trial, concluding that cladribine “demonstrated significant efficacy benefits,” including in patients with “SPMS with ongoing relapses” (i.e., with disease activity). EX1006, 1; EX1002, ¶¶64. And in May 2017, Alvarez-Gonzalez published a case study where a PP-active patient “was successfully treated” with subcutaneous cladribine. EX1009, 506, 509; EX1002, ¶¶66-67.

In sum, before November 24, 2017, it was understood in the art that cladribine effectively treated each of RRMS, ESPMS, SPMS (e.g., SPMS-active), and PPMS (e.g., PP-active). EX1002, ¶¶68. Dr. Miller prepared the following timeline showing exemplary publications that reported using parenteral (green) and oral (purple) cladribine to treat MS that preceded filing of the '919 patent:



EX1002, ¶¶68.

C. Oral cladribine regimens were preferred and available

Before 2017, it was known that “parenteral administration [of cladribine]

may present relative or absolute barriers to acceptance of the therapy.” EX1008, 317; EX1002, ¶53. As such, the art reported preference for oral delivery of drugs, e.g., cladribine, to parenteral delivery, the “foremost” reason being “patient compliance.” EX1026, 2:9-13; EX1002, ¶52. By 2017, oral cladribine dosages had been publicly disclosed as convenient and effective options for treating MS. EX1026, 5:4-7; EX1010, 14:6-32, 16:45-49; EX1007, Abstract; EX1038, Abstract, 6:45-49; EX1002, ¶¶50-54.

For example, in 2004, Bodor described a 10-mg oral cladribine tablet that “achieves lower interpatient and/or inpatient variation of the drug.” EX1026, 5:4-7; EX1002, ¶52. And De Luca disclosed using a 10-mg oral cladribine tablet prepared “as described in [Bodor]” to successfully “decrease [] brain lesions” in MS patients. EX1010, 14:6-32, 16:45-49; EX1002, ¶54. In 2010, Giovannoni disclosed the use of 10-mg cladribine oral tablets in CLARITY. EX1007, 417-418; EX1002, ¶¶55-56. In 2011, Schreiber summarized CLARITY’s successful results in treating disease activity, and concluded the “cladribine tablets [used in CLARITY] allow for a very convenient short-course annual dosing regimen.” EX1008, 324; EX1002, ¶65. And in 2014, Leist reported that “[t]reatment adherence” in the ORACLE trial, which used the same oral cladribine regimen as in CLARITY, “was nearly 100%.” EX1027, 262; EX1002, ¶57.

D. Petitioner's grounds rely on the following publications

The grounds in this IPR rely on the combinations of (a) Alvarez-Gonzalez and Giovannoni; (b) Alvarez-Gonzalez, Giovannoni, and Montalban; and (c) Clinicaltrials.gov, Schreiber, and Montalban. Additionally, the background art discussed above and in Dr. Miller's declaration confirms the general knowledge of POSAs before November 24, 2017, which must be taken into account when evaluating obviousness. *See Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1336 (Fed. Cir. 2006); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013).

1. Alvarez-Gonzalez (EX1009)

Alvarez-Gonzalez is prior art. Alvarez-Gonzalez published in the journal *Annals of Clinical and Translational Neurology* online on May 17, 2017, and in print in July 2017, approximately 6 months before the alleged November 24, 2017 priority date for the '919 patent. EX1009; EX1065, ¶¶11-19. Alvarez-Gonzalez, therefore, is prior art to the '919 patent under 35 U.S.C. § 102(a) (AIA). Merck cannot show that Alvarez-Gonzalez falls under any exception to 35 U.S.C. § 102(b) (AIA), and therefore it is prior art to the '919 patent.

As an initial matter, Alvarez-Gonzalez plainly does not fall under the second exception of § 102(b)(2)—“disclosures appearing in applications and patents”—as the reference is not a patent or patent application.

The exception of § 102(b)(1)(A) does not apply as none of the authors of

Alvarez-Gonzalez are named inventors, and the subject matter was not disclosed from an inventor because Alvarez-Gonzalez does not mention or discuss any of the named inventors of the '919 patent or their work, the ONWARD trial, or other work from *any* Merck personnel disclosing treatment of progressive forms of MS. See EX1009; *see also* M.P.E.P. § 2153.01. In fact, Alvarez-Gonzalez's authors explain they administered a subcutaneous "off-label" dosage of cladribine because of the "lack of licensed" drugs available to them, providing further evidence that the authors did not obtain any subject matter of their disclosure from the named inventors or even Merck. EX1009, 507, 509; EX1002, ¶96.

The exception of § 102(b)(1)(B) does not apply; Hopewell is unaware of any papers, patents, or other publications authored by the inventors or containing subject matter obtained from the inventors that includes the subject matter of Alvarez-Gonzalez—namely, the treatment of a PP-active patient with a cladribine dosage resembling that disclosed in Giovannoni—in the one-year period before the filing date of the '919 patent and before the publication of Alvarez-Gonzalez. See M.P.E.P. § 2153.02. For these reasons, Alvarez-Gonzalez is prior art to the '919 patent.

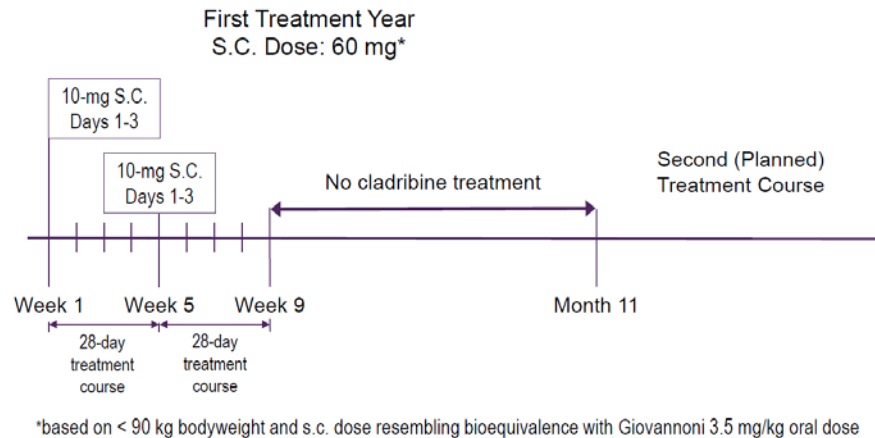
Alvarez-Gonzalez's Disclosure. Alvarez-Gonzalez reported a PP-active patient who was "successfully treated with [c]ladribine as an off-label 'rescue' therapy." EX1009, 506; EX1002, ¶90. The patient had previously been treated with

fingolimod, and subsequently developed 45 active lesions after fingolimod was stopped. EX1009, 506, 507; EX1002, ¶90. “Given the significant clinical and MRI-detected disease,” this patient was then treated with 60 mg subcutaneous cladribine over 5 weeks. EX1009, 507; EX1002, ¶91.

Alvarez-Gonzalez’s rationale for the selection of cladribine was: (a) while PPMS often exhibits a “relative quiescence” of disease activity, there are many exceptions, which is “supported by the [2014 Committee’s] revised classification of MS into active and non-active,” and (b) “DMT [disease-modifying treatment] [such as cladribine]... would have a reasonable likelihood of success” in treating a PPMS patient with disease activity in view of, *inter alia*, “previous phase III trials” (citing CLARITY and ORACLE) providing “evidence for [c]ladribine being effective” against such disease activity. EX1009, 506, 507, 509; EX1002, ¶91.

Alvarez-Gonzalez also explained they selected 60 mg subcutaneous cladribine per year specifically because it “resembles bio-equivalence with” the cumulative 3.5 mg/kg oral dose used in CLARITY as specifically disclosed in Giovannoni (*see* §IV.E.2, *infra*). EX1009, 507, 509; EX1002, ¶66. Accordingly, Alvarez-Gonzalez administered “[c]ladribine 10 mg s.c. [] on days 1, 2, and 3 in week one,” and “administered further doses [of] [c]ladribine of 10 mg s.c. on days 1, 2 and 3 in week 5,” with “[a] second treatment cycle [] planned 11 months after the first.” EX1009, 509; EX1002, ¶67.

Dr. Miller prepared the following schematic to illustrate how POSAs would have understood Alvarez-Gonzalez's regimen (EX1009, 509; EX1002, ¶¶67):



Schematic 2.

Following treatment with cladribine, Alvarez-Gonzalez observed “[n]o adverse effects,” “[c]linically, the patient improved,” and “no disease activity [was] detected on follow-up MRI.” EX1009, 509; EX1002, ¶¶95. Alvarez-Gonzalez concluded that “[c]ladribine is a promising candidate” for the treatment of PPMS patients with disease activity. EX1009, 509; EX1002, ¶¶91.

2. Giovannoni (EX1007)

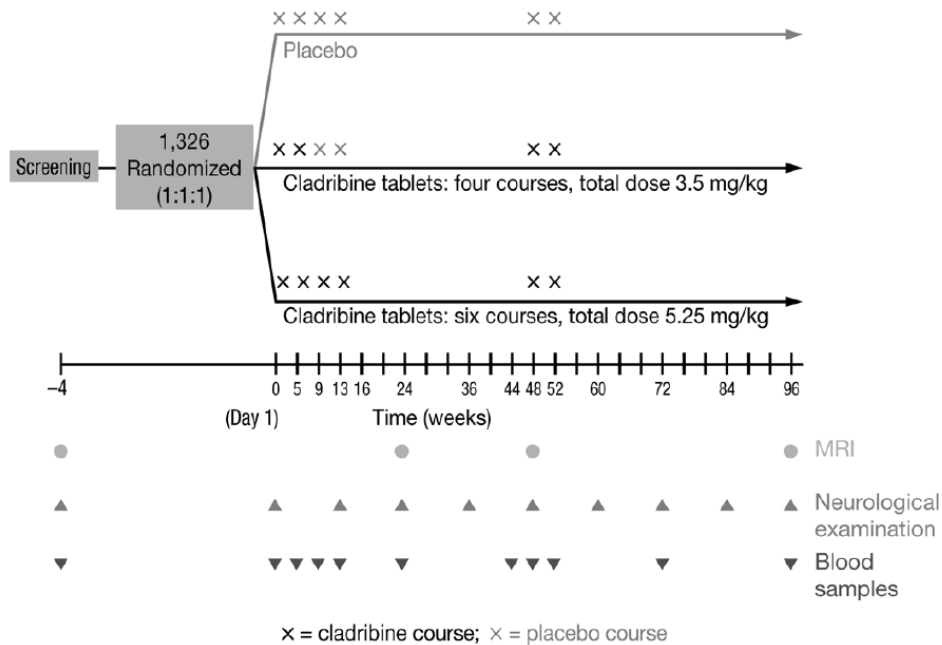
Giovannoni published in *The New England Journal of Medicine* on January 20, 2010. EX1007, 416; EX1065, ¶¶19-27. Giovannoni, therefore, is prior art under 35 U.S.C. § 102(a) (AIA) to the '919 patent.

Giovannoni reported “the results of a 96-week phase 3 trial of a short-course oral tablet therapy” of cladribine in patients with RRMS, known as the CLARITY

study (sponsored by Merck). EX1007, 416, 418; EX1002, ¶94. Giovannoni treated patients with oral cladribine, noting parenteral therapies had limited treatment adherence. EX1007, 417; EX1002, ¶96. Giovannoni explained that the patients were randomized into groups receiving cumulative doses of cladribine of either “3.5 mg or 5.25 mg per kilogram of body weight[] or matching placebo.” EX1007, 417; EX1002, ¶94.

Giovannoni provided the details for each regimen. EX1007, 417-418, Supplementary FIG. 1; EX1002, ¶56. POSAs also would have understood Giovannoni’s regimen to be the same dosing regimen as in the ’919 patent’s challenged claims, e.g.: i) each group received one or two 10-mg cladribine tablets, given once daily for “4 or 5 days of a 28-day period;” ii) “[i]n the first 48-week treatment period, patients received either two courses of cladribine... (in the 3.5-mg group) [or] four courses of cladribine (in the 5.25-mg group) ... starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment);” and iii) “[i]n the second 48-week period, both cladribine groups received two courses of cladribine ... starting at weeks 48 and 52 (8 to 10 days of treatment).” EX1007, 416-418, Supplemental FIG. 1; EX1002, ¶94. Consistent with this disclosure, Giovannoni provides the below figure illustrating the timing of cladribine administration for both groups, and shows that patients in the 3.5 mg/kg group received cladribine starting on day 1, and again at weeks 5, 48, and 52:

Supplemental Figure 1. Study design and timing of assessments



EX1007, Supplemental FIG. 1; EX1002, ¶56.

Giovannoni stated that as compared with placebo, cladribine reduced disease activity: namely, “the rates of clinical relapse and in the risk of disability progression and in the suppression of active inflammatory lesions, as visualized on MRI.” EX1007, 425; EX1002, ¶55. According to Giovannoni, “[b]oth the regimens of 3.5 mg and 5.25 mg per kilogram appeared to be equally efficacious.” EX1007, 425; EX1002, ¶55. Giovannoni concluded that, “short-course treatment with cladribine tablets... provided a significant benefit” against disease activity. EX1007, 425-426; EX1002, ¶55.

3. Clinicaltrials.gov (EX1005)

Clinicaltrials.gov is prior art. The Clinicaltrials.gov webpage for trial

NCT00436826 provides the study details and protocol for the ONWARD trial. *See* EX1005, 9-13; EX1002, ¶58. This information was publicly posted to the Clinicaltrials.gov webpage no later than July 3, 2013, as captured by the Wayback Machine. EX1005, 9-13. Thus, Clinicaltrials.gov is a printed publication that is prior art to the '919 patent under 35 U.S.C. § 102(a) (AIA).

POSAs could have located Clinicaltrials.gov exercising reasonable diligence. *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008). The Clinicaltrials.gov website provides “the public easy access” to clinical trial information. EX1060; EX1002, ¶¶58-61. POSAs would have routinely accessed Clinicaltrials.gov for up-to-date information on MS-related clinical trials, and would have easily found Clinicaltrials.gov through a routine search of the Clinicaltrials.gov public database, in view of other publications in the art reporting the use of oral cladribine in MS clinical trials, and specifically discussing the ONWARD trial. EX1002, ¶¶58-61.

Second, Clinicaltrials.gov was also publicly accessible by July 3, 2013: namely, it was archived by the Wayback Machine on July 3, 2013 as attested to in the notarized Affidavit from a Records Request Processor at the Internet Archive. EX1005.

Clinicaltrials.gov is thus prior art under 35 U.S.C. § 102(a) (AIA). *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29, at 18 (P.T.A.B.

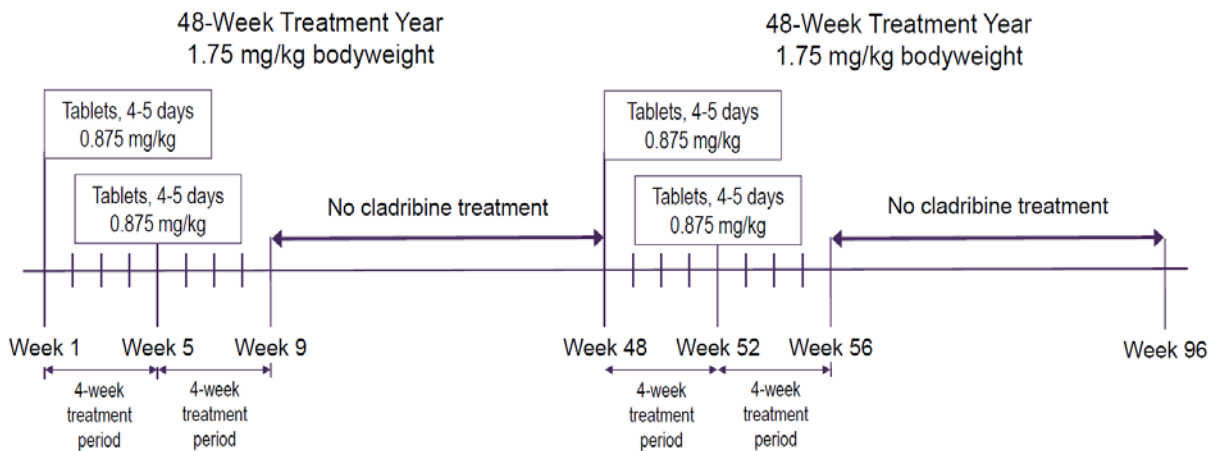
Dec. 20, 2019) (“*Hulu*”) (*precedential*) (citing *Sandoz v. Abbvie Biotechnology Ltd.*, IPR2018-00156, Paper 11, at 8-13 (P.T.A.B. June 5, 2018) and noting that a package insert for a drug, supported with a screenshot of an FDA webpage from the Wayback Machine, a declaration from the Internet Archive, and expert testimony asserting its accessibility “was sufficient evidence for instituting” an IPR); *Grunenthal GmbH v. Antecip Bioventures II, LLC*, PGR2019-00003, Paper 7, at 22 (P.T.A.B. May 7, 2019) (evidence showing clinical trial protocol was posted to clinicaltrials.gov before the priority date satisfied petitioner’s burden that the protocol was prior art).

Clinicaltrials.gov’s Disclosure. Clinicaltrials.gov’s stated goal was “to evaluate the safety, tolerability, and effectiveness of oral cladribine when taken in combination with Interferon-beta (IFN-beta) therapy for the treatment of multiple sclerosis (MS).” EX1005, 10; EX1002, ¶62. Clinicaltrials.gov disclosed the eligibility criteria for the study, requiring that patients, *inter alia*, “have relapsing forms of MS, such as [RRMS] or SPMS with superimposed relapses.” EX1005, 12; EX1002, ¶202. POSAs would have understood these “relapses” were indicators of disease activity, and thus Clinicaltrials.gov taught to treat patients with SPMS with activity (i.e., SPMS-active). EX1002, ¶202.

Clinicaltrials.gov also disclosed the same 3.5 mg/kg cladribine treatment regimen disclosed in Giovannoni and Schreiber (below) (the CLARITY trial),

which is also the same as the dosing regimen later claimed in the '919 patent's challenged claims.⁵ EX1005, 11; EX1007, 417-418, Supplementary FIG. 1; EX1008, 320, 326; EX1002, ¶¶20,64,209.

Specifically, Clinicaltrials.gov disclosed that “subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11; EX1002, ¶62. Dr. Miller prepared the following schematic to illustrate how POSAs would have understood Clinicaltrials.gov's regimen (EX1002, ¶63):



Schematic 3.

⁵ The only exception is that Clinicaltrials.gov is silent as to the specific strength of the cladribine tablets. See EX1005, generally; EX1002, ¶212.

4. Schreiber (EX1008)

Schreiber published in the journal *Clinical Investigation* in February 2011. EX1008 (substantively identical to EX1057); EX1065, ¶¶37-45. Schreiber, therefore, is prior art under 35 U.S.C. § 102(a) (AIA) to the '919 patent.

In discussing drugs available for treating MS, Schreiber explained that “parenteral administration [of the drugs] may present relative or absolute barriers to acceptance of the therapy.” EX1008, 317, 319; EX1002, ¶65. Schreiber, thus, reviewed the use of oral cladribine for MS, concluding that an “oral dosing regimen is convenient” and “[e]fficacy is high.” EX1008, 317, 324; EX1002, ¶65. Specifically, citing Giovannoni, Schreiber described the very same oral cladribine dosing regimen used in the CLARITY trial, and the very same regimen later claimed in the '919 patent. EX1008, 320, 326; EX1002, ¶¶20,209. Schreiber concluded (a) “[t]reatment with cladribine tablets significantly reduced the annual relapse rates,” and (b) cladribine reduced active lesions detected on MRI. EX1008, 320, 324, 326; EX1002, ¶229. Schreiber also concluded that “[t]he formulation and sustained effects of cladribine tablets [used in CLARITY] allow for a very convenient short-course annual dosing regimen.” EX1008, 324; EX1002, ¶19.

5. Montalban (EX1006)

Montalban published in the journal *Neurology* on April 4, 2016. EX1006. Montalban, therefore, is prior art under 35 U.S.C. § 102(a) (AIA). EX1006, 1;

EX1065, ¶¶28-36.

One of the authors of Montalban is Fernando Dangond, who is also a named inventor on the '919 patent. EX1006, 1; EX1001, (72). Merck cannot dispute that Montalban reported the final results from the Phase II ONWARD study, the same study disclosed in Clinicaltrials.gov. EX1006, 1; EX1005; EX1002, ¶¶19,211. Montalban explained that the ONWARD trial “assess[ed] the efficacy of cladribine tablets (3.5 mg/kg)” plus IFN- β , in “patients with active relapsing MS,” including patients who “had SPMS at baseline.” EX1006, 1; EX1002, ¶¶211,258. According to Montalban, the cladribine-treated patients had better outcomes with respect to indicators of disease activity, including lower numbers of “qualifying relapses,” and fewer “new” active lesions detected on MRI (compared to the placebo plus IFN- β group). EX1006, 1; EX1002, ¶211. Montalban further concluded that “[i]n patients with active relapsing MS,” including in patients with “SPMS with ongoing relapses,” treatment with cladribine tablets “demonstrated significant efficacy benefits.” EX1006, 1; EX1002, ¶211.

V. PERSON OF ORDINARY SKILL IN ART

Because the '919 patent relates to methods of human therapeutic treatments, the level of skill required in this field is high. EX1002, ¶¶23-24. POSAs here would draw upon the knowledge and experience of related disciplines of a multi-disciplinary team that might lie outside the POSA's primary training. *Id.*, ¶¶23-24.

For example, a physician might rely upon the knowledge and experience of a pharmacologist on a multi-disciplinary team to determine the appropriate dose for a particular patient.

POSAs for the '919 patent would have the 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. *Id.*, ¶¶23-24. 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.*, ¶¶23-24.

VI. CLAIM CONSTRUCTION

“A progressive form of multiple sclerosis.” Because the claims broadly recite “a progressive form” of MS without specifying whether the form exhibits activity, progression, or both, the plain language of the claims encompasses “a progressive form” of MS that exhibits disease activity, and thus encompasses SPMS-active and PP-active. EX1002, ¶¶75-76; *see Jazz Pharms., Inc. v. Amneal Pharms., LLC*, 895 F.3d 1347, 1361 (Fed. Cir. 2018) (“periodic reports” encompassed those generated at regular and irregular intervals as “[t]he claim does

not define the word ‘periodic’” and the ordinary meaning of “periodic reports” was consistent with reports generated at regular or irregular intervals).

The specification and the file history are consistent with the construction of “a progressive form of [MS]” that encompasses SPMS-active and PP-active because it explicitly contemplates using the claimed methods to treat both.

EX1001, 60:54-57; EX1004, generally; EX1002, ¶76. The specification states that a “PPMS population with greater MRI activity” (i.e., PP-active patients) “may be more suitable to treatment” with the claimed method. EX1001, 60:54-57; EX1002, ¶76. The specification further states that the claimed method reduced the risk of “qualifying relapse” in SPMS, i.e., it treated disease activity in SPMS-active. EX1001, 3:25-67; EX1002, ¶76.

Finally, as discussed above in § IV.A, the proposed construction is also consistent with how POSAs would have understood the term “a progressive form of [MS],” as such forms include SPMS and PPMS, which may exhibit disease activity in the case of PP-active and SPMS-active. EX1002, ¶76.

“Early Secondary Progressive Multiple Sclerosis (ESPMS).” It is clear from the plain language of the claims that the term “ESPMS” refers to a progressive form of MS that is distinct from the other claimed progressive forms (specifically, SPMS). EX1002, ¶¶77-80; *Amgen Inc. v. Sandoz Inc.*, 923 F.3d 1023, 1031 (Fed. Cir. 2019) (“different claim terms are presumed to have different

meanings”).

The ’919 patent specification further explains that ESPMS “is some form of Multiple Sclerosis that marks some kind of transition state” between RRMS and SPMS. EX1001, 2:63-67. Thus, the specification also supports “ESPMS” being distinct from SPMS. EX1002, ¶78.

Merck’s arguments during prosecution are consistent with the proposed construction. To overcome the Examiner’s rejection in view of De Luca, which taught, *inter alia*, treating ESPMS with orally administered cladribine, Merck stated that SPMS “*does not include*” ESPMS. EX1004, 317-318; § III.C, *infra*. Thus, Merck itself reinforced that ESPMS is distinct from SPMS in order to obtain allowance of the claims. *Data Engine Technologies LLC v. Google LLC*, 10 F.4th 1375, 1382-83 (Fed. Cir. 2021) (appropriate to “giv[e] effect to [applicant’s] express definition in the prosecution history”).

Finally, as discussed above in § IV.A, the proposed construction is also consistent with how POSAs would have understood the term “ESPMS,” as the art recognized the transition period between RRMS and SPMS was a distinct form of MS. EX1016, 63; EX1018, 1655; EX1010, 1:19-22, 18:7-25; EX1002, ¶80.

“Week/month/year.” The specification explains that in a medical context, “a week” is referred to “a period of time of about 5, about 6 or about 7 days, more preferably about 7 days,” “a month” is referred to as “about 28, about 29, about 30

or about 31 days,” and “a year” is referred to as “12 months, or about 48 or about 52 weeks.” EX1001, 53:45-67; EX1002, ¶81. This petition adopts these definitions of the claimed terms.

The remaining terms of the challenged claims should be given their plain and ordinary meaning. EX1002, ¶82.

VII. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 42.104(B))

Hopewell requests IPR based on the grounds summarized below.

Ground	35 U.S.C. Section (AIA)	Claims	References
1	§ 103(a)	1-6, 8, 9, 12, 14-16, 18-20, 24-27, 34	Alvarez-Gonzalez (EX1009) and Giovannoni (EX1007)
2	§ 103(a)	11, 23, 33	Alvarez-Gonzalez (EX1009), Giovannoni (EX1007), and Montalban (EX1006)
3	§ 103(a)	1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33, 34	Clinicaltrials.gov (EX1005), Schreiber (EX1008), and Montalban (EX1006)

VIII. GROUND 1: CLAIMS 1-6, 8, 9, 12, 14-16, 18-20, 24-27, AND 34 WOULD HAVE BEEN OBVIOUS OVER ALVAREZ-GONZALEZ AND GIOVANNONI

A. Claim 1

1. POSAs would have had a reason to combine Alvarez-Gonzalez and Giovannoni to arrive at the claimed methods

POSAs would have been motivated to use cladribine to treat PPMS (which

by definition is not ESPMS, §IV.A) with oral cladribine using “a fixed dose per patient, per body weight and per treatment year” “in a range of 1.5 mg/kg to 4.0 mg/kg” because Alvarez-Gonzalez described a “successful treatment” of a PP-active patient with “significant clinical and MRI-disease activity” with cladribine. EX1009, 507, 509; EX1002, ¶¶66,93,95-99. Alvarez-Gonzalez’s choice of cladribine to treat PPMS was consistent with the general knowledge in the field (e.g., Giovannoni (EX1007), Sipe (EX1025), Rice (EX1036), and Beutler (EX1034)), which, according to Alvarez-Gonzalez, provided “evidence of efficacy” of cladribine in progressive MS. EX1009, 509, 510; EX1002, ¶95.

POSAs would have been further motivated to substitute Alvarez-Gonzalez’s fixed yearly dose of subcutaneous cladribine⁶ with oral cladribine, because it was well-known that “[o]ral delivery of drugs is often preferred to parenteral delivery” because of, e.g., issues with “patient compliance.” EX1026, 2:9-11; EX1002, ¶96. POSAs would have chosen Giovannoni’s oral dose and regimen specifically because Alvarez-Gonzalez’s subcutaneous dose resembled “bio-equivalence” with Giovannoni’s. EX1009, 509, 510; EX1002, ¶97. And because Giovannoni reported administering a cumulative dose of 3.5 mg/kg of cladribine in four treatment

⁶ When choosing subcutaneous cladribine, Alvarez-Gonzalez noted a “lack of any licensed options” available to them at the time. EX1009, 506, 509; EX1002, ¶96.

periods over two treatment years (starting on day 1, and on weeks 5, 48, and 52) without differentiating between the treatment periods, POSAs would have understood that the most obvious and logical way to administer Giovannoni's oral dose would be to administer the same amount of cladribine in each period.⁷ EX1007, 416, 417-418, Supplementary FIG. 1; EX1002, ¶98. Thus, POSAs would have been motivated to administer a cladribine dose of 0.875 mg/kg per treatment period ($3.25 \text{ mg/kg} / 4 = 0.875 \text{ mg/kg}$), which equals 1.75 mg/kg/year ($0.875 \text{ mg/kg} * 2 \text{ treatments/year}$), or a "fixed dose per patient, per bodyweight and per treatment year" of 1.75 mg/kg, that is "in a range of 1.5 mg/kg to 4.0 mg/kg," as claimed. *Id.*

2. POSAs would have had a reasonable expectation of success

Given the teachings of Alvarez-Gonzalez and Giovannoni, which teach all claimed elements, coupled with the high level of skill in the art, POSAs would have had a reasonable expectation of success that the claimed treatment method would be effective in treating PPMS. EX1002, ¶¶100-102. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[o]bviousness does not require absolute predictability of success," only "a reasonable expectation of

⁷ Indeed, this is how cladribine was administered in Giovannoni's CLARITY trial. EX1066, 6; EX1002, ¶56.

success.”).

POSAs would have reasonably expected oral cladribine at a fixed dose of 1.75 mg/kg/year to successfully treat PPMS because Alvarez-Gonzalez’s fixed *subcutaneous* cladribine dose that “resembled bioequivalence” with Giovannoni’s fixed *oral* dose of 1.75 mg/kg “successfully treated” a PP-active patient. EX1009, Abstract, 506, 509; EX1002, ¶100. Indeed, Alvarez-Gonzalez reported that “no disease activity” was detected on MRI following cladribine treatment, and the patient’s overall neurological disability and inflammatory activity “improved.” EX1009, Abstract, 506, 509; EX1002, ¶100. Alvarez-Gonzalez’s reported success was consistent with the general knowledge in the art (e.g., Rice, Sipe, and Beutler), which, as Alvarez-Gonzalez noted, provided “evidence” of cladribine’s “efficacy” in progressive MS. EX1009, 509, 510; EX1002, ¶95.

POSAs would also have had a reasonable expectation of success in substituting Alvarez-Gonzalez’s subcutaneous dose with Giovannoni’s oral one, given Giovannoni’s detailed disclosure regarding the particulars of its oral dosage form and corresponding dosing regimen—e.g., the timeframe for administering the tablets, the tablet strength, the number of tablets to administer, and the cumulative dose based on bodyweight—which POSAs would have readily followed to achieve successful treatment of PPMS. EX1009, 417-418, Supplementary FIG. 1; EX1002, ¶101.

B. Claims 2 and 3

Claim 2 depends from claim 1, and specifies that the “fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/-0.2 mg/kg.”

EX1001, 64:57-60; EX1002, ¶103. Claim 3 depends from claim 1, and specifies that the “progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis.” EX1001, 64:61-64; EX1002, ¶106.

As discussed in § VIII.A, POSAs would have been motivated to treat PPMS with a fixed dose of 1.75 mg/kg/year of oral cladribine, and had a reasonable expectation of success in doing so, given Alvarez-Gonzalez’s successful treatment of a PP-active patient with a subcutaneous cladribine dose that was bioequivalent to Giovannoni’s oral dose, arriving at each of claims 2 and 3. EX1009, 506; EX1007, Abstract; EX1002, ¶¶104-105,107-108.

C. Claims 4-6, 8, and 12

Each of claims 4-6, 8, and 12 depends from claim 1, directly or indirectly, and adds nothing more than the previously-disclosed particulars of Giovannoni’s oral cladribine dosing regimen (EX1002, ¶¶110,113,119):

Additional limitations in claims 4-6, 8, and 12 (EX1001, 64:57-65:43; EX1002, ¶¶109,112,118)	Giovannoni’s regimen⁸ (EX1007, 417-418, Supplementary FIG. 1)
4. “fixed dose is orally administered to	“In the first 48-week treatment

⁸ See also Schematic 1, §II.

said patient within two adjacent months within said treatment year.” 5. “fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.” 6. “said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.” 8. “each treatment year comprises: (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.” 12. “said Cladribine is orally administered as a liquid, a tablet, or a capsule.”	period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment).” EX1007, 417. “The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.
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As discussed in § VIII.A, POSAs would have been motivated to treat PPMS with a fixed dose of 1.75 mg/kg/year of oral cladribine, and had a reasonable expectation of success in doing so, given Alvarez-Gonzalez’s successful treatment

of a PP-active patient with a subcutaneous cladribine dose that was bioequivalent to Giovannoni's oral dose. EX1009, 506; EX1007, Abstract; EX1002, ¶¶110,113. It would have been logical and convenient to POSAs to use Giovannoni's entire 2-year-long dosing regimen because the regimen was designed for, and successfully implemented with, Giovannoni's oral dosage form. EX1007, Abstract; EX1002, ¶¶110,113. In doing so, POSAs would have arrived at each of claims 4-6, 8, and 12 with a reasonable expectation of success. EX1009, 506; EX1007, 417-418; EX1002, ¶¶111,114,120.

D. Claim 9

Claim 9 depends from claim 1, and combines the limitations of claims 2 and 3 into one claim, and further recites that "orally administering Cladribine comprises at least two treatment years." EX1001, 65:21-27; EX1002, ¶115. As discussed in §§VIII.A and VIII.B, POSAs would have been motivated to treat PPMS with a fixed dose of 1.75 mg/kg/year of oral cladribine, and had a reasonable expectation of success in doing so. EX1009, 506; EX1007, Abstract; EX1002, ¶116. As also discussed, it would have been logical and convenient to POSAs to use Giovannoni's entire 2-year long dosing regimen, thus arriving at claim 9 with a reasonable expectation of success. EX1009, 506; EX1007, 417-418; EX1002, ¶¶116-117.

E. Claims 14-16, 18, and 19

Independent claim 14 recites a method of treating, e.g., PPMS, comprising administering a specific dosing regimen of oral cladribine that contains the same elements as recited in claims 1-6 and 9, discussed above. EX1001, 65:59-66:14; EX1002, ¶¶121-122. Merck cannot dispute that the exact regimen recited in claim 14 is disclosed in Giovannoni. EX1007, Supplemental FIG. 1; EX1002, ¶¶123-133. Claim 15 depends from claim 14, and claim 16 depends from claim 15; neither adds anything more than the previously-disclosed particulars of Giovannoni’s oral cladribine dosing regimen (EX1002, ¶¶134-136):

Additional limitations in claims 15 and 16 (EX1001, 66:12-37)	Giovannoni’s regimen⁹ (EX1007, 417-418, Supplementary FIG. 1)
15. “each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.”	“The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.” EX1007, 417.
16. “patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.”	

Claim 18 depends from claim 14 and requires that the progressive form of MS is “selected from group consisting of [PPMS and SPMS].” EX1001, 66:4-11;

⁹ See also Schematic 1, §II.

EX1002, ¶¶137-139. Claim 19 depends from claim 18 and requires that the treatment week “consists of 4 or 5 days on which said patient receives 10 mg or 20 mg” oral cladribine. EX1001, 66:32-34; EX1002, ¶¶140-142.

As discussed in § VIII.C, it would have been logical and convenient to POSAs to use Giovannoni’s entire dosing regimen in treating PPMS because the regimen was designed for, and successfully implemented with, Giovannoni’s oral dosage form. EX1007, Abstract; EX1002, ¶¶129,135. In doing so, POSAs would have arrived at claims 14-16, 18, and 19 with a reasonable expectation of success, given Alvarez-Gonzalez’s successful treatment of a PP-active patient with a subcutaneous cladribine dose that was bioequivalent to Giovannoni’s oral dose. EX1009, 506; EX1007, Abstract; EX1002, ¶¶126-133,136,139,142.

F. Claim 20

Claim 20 depends from claim 14 and requires that the patient “is between 18 and 65 years old.” EX1001, 66:36-37; EX1002, ¶143. Alvarez-Gonzalez discloses administering cladribine to a patient who developed PPMS at the age of 28, was enrolled in a clinical trial 5 years later, and developed disease activity about 5 years after that. EX1009, 506-507; EX1002, ¶144. Thus, Alvarez-Gonzalez teaches administration of cladribine to a patient who was about 38 years old. EX1009, 506-507; EX1002, ¶144. As discussed in § VIII.A, POSAs would have been motivated to treat PPMS with a fixed dose of 1.75 mg/kg/year of oral cladribine, and had a

reasonable expectation of success in doing so, given Alvarez-Gonzalez's successful treatment of an about 38-year old PP-active patient with a subcutaneous cladribine dose that was bioequivalent to Giovannoni's oral dose, arriving at each of claim 20. EX1009, 506; EX1007, Abstract; EX1002, ¶¶144-145.

G. Claim 24

Independent claim 24 recites a method of treating, e.g., PPMS, comprising the following regimen taught by Giovannoni (EX1002, ¶¶146-156):

Claim 24 (EX1001, 66:51-67:39)	Giovannoni's regimen¹⁰ (EX1007, 417-418, Supplementary FIG. 1)
orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a treatment year comprising the following regimen: (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;	“In the first 48-week treatment period , patients received either two courses of cladribine , followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). ” EX1007, 417; EX1002, ¶¶150-151. “The study drugs were administered orally as short courses , each consisting of one or two 10-mg

¹⁰ See also Schematic 1, §II.

	cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period. ” EX1007, 417; EX1002, ¶¶150-151.
(ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;	“In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix).” EX1007, 418; EX1002, ¶156.

Claim 24 further recites that “patients having a bodyweight in the range of 50 to less than 60 kg are administered... 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course.” EX1001, 66:51-67:39; EX1002, ¶¶147-148.

As discussed in § VIII.C, it would have been logical and convenient to POSAs to use Giovannoni’s entire dosing regimen in treating PPMS because the regimen was designed for, and successfully implemented with, Giovannoni’s 10-

mg tablets. EX1007, 417-418; EX1002, ¶¶157-164. Because Giovannoni taught administering “one or two 10-mg cladribine tablets” “for the first 4 or 5 days” of each treatment month (two months total) at the fixed dose of 0.875 mg/kg/treatment week (EX1007, 417-418), POSAs would have readily determined the total number of cladribine tablets to be administered in each treatment week for a given patient. For example, for a patient weighing approximately 57 kg (~126 lbs), POSAs would have easily performed the following calculation, arriving at the dose of about 50 mg/week (EX1002, ¶¶152-155):

$$\text{Dose of cladribine needed (in mg)} = 0.875 \frac{\text{mg}}{\text{kg}} \times 57 \text{ kg} = 49.9 \text{ mg}$$

To achieve the 50 mg/week dose for this particular patient, POSAs would have administered five of Giovannoni’s 10-mg tablets (~50 mg/10 mg=5 tablets) per treatment, as claimed. EX1007, 417; EX1002, ¶155.

H. Claims 25-26

Claim 25 depends from claim 24 and requires that the method “further comprises at least one subsequent additional treatment year” that is “substantially identical to said treatment year.” EX1001, 67:40-43; EX1002, ¶165. Claim 26 depends from claim 25 and requires that the subsequent additional treatment year “is directly adjacent” to the first. *Id.*, 67:44-47; EX1002, ¶168. Giovannoni discloses a regimen that includes “the first 48-week treatment period” and “the

second 48-week period:” *i.e.*, “the first treatment year” and “the second treatment year,” as claimed. EX1007, 418; EX1002, ¶166; *see* §VI (the specification defines “a year” as “12 months, or about 48 or about 52 weeks.” EX1001, 53:45-67; EX1002, ¶81). In Giovannoni’s regimen, the two treatment years are directly adjacent and identical to each other. EX1007, 418, Supplemental FIG. 1; EX1002, ¶169. As discussed in § VIII.C, it would have been logical and convenient to POSAs to use Giovannoni’s entire dosing regimen in treating PPMS because the regimen was designed for, and successfully implemented with, Giovannoni’s 10-mg tablets. EX1007, 417-418; EX1002, ¶¶166,169. In doing so, POSAs would have arrived at each of claims 25 and 26. EX1009, 506; EX1007, 417-418; EX1002, ¶167,170.

I. Claim 27

Claim 27 is similar to claim 24, but claim 27 further requires that the first treatment year is followed by the second treatment year comprising a “course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month,” followed by “a second Cladribine-free period lasting 10 months.” EX1001, 68:1-8; EX1002, ¶¶171-173. As explained in §VIII.G, Giovannoni’s regimen includes two treatment years where “one or two 10-mg cladribine tablets” are given “once daily for the first 4 or 5 days of a 28-day period” in each treatment

year, each followed by a 10-month long cladribine-free period, as claimed in claim 27. EX1007, 417, Supplementary FIG. 1; EX1002, ¶¶174-177.

As discussed for claim 24, it would have been logical and convenient to POSAs to use Giovannoni's entire dosing regimen in treating PPMS because the regimen was designed for, and successfully implemented with, Giovannoni's 10-mg tablets, where POSAs would have readily determined the total number of cladribine tablets to be administered in each treatment week for a given patient (e.g., a 57-kg patient). EX1007, 417-418; EX1002, ¶¶178-185. In doing so, POSAs would have arrived at claim 27. EX1009, 506; EX1007, 417-418; EX1002, ¶186.

J. Claim 34

Claim 34 depends from claim 27, and requires that the progressive form of MS "is selected from the group consisting of [PPMS] and [SPMS]." EX1001, 69:24-27; EX1002, ¶187. As discussed in § VIII.F, POSAs would have been motivated to treat PPMS with Giovannoni's entire dosing regimen, and had a reasonable expectation of success in doing so, given Alvarez-Gonzalez's successful treatment of a PP-active patient with a subcutaneous cladribine dose that was bioequivalent to Giovannoni's oral dose, arriving at claim 37. EX1009, 506; EX1007, Abstract; EX1002, ¶¶188-189.

IX. GROUND 2: CLAIMS 11, 23, 33 WOULD HAVE BEEN OBVIOUS OVER ALVAREZ-GONZALEZ, GIOVANNONI, AND MONTALBAN

Claim 11 depends from claim 1 and further specifies that cladribine is administered “in one or two treatment years,” “followed by at least one year in which no Cladribine is administered.” EX1001, 65:44-48; EX1002, ¶190. Claim 23 depends from claim 14, and requires that after the completion of the two treatment years, “no Cladribine is administered to the patients in the subsequent 1 or 2 years.” EX1001, 66:46-50; EX1002, ¶190. And claim 33 depends from claim 27, and requires that “no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4” after completion of the “2 treatment courses of one year each.” EX1001, 69:20-23; EX1002, ¶190.

As discussed in §§ VIII.A, VIII.E, and VIII.I, POSAs would have been motivated to substitute Alvarez-Gonzalez’s subcutaneous cladribine with Giovannoni’s oral cladribine dosed at 1.75 mg/kg/year (cumulative dose of 3.5 mg/kg), administered in two treatment years (one course/year), to treat PPMS. EX1009, 509, 510; EX1007, 416, 417-418, Supplementary FIG. 1; EX1002, ¶191. POSAs would have further had a reason to follow the two-year-long cladribine treatment with one or two cladribine-free years because POSAs would have understood from Montalban that “the clinical benefits of” Giovannoni’s oral cladribine regimen “were maintained ... for 4 years or more without further active

treatment.” EX1006, 1; EX1002, ¶¶191-192. Further, given the extended efficacy of cladribine for years beyond the actual treatment, including a cladribine-free period would have been logical to POSAs because cladribine, as an immunosuppressive, could exhibit “hematological toxicity [] (bone marrow depression).” EX1035, 5; EX1002, ¶193. POSAs, therefore, would have understood that giving a patient an extended cladribine-free period would help control cladribine’s toxicity and be beneficial to the patient overall, without sacrificing treatment efficacy. EX1006, 1; EX1002, ¶193.

POSAs would have had a reasonable expectation of success that following the two years of cladribine treatment with one or two cladribine-free years would provide an efficacious PPMS treatment because Montalban reported that “the clinical benefits of” oral cladribine “were maintained ... for 4 years or more without further active treatment.” EX1006, 1; EX1002, ¶193.

Thus, in addition to the reasons discussed for claims 1, 24, and 27, claims 11, 23, and 33 would have been *prima facie* obvious. *Id.*, ¶194.

X. GROUND 3: CLAIMS 1-6, 8, 9, 11, 12, 14-16, 18-20, 23-27, 30, 33-34 WOULD HAVE BEEN OBVIOUS OVER CLINICALTRIALS.GOV, MONTALBAN, AND SCHREIBER

A. Claim 1

1. POSAs would have had a reason to combine Clinicaltrials.gov, Montalban, and Schreiber to arrive at the claimed methods

POSAs would have been motivated to treat a fully transitioned SPMS patient with disease activity (and thus by definition not an ESPMS patient, §IV.A) using a fixed dose of cladribine of 1.75 mg/kg/year because Montalban reported that oral cladribine, administered according to the regimen taught in Clinicaltrials.gov, reduced “the mean number of qualifying relapses” in patients with “SPMS with superimposed relapses.” EX1005, 11-12; EX1006, 1; EX1002, ¶¶195-203,205-206. Merck cannot dispute that the dosing regimen of claim 1 (and, in fact, of all the challenged claims) is the same dosing regimen (sans the exact tablet dosage) that Clinicaltrials.gov published more than four years prior to the earliest priority date of the '919 patent. EX1005, 11-12; EX1002, ¶¶20,204. Montalban, following the teachings of Clinicaltrials.gov, successfully implemented the regimen and reported that cladribine tablets “demonstrated significant efficacy benefits” in SPMS. EX1006, 1; EX1002, ¶206. Thus, Montalban’s results would have given POSAs ample reason to use Clinicaltrials.gov’s regimen to treat SPMS patients, including those who fully transitioned from RRMS but were still experiencing

relapses. EX1002, ¶¶205-206.

In using the Clinicaltrials.gov's regimen to treat SPMS, POSAs would have selected a suitable oral dosage form because neither Clinicaltrials.gov nor Montalban taught a specific dosage form. EX1002, ¶207. In doing so, POSAs would have used Schreiber's 10-mg cladribine tablets because the tablets "allow for a very convenient short-course annual dosing regimen" of cladribine. EX1008, 324; EX1002, ¶¶207-208. What is more, POSAs would have understood that Schreiber's regimen, which was originally described by Giovannoni, is essentially identical to Clinicaltrials.gov's regimen (but Clinicaltrials.gov does not disclose the exact tablet dosage), and thus Schreiber's 10-mg cladribine tablets would have been an obvious choice for use with Clinicaltrials.gov's regimen. EX1008, 320, 324; EX1005, 6; EX1002, ¶¶207-208.

2. POSAs would have had a reasonable expectation of success

POSAs would have reasonably expected that Clinicaltrials.gov's fixed 1.75 mg/kg yearly dose would successfully treat SPMS because Montalban disclosed that that very dose "demonstrated significant efficacy benefits" in patients with "SPMS with ongoing relapses" (i.e., SPMS-active). EX1006, 1; EX1002, ¶¶209-210. This reasonable expectation of success was confirmed by the general knowledge in the art as reflected by Schreiber. EX1008, 320, 324; EX1002, ¶210. Indeed, Schreiber reported that early cladribine trials in progressive MS, e.g., by

Sipe (EX1025) and Rice (EX1036), demonstrated that active lesions “were markedly reduced” in “cladribine-treated groups,” i.e., cladribine treated disease activity in progressive MS. EX1008, 320; EX1002, ¶210.

POSAs would also have had a reasonable expectation of success in using Schreiber’s 10-mg cladribine tablets in Clinicaltrials.gov’s regimen because Schreiber explained that these tablets were given once daily in the same dosing regimen (sans the exact tablet dosage) disclosed by Clinicaltrials.gov, and were “very convenient” and provided “high” efficacy against disease activity. EX1008, 320, 324; EX1002, ¶211.

B. Claims 2, 3, and 9

As discussed in § X.A, POSAs would have been motivated to treat SPMS with a fixed dose of 1.75 mg/kg/year of oral cladribine using Schreiber’s 10-mg tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMS-active patients with Clinicaltrials.gov’s oral cladribine dose. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶213-215,216-218,226-228. As also discussed, it would have been logical and convenient to POSAs to use Clinicaltrials.gov’s entire 2-year long dosing regimen, thus arriving at claims 2, 3, and 9. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶213-215,216-218,226-228.

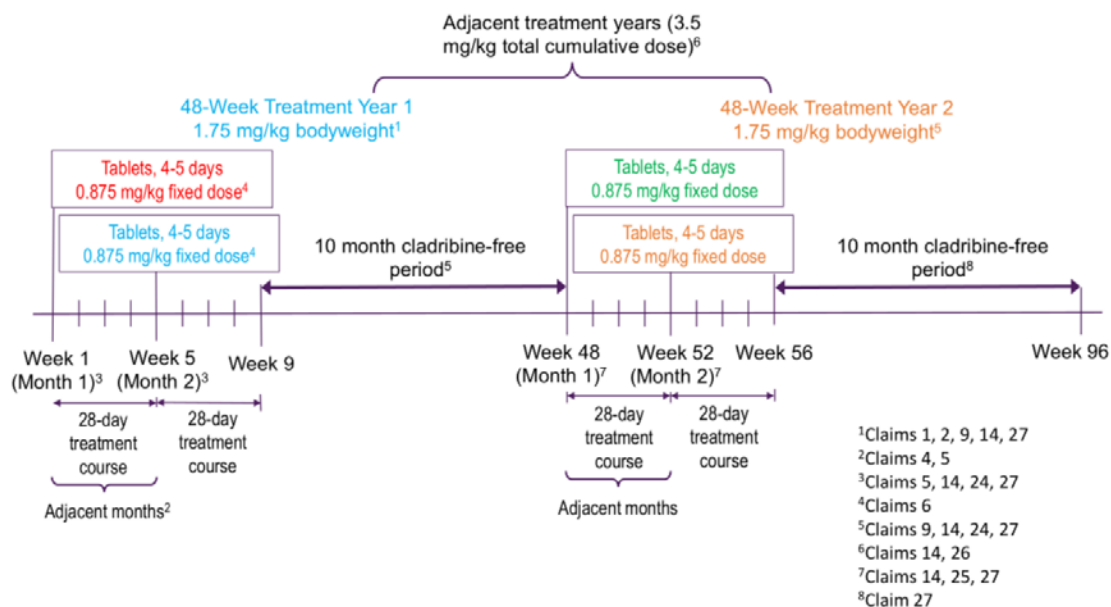
C. Claims 4-6, 8, and 12

Each of claims 4-6, 8, and 12 depends from claim 1, directly or indirectly, and adds nothing more than the previously-disclosed particulars of Clinicaltrials.gov’s regimen (EX1002, ¶¶219-225,233-235):

Additional limitations in claims 2, 4-6, 8, and 12 (EX1001, 64:57-65:43)	Clinicaltrials.gov’s regimen (EX1005)
4. “fixed dose is orally administered to said patient within two adjacent months within said treatment year.” 5. “fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.” 6. “said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.” 8. “each treatment year comprises: (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and (ii) a Cladribine-free period lasting 10 months, during which no	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks.” EX1005, 11.

Cladribine is administered.”	
12. “said Cladribine is orally administered as a liquid, a tablet, or a capsule.”	

Dr. Miller prepared the following graphic summarizing how the claimed methods correspond to the 2-year-long dosing regimen disclosed in Clinicaltrials.gov (EX1005, 11-12; EX1002, ¶220):



Schematic 4.

As discussed in § X.A, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMS-active patients with Clinicaltrials.gov’s oral cladribine regimen. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶220,223,224. In

doing so, POSAs would have arrived at claims 4-6, 8, and 12 with a reasonable expectation of success. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶221,225.

D. Claim 11, 23, and 33

As discussed for Ground 2 (§IX), POSAs would have had a reason to follow a two-year-long cladribine treatment, which Clinicaltrials.gov also discloses, with one or two cladribine-free years because “the clinical benefits of” the 2-year-long oral cladribine regimen “were maintained ... for 4 years or more without further active treatment.” EX1006, 1; EX1005, 11-12; EX1002, ¶¶229-231,261-263,310-312. Thus, including a cladribine-free period would have helped control cladribine’s toxicity and be beneficial to the patient overall, without sacrificing treatment efficacy because cladribine, as an immunosuppressive, could exhibit “hematological toxicity [] (bone marrow depression).” EX1035, 5; EX1006, 1; EX1002, ¶¶231,263,312. In doing so, POSAs would have arrived at claims 11, 23, and 33 with a reasonable expectation of success. EX1002, ¶¶232,264,313.

E. Claims 14-16, 18, and 19

Merck cannot dispute that the regimen recited in claim 14 is disclosed in Clinicaltrials.gov. EX1005, 11-12; EX1002, ¶¶236-240. Claim 18 specifies treatment of SPMS, and claims 15, 16, and 19 recite that the patient receives a 10-mg tablet, which, as discussed in §X.A, POSAs would have found in Schreiber’s

teachings. EX1008, 324; EX1002, ¶¶249,252-253,255-256. To the extent that claim 15 recites additional particulars of the regimen, Clinicaltrials.gov’s discloses these details (EX1002, ¶250):

Additional limitations in claim 15 (EX1001, 66:12-16)	Clinicaltrials.gov’s regimen¹¹ (EX1005, 11-12)
15. “each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.”	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks. ” EX1005, 11.

As discussed in § X.A, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMS-active patients with Clinicaltrials.gov’s oral cladribine regimen. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶241-247,250,253,256. In doing so, POSAs would have arrived at claims 14-16, 18, and 19. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶248,251,254,257.

¹¹ See also Schematic 4, §X.C.

F. Claim 20

As discussed in § X.A, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMS-active patients with Clinicaltrials.gov’s oral cladribine regimen. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶258-259. And because Clinicaltrials.gov expressly taught treating SPMS patients who are “18 Years to 65 Years” with its regimen, POSAs would have followed this teaching, thus arriving at claim 20. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶259-260.

G. Claim 24

Claim 24 recites a method of treating, e.g., SPMS, comprising the following regimen taught by Clinicaltrials.gov using 10-mg tablets, which, as discussed in §X.A, POSAs would have found in Schreiber’s teachings (EX1008, 324; EX1002, ¶¶265-277):

Claim 24 (EX1001, 66:51-67:39)	Clinicaltrials.gov’s regimen¹² (EX1005, 11-12)
(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a	“Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days

¹² See also Schematic 4, §X.C; EX1002, ¶220.

treatment week of from 3 to up to 6 days each month; (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;	at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks. ” EX1005, 11.
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As discussed in § X.A, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMS-active patients with Clinicaltrials.gov’s oral cladribine regimen. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶278-281. Because Schreiber taught administering “10 mg tablets given once daily for the first 4–5 days of a 28-day period” of each treatment month (two months total) at the fixed dose of 0.875 mg/kg/treatment week (EX1009, 324), POSAs would have readily determined the total number of cladribine tablets to be administered in each treatment week for a given patient, as explained in §VIII.G, thus arriving as claim 24 with a reasonable expectation of success. EX1002, ¶¶282-285.

H. Claims 25-26

As Schematic 3 and §X.A illustrates, Clinicaltrials.gov discloses a regimen that includes two identical 48-week treatment years, adjacent to each other, as claimed. EX1005, 11-12; EX1002, ¶¶63,286-287,289-290; see §VI (the

specification defines “a year” as “12 months, or about 48 or about 52 weeks.”

EX1001, 53:45-67; EX1002, ¶81). As discussed in § X.A, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMS-active patients with Clinicaltrials.gov’s oral cladribine regimen. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶287,290. In doing so, POSAs would have arrived at claims 25-26 with a reasonable expectation of success. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶288,291.

I. Claim 27

As Schematic 3 and §X.A illustrates, Clinicaltrials.gov discloses a regimen where the first treatment year is followed by the second treatment year comprising a “course lasting 2 months ... on 3 to up to 6 days each month,” followed by “a second Cladribine-free period lasting 10 months,” as claimed. EX1001, 68:1-8; EX1005, 11-12; EX1002, ¶¶292-294. As discussed in §§ X.A and X.G, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, where POSAs would have readily determined the total number of cladribine tablets to be administered in each treatment week for a given patient (e.g., a 57-kg patient). EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶295-298. In doing so, POSAs would have arrived at claim 27 with a

reasonable expectation of success. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶¶299-306.

J. Claims 30 and 34

Claims 30 and 34 each depends from claim 27, and specify that the progressive form of MS is SPMS. EX1001, 69:9-11, 69:24-27; EX1002, ¶307. As discussed in § X.A, POSAs would have been motivated to treat SPMS with Clinicaltrials.gov’s regimen using Schreiber’s 10-mg cladribine tablets, and had a reasonable expectation of success in doing so, given Montalban’s successful treatment of SPMC-active patients with Clinicaltrials.gov’s oral cladribine regimen. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶308. And POSAs would have readily determined the total number of cladribine tablets to be administered in each treatment week for a given patient, as discussed in §X.F. EX1008, 324; EX1002, ¶308. In doing so, POSAs would have arrived at claims 30 and 34 with a reasonable expectation of success. EX1006, 1; EX1005, 11-12; EX1008, 324; EX1002, ¶309.

XI. THERE ARE NO OBJECTIVE INDICIA THAT WEIGH AGAINST THE STRONG OBVIOUSNESS SHOWING HERE

No Unexpected Results. There is no evidence that the claimed invention provides unexpected results *as compared with the closest prior art*. The ’919 specification alleges that the claimed methods provide an “unexpected advantage”

and “surprisingly show” a decreased likelihood of relapses for patients with SPMS *as compared with patients having RRMS*. EX1001, 3:36-54. But patients having RRMS are not the closest prior art. Here, Montalban and Clinicaltrials.gov are closer prior art, because they disclose the effective treatment of disease activity in patients *with SPMS*, using the same dosing regimen later claimed in the ’919 patent. *See* §§IV.D.3 and IV.D.5. Alvarez-Gonzalez also is closer prior art than art regarding RRMS patients, because Alvarez-Gonzalez showed that cladribine successfully treated a *PPMS* patient using an amount of cladribine bioequivalent to the claimed amounts. *See In re Merchant*, 575 F.2d 865 (CCPA 1978) (emphasis in original). EX1002, ¶315. Not only has Merck failed to show unexpected results as compared with the closest prior art, Merck did not disclose to the Patent Office inventor-authored Montalban, Clinicaltrials.gov, or Alvarez-Gonzalez. And the Examiner failed to find these references. EX1002, ¶315.

Even if one were to consider Merck’s allegation of a “significant difference in efficacy” in treating SPMS patients as compared with RRMS patients, such an allegation is contradicted by other statements in the patent and statements that Merck made to the European Medical Association. Specifically, the ’919 patent concedes that in the ONWARD study “[t]here was no difference in annualized relapse rate[s] between patients with [RRMS] and patients with [SPMS] with relapses.” EX1001, 47:60-48:1; EX1002, ¶316. And Merck told the European

Medical Association that “there was no difference in annualised relapse rate between patients with relapsing-remitting MS and patients with secondary progressive MS with relapses” in ONWARD. EX1023, 13; EX1002, ¶316.

Even if there were a difference in efficacy of cladribine in patients with SPMS compared to RRMS—which Merck stated there was not—it would be a difference in degree, not kind. EX1002, ¶317. But “[u]nexpected results that are probative of nonobviousness are those that are ‘different in kind and not merely in degree from the results of the prior art’ (citations omitted)). *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

Finally, Merck’s allegedly “surprising” data obtained with SPMS patients are not commensurate in scope with the ’919 patent claims, at least because such claims are directed to treating multiple forms of progressive MS, not just SPMS. EX1001, 3:25-345; EX1002, ¶317.

Therefore, Merck has not provided evidence of unexpected results that are probative of non-obviousness.

Other Objective Evidence. Merck did not present any additional objective evidence during prosecution, and Hopewell is not aware of any. If Merck provides alleged objective evidence in its preliminary response, the Board should nonetheless institute trial, because “detailed consideration of [a patentee’s] secondary consideration evidence may not be undertaken until [the petitioner] has

had an opportunity to test it.” *Amneal Pharms., LLC v. Supernus Pharms., Inc.*, IPR2013-00368, Paper 8, at 12-13 (P.T.A.B. Dec. 17, 2013).

XII. THE FACTS AND LAW WEIGH AGAINST DISCRETIONARY DENIAL UNDER § 325(D)

Advanced Bionics does not support discretionary denial under §325(d). *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

The references and arguments in Hopewell’s petition were not previously before the Office. First, Clinicaltrials.gov, Montalban, Alvarez-Gonzalez, and Schreiber—each cited within Hopewell’s Grounds in this Petition—were not previously before the Office during prosecution of the ’919 patent. *See generally* EX1004. While Merck disclosed the results of the ONWARD clinical trial during prosecution as part of the specification, it did not provide the Examiner with Clinicaltrials.gov or Montalban so that the Examiner could see that the trial and its results had been disclosed in the prior art.

Nor are Hopewell’s arguments cumulative of what was previously before the Office. EX1002, ¶73; *Advanced Bionics* at 7-11 (Board will not exercise discretionary denial under § 325(d) where the grounds presented in the petition do not rely on “the same or substantially the same” art or arguments previously presented). Merck argued that its application “appears to be the only source of

clinical data showing the efficacy of [cladribine]” on SPMS or PPMS patients.

EX1004, 317-319, 333-338; EX1002, ¶73. The Examiner (incorrectly) accepted Merck’s representation, but did so only because Merck did not disclose prior art such as Clinicaltrials.gov, Montalban, or Alvarez-Gonzalez, describing using cladribine to treat progressive MS patients, including data showing efficacy.

EX1002, ¶73. Therefore, the art relied upon teaching the use of a fixed oral dose of cladribine to treat progressive MS, and the art showing its efficacy for SPMS and PPMS patients, was not before the Examiner during the prosecution of the ’919 patent. EX1002, ¶73. Accordingly, the Board should not deny trial. *Thorne Research, Inc. v. Trustees of Dartmouth College*, IPR2021-00491, Paper 18, at 9 (P.T.A.B. Aug. 12, 2021) (declining to deny institution where the references and arguments in the petition were never previously before the Office and were not cumulative).

The Examiner materially erred. The Board should also not deny trial under § 325(d) because the Examiner materially erred by failing to find Clinicaltrials.gov and Montalban, or apply them in a rejection. Specifically, Merck told the Examiner that the claimed method was based on results shown in the ONWARD trial regarding the treatment of SPMS with cladribine, but failed to provide the Examiner with the prior art disclosing the ONWARD trial (i.e., Clinicaltrials.gov and Montalban). EX1001, 3:25-46; *see generally* EX1004; EX1002, ¶74. In turn,

the Examiner materially erred by not finding the references in the prior art and in not applying either reference in a rejection. EX1002, ¶315. Similarly, the Examiner materially erred in not finding Alvarez-Gonzalez and applying it in a rejection, even though it disclosed treating a PPMS patient with a bioequivalent amount of cladribine as claimed. EX1002, ¶315.

XIII. *FINTIV* DOES NOT SUPPORT DISCRETIONARY DENIAL.

Fintiv does not support discretionary denial. *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, at 6 (P.T.A.B. Mar. 20, 2020) (precedential) (“*Fintiv*”).

Fintiv Factor 4—the overlap between issues in the petition and the parallel proceedings—is **by itself** sufficient for the Board to decline to exercise its discretion to deny institution. Specifically, pursuant to *Sotera Wireless*, if the Board institutes trial, Hopewell will not pursue, in any further proceedings at the district court, the specific grounds asserted in the *inter partes* review, or on any other ground that was raised or could have been reasonably raised in an IPR (i.e., any ground that could be raised under §§ 102 or 103 on the basis of prior art patent or printed publications). See *Sotera Wireless, Inc. v. Masimo Corporation*, IPR2020-01019, Paper 12, at 18-19 (P.T.A.B. Dec. 1, 2020) (precedential as to § II.A). Under the Interim Procedure, “the PTAB will not discretionarily deny institution in view of parallel district court litigation where a petitioner presents a stipulation not to pursue in a parallel proceeding the same grounds or any grounds

that could have reasonably been raised before the PTAB.” EX1043, 3, 7.

The remaining factors also do not support discretionary denial. Hopewell diligently filed this Petition before any substantive proceedings have occurred or trial dates have been set in the parallel litigations. The Final Written Decision here is expected well before any trial in those cases, strongly favoring institution under factors 2 and 3. EX1044; EX1045; EX1047, 14; EX1046; *Fintiv*, 9-10; *Micron Tech., Inc. v. Godo Kaisha IP Bridge 1*, IPR2020-01007, Paper 15, at 16 (P.T.A.B. Dec. 7, 2020).

Factor 6 also favors institution and is dispositive under the Interim Procedure because Hopewell’s Petition presents compelling evidence of unpatentability. EX1043, 2.

Factor 1 weighs in favor of institution or is at least neutral as the *Accord* litigation is stayed until final judgment or termination of any action involving the ’919 patent, EX1046, and the parties in the *Hopewell* and *Aurobindo* litigations have not yet requested a stay. *Fintiv*, 8; *Sand Revolution II, LLC v. Continental Intermodal Group – Trucking LLC*, IPR2019-01393, Paper 24, at 7 (P.T.A.B. June 16, 2020) (informative).

Factor 5 weighs in favor of institution. Hopewell is not a party to the *Accord* or *Aurobindo* litigations, *Fintiv*, 13-14, and, while Hopewell is the defendant in the *Hopewell* litigation, that case is still in the earliest stages and it is clear that the

Board will evaluate the patentability of the '919 patent first. *Micron Tech.*, IPR2020-01007, Paper 15, at 18.

Accordingly, *Fintiv* weighs in favor of institution. *Fintiv*, 5-6.

XIV. CERTIFICATION AND STANDING (37 C.F.R. § 42.104(A))

Hopewell certifies that the '919 patent is available for IPR and Hopewell is not barred or estopped from requesting IPR of any claim.

XV. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

Real party-in-interest (37 C.F.R. § 42.8(b)(1)): Petitioner certifies the following information: Hopewell Pharma Ventures, Inc., Hopewell Pharma Ventures LLC, Levy SPV, LLC, GLS Capital Partners Fund I, LP, GLS Capital Partners GP, LLC and GLS Capital, LLC are the real parties in interest (collectively, "RPI"). Levy SPV, LLC, a Delaware limited liability company, is owned by GLS Capital Partners Fund I, LP, a Delaware limited partnership. GLS Capital Partners GP, LLC, a Delaware limited liability company, is the general partner of GLS Capital Partners Fund I, LP, and GLS Capital, LLC, a Delaware limited liability company, is the investment manager to GLS Capital Partners Fund I, LP and Levy SPV, LLC. No other person (including any investor, limited partner, or member or any other person in any of Levy SPV, LLC, GLS Capital Partners Fund I, LP, GLS Capital Partners GP, LLC, or GLS Capital, LLC) has authority to direct or control (i) the timing of, filing of, content of, or any decisions

or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition are expected to be borne by Hopewell Pharma Ventures, Inc., Hopewell Pharma Ventures LLC, Levy SPV, LLC, GLS Capital Partners Fund I, GLS Capital Partners GP, LLC, or GLS Capital, LLC.

Related Matters (37 C.F.R. § 42.8(b)(2)): The '919 patent has been asserted in *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), and *Merck KGaA et al v. Aurobindo Pharma USA, Inc. et al*, 1-23-cv-00039 (D. Del.). Petitioner has also filed IPR2023-00480 against Patent No. 7,713,947 and IPR2023-00481 against Patent No. 8,377,903, also directed to treating MS with cladribine and owned by Merck Serono S.A., believed to be owned by an affiliate of Ares. IPR2023-00049 and IPR2023-00050, filed by Twi, also challenge the '947 and '903 patents, respectively.

Pending Appl. No. 17/932,796 claims priority to pending Appl. No. 16/949,278, which, in turns claims priority to Appl. No. 16/199,119, issued as the '919 patent.

Lead and back-up counsel (37 C.F.R. § 42.8(b)(3)) for Hopewell Pharma Ventures, Inc. are:

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Notice of Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence regarding this Petition to counsel at the above addresses and PTAB@sternekeessler.com. Hopewell Pharma Ventures, Inc. consents to service by email at the addresses above.

Procedural Statements This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith are a Power of Attorney and Exhibit List under 37 C.F.R. §§ 42.10(b) and 42.63(e), respectively. The required fee is paid through Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C

/Eldora L. Ellison/

Date: February 10, 2023
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CERTIFICATE OF WORD COUNT (37 C.F.R. §42.24(d))

Petitioner certifies that this Petition is 13,031 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Respectfully submitted,
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CERTIFICATE OF SERVICE (37 C.F.R. §§ 42.6(e)), 42.105(a))

I certify that the above-captioned **PETITION FOR *INTER PARTES***
REVIEW FOR U.S. PATENT NO. 10,849,919, and all associated Exhibits were
served in their entireties upon the Patent Owner on February 10, 2023, via FedEx®
Express at the following address:

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