

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWI PHARMACEUTICALS, INC.,
Petitioner,

v.

MERCK SERONO SA,
Patent Owner.

IPR2023-00050
Patent 8,377,903 B2

Before ERICA A. FRANKLIN, ULRIKE W. JENKS, and
TINA E. HULSE, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

TWi Pharmaceuticals, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 17, 19, 20, and 22–29 of U.S. Patent No. 8,377,903 B2 (Ex. 1002, “the ’903 patent”). Paper 1 (“Petition” or “Pet.”). Merck Serono SA (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”).

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314 (2018). Upon considering the parties’ arguments and evidence, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we do not institute an *inter partes* review of the challenged claims.

A. *Real Parties-in-Interest*

Petitioner identifies itself as a real parties-in-interest. Pet. xiii. Patent Owner identifies Merck Serono SA, Merck KGaA, and Ares Trading SA as real parties-in-interest, stating that “Merck Serono SA and Ares Trading SA are wholly owned subsidiaries of Merck KGaA.” Paper 4, 1.

B. *Related Matters*

The parties explain that the ’903 patent has been asserted in *Merck KGaA, Merck Serono SA, and Ares Trading SA v. Accord Healthcare, Inc.*, 1:22-cv-00974-GBW (D. Del.). Pet. xiii; Paper 4, 1. Petitioner notes that it is not a party to that district court proceeding. Pet. xiii. Patent Owner also identifies *Merck KGaA, Merck Serono SA, and Ares Trading SA v. Hopewell Pharma Ventures, Inc.*, No. 1:22-cv-1365-GBW (D. Del.) as a related matter. Paper 4, 1.

The parties also identify as a related matter the petition filed in IPR2022-00049, which challenges claims of U.S. Patent No. 7,713,947 B2. Pet. xiii; Paper 4, 1.

C. The '903 Patent

The '903 patent “relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.” Ex. 1001, 1:17–20. The Specification explains,

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete.

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset.

Id. at 1:48–58 (citation omitted).

The '903 patent explains that there have been studies regarding the intravenous or subcutaneous administration of cladribine to treat multiple sclerosis (“MS”). *Id.* at 2:28–49. Those studies provided evidence that cladribine had positive effects in patients with MS but some adverse effects, “such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses.” *Id.* at 2:50–63. Another study directed to the oral administration of cladribine observed the same side effects but to a lesser degree than subjects administered with cladribine intravenously. *Id.* at 3:3–16. However, the '903 patent states that “the therapeutic efficacy of the oral regimen above

versus the i.v. infusion therapy was questioned” and there was a group of subjects that did not respond to the treatment. *Id.* at 3:17–21.

According to the ’903 patent:

it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible. A sustained benefit of Cladribine treatment between the treatment periods is also desirable.

Id. at 3:22–30. In view of this, the ’903 patent describes the “use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered.” *Id.* at 3:34–37. The ’903 patent states that each of the induction and the maintenance periods may last up to about four months. *Id.* at 4:58–59, 5:11–12.

D. Illustrative Claim

Petitioner challenges claims 17, 19, 20, and 22–29 of the ’903 patent. Claim 17, set forth below, is the only the independent claim challenged and is illustrative of the claimed subject matter.

17. A method of treating relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis comprising the oral administration of a formulation comprising cladribine to an individual having relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

- (ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;
- (iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg; and
- (iv) a cladribine-free period wherein no cladribine is administered.

Ex. 1001, 18:7–26. Dependent claims 19, 20, and 22–29 recite additional limitations to the method of claim 17. Dependent claims 19 and 22–24 recite time periods for the induction period, cladribine-free period, and maintenance period. Dependent claims 20, 25, and 26 recite doses. Dependent claim 27 recites that the formulation is administered 1–7 days per month during the induction period. Dependent claim 28 recites that certain steps of claim 17 are repeated. Dependent claim 29 requires the formulation of claim 17 to be administered in combination with interferon-beta.

E. Asserted Grounds of Unpatentability

Petitioner asserts that claims 17, 19, 20, and 22–29 are unpatentable on the following three grounds:

Claims Challenged	32 U.S.C. §¹	Reference(s)
17, 19, 20, 22–29	102(e)	Bodor ²
17, 19, 20, 22–29	103(a)	Bodor, knowledge of a POSITA ³

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the ’947 patent issued has an effective filing date before that date, the pre-AIA version of § 103 applies.

² US 7,888,328 B2, issued Feb. 15, 2011 (Ex. 1029, “Bodor”).

³ “POSITA” refers to “person of ordinary skill in the art.” The parties and this Decision similarly refer to a “PHOSITA,” i.e., “person having ordinary skill in the art.”

Claims Challenged	32 U.S.C. § ¹	Reference(s)
17, 19, 20, 22–29	103(a)	Bodor, Rice ⁴

Petitioner also relies upon the Declaration of Benjamin M. Greenberg, M.D. (Ex. 1005).

II. ANALYSIS

A. *Person of Ordinary Skill in the Art*

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int’l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that “[a] person having ordinary skill in the art at the time of the alleged invention would have a Doctor of Medicine and at least two-years’ experience treating neurological conditions and prescribing immunotherapies to treat neurological conditions.” Pet. 8 (citing Ex. 1005 ¶¶ 1–14, 17–19). Patent Owner does not dispute Petitioner’s definition for one of ordinary skill in the art but “reserves the right to challenge Petitioner’s definition of a POSA at a later stage in this proceeding, should the Board institute trial.” Prelim. Resp. 7.

Because Petitioner’s uncontested definition of one of ordinary skill in the art is reasonable and consistent with the ’903 patent and the prior art of record, we adopt Petitioner’s definition for purposes of this Decision.

⁴ Rice et al., *Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial*, NEUROLOGY, 54(5):1145–1155 (2000) (Ex. 1008, “Rice”).

B. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b).

37 C.F.R. § 100(b) (2019). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioner “asserts that all claim terms should be given their plain and ordinary meaning.” Pet. 25 (citing Ex. 1005 ¶¶ 34–35).

Patent Owner notes Petitioner’s assertion in its challenge of the claims that “limitations regarding treatment of or administering to patients having ‘RRMS or early SPMS’ have no patentable weight.” Prelim. Resp. 7 (quoting Pet. 27–28). Patent Owner disagrees because the portion of the preamble regarding the oral administration of cladribine to an individual having RRMS or early SPMS is limiting. *Id.* at 7–8.

Based upon our review of the current record and our analysis of the issues, we determine that no claim terms require express construction for purposes of deciding whether to institute an *inter partes* review of the challenged claims. See *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (stating only those terms

that are in controversy need be construed, “and only to the extent necessary to resolve the controversy.”).

C. Anticipation by Bodor

Petitioner asserts that claims 17, 19, 20, and 22–29 are anticipated by Bodor. Pet. 27–42. Patent Owner disagrees. Prelim. Resp. 21–41.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Schering Corp. v. Geneva Pharms*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

1. Bodor

Bodor “relates to a composition comprising a complex cladribine-cyclodextrin complex formulated into a solid oral dosage form and to a method for enhancing the oral bioavailability of cladribine.” Ex. 1029, 1:17–20. Bodor teaches that “[c]ladribine is an antimetabolite which has use in the treatment of lymphoproliferative disorders” and as “a modality for the treatment of a variety of autoimmune conditions including . . . multiple sclerosis.” *Id.* at 1:46–54. According to Bodor, “[o]ral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations.” *Id.* at 1:61–63.

Bodor states that oral delivery of cladribine had been “plagued by low bioavailability.” *Id.* at 2:10–11. However, Bodor further states that “[i]t has now been found that amorphous cyclodextrins can be combined with cladribine to form a particularly advantageous product which can be incorporated into a solid oral dosage form.” *Id.* at 3:25–28. According to Bodor, “[t]his product is a complex cladribine-cyclodextrin complex, and the

solid oral dosage form containing it improves oral bioavailability and/or achieves lower interpatient and/or inpatient variation of the drug.” *Id.* at 3:28–31.

Bodor explains that “[t]herapeutically effective dosages described in the literature include those for . . . multiple sclerosis (from about 0.04 to about 1.0 mg/kg/day.” *Id.* at 12:55–59 (citing U.S. Patent No. 5,506,214). Bodor notes that the route of administration for such dosages taught in the literature, i.e., intravenous administration, should be taken into consideration. *Id.* at 13:9–11. According to Bodor, “even optimal bioavailability from oral dosage forms is not expected to approach bioavailability obtained after intravenous administration.” *Id.* at 13:13–15. Bodor envisions,

for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment

Id. at 13:19–25. Bodor explains that therapeutically effective amounts may be easily determined by starting at relatively low dosage amounts and then adjusting it in step-wise increments with concurrent evaluation of beneficial effect. *Id.* at 13:37–40. According to Bodor,

A practitioner will appreciate that the complexes, compositions, dosage forms and methods described herein are to be in concomitance with continuous clinical evaluations by a skilled practitioner . . . to determine subsequent therapy. Such evaluations will aid and inform in evaluation whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.

Id. at 14:40–46.

2. Discussion

Petitioner identifies the disclosures in Bodor that it relies on for each limitation of independent claim 17 and dependent claims 19, 20, and 22–29. Pet. 27–42. In particular, we focus on Petitioner’s reliance on Bodor as disclosing a method of treating multiple sclerosis comprising administering orally a cladribine formulation in: (a) an induction period, wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg; and (b) a maintenance period, wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg. *Id.* at 28–39. For the total dose of cladribine in the induction period, Petitioner directs us to Bodor’s disclosure of administering a 10 mg tablet of cladribine daily for 10 to 14 days. *Id.* at 29 (citing Ex. 1029, 13:19–25; 17:52–67). According to Petitioner, “Bodor further teaches that a patient’s weight is considered when dosing the ‘therapeutically effective amount’ of cladribine.” *Id.* (citing Ex. 1029, 12:53–64). Petitioner also relies on Bodor’s reference to a dosage of about 0.04 to about 1.0 mg/kg/day for cladribine, while recognizing that dosage is for subcutaneous administration. *Id.* (citing Ex. 1029, 12:55–59, 4:36–46).

Additionally, Petitioner asserts that a skilled artisan “would have inferred that Bodor teaches considering patient weight to determine the therapeutically effective dose” from Bodor’s teaching to administer 10 mg daily for 10–14 days, which corresponds to a dosage range from 100 to 140 mg of cladribine. Pet. 29. According to Petitioner, a skilled artisan would have inferred that Bodor’s description of a range of dosages is a teaching to “account for patient weight in determining the therapeutically effective amount of cladribine.” *Id.* at 30. In particular, Petitioner contends that the skilled artisan would have understood from Bodor’s dosing schedule

that “lighter patients would receive less drug (e.g., 100 mg over 10 days), whereas heavier patients would receive more drug (e.g., 140 mg over 14 days).” *Id.* at 29.

Beyond asserting that Bodor provides an inference for a weight-based dosing schedule, Petitioner contends that Bodor anticipates a 1.7 mg/kg total dosage for a patient having an average human weight of 70 kilograms who is treated for twelve days. *Id.* at 32–33. Petitioner asserts such a patient would be administered 120 mg of cladribine, which results in 1.71 mg/kg. *Id.* Petitioner provides other examples involving hypothetical patients weighing more or less than 70 kg, wherein the number of treatment days is increased or decreased in a manner that would also result in the patients receiving a dosage that reaches about 1.7 mg/kg. *See id.* at 33.

For the maintenance period total dosage limitation, Petitioner asserts that Bodor teaches a total dosage of 1.7 mg/kg in this maintenance period for the same reasons Petitioner asserted for that dosage in the induction period. Pet. 38–40. According to Petitioner, “[b]ecause Bodor did not teach different dosages for a subsequent cladribine administration round, a PHOSITA would infer that the same dosages would be administered to the patient in both the first cladribine administration round and the second administration round.” *Id.* at 38–39 (citing Ex. 1005 ¶¶ 117–118).

Further, Petitioner asserts that Patent Owner agreed that a skilled artisan would have administered the same dosage in Bodor’s maintenance period as that administered in the induction period when Patent Owner argued, in response to a rejection by the Examiner, that “the teachings of [Bodor] would suggest that the same dosing regimen be applied to the patient . . . result[ing] in the same total dose of cladribine being administered

to the patient in both the induction phase and the maintenance phase.” *Id.* at 39 (citing Ex. 1004, 156; Ex. 1005 ¶ 123).

Turning to Patent Owner’s arguments, among other things, Patent Owner asserts that Bodor does not disclose expressly or inherently a weight-based, total induction period cladribine dose of about 1.7 or 1.7–3.5 mg/kg. Prelim. Resp. 22. Patent Owner contends that “[w]hile Bodor mentions weight-based cladribine dosages for treating MS in the context of prior art . . . it never teaches dosing its oral cladribine formulation based on body weight.” *Id.* at 27. Patent Owner asserts that Bodor instead discloses a method of treating MS with “fixed oral doses” of cladribine, i.e., 10 mg daily, for five to seven days. *Id.* (citing Ex. 1029, 13:19–25, 18:65–66, 20:15–17). According to Patent Owner, “[b]ecause Bodor does not disclose any relationship between dosage and patient weight, the disclosed doses of 100, 120, and 140 mg (10 mg for 10, 12, or 14 days, respectively) are *flat* for all patients and not weight-adapted.” *Id.*

Patent Owner asserts that Petitioner improperly relies on hindsight to arrive at the claimed about 1.7 or 1.7–3.5 mg/kg dosage limitations. Prelim. Resp. 31. Patent Owner contends that it is “[o]nly by rewriting Bodor with hindsight knowledge of the claimed dosing regimen, and ignoring Bodor’s express teaching of flat, fixed-dose dosing . . . can Petitioner argue a POSA would infer the claimed total induction period dose of about 1.7 or 1.7–3.5mg/kg from Bodor.” *Id.*

Based upon our review of the arguments and evidence, we agree with Patent Owner that Petitioner has not demonstrated a reasonable likelihood of establishing that Bodor expressly or inherently discloses a method of treating MS with an oral dosage of cladribine, wherein the total dose of cladribine reached at the end of the induction period and at the end of the

maintenance period is from about 1.7 mg/kg, or any amount that is weight-based.

As Patent Owner correctly observes, Bodor's discussion of weight-based dosages relied upon by Petitioner expressly refers to "[t]herapeutically effective dosages described in the literature," i.e., in the prior art. *See* Ex. 1029, 12:55–59; Pet. 28; Prelim. Resp. 27. In that passage, Bodor describes the prior art dosage approach for MS was "from about 0.04 to about 1.0 mg/kg/day." Ex. 1029, 12:57–59 (citing U.S. Patent No. 5,506,214). Petitioner has not shown, nor do we see, any description in Bodor implementing that weight-based dosage approach for Bodor's treatment method. Instead, after recognizing the prior art approach, Bodor expressly discloses that it envisions treating MS by orally administering 10 mg of the cladribine-cyclodextrin complex for a period of five to seven days in the first month, and five to seven days in the second month. *Id.* at 13:19–25. Whether administered for 10 days or up to 14 days during the treatment period, the daily dosage remains a fixed amount.

Even when explaining that the invention "provides a method to tailor the administration/treatment," Bodor does not refer to any consideration of the weight of a patient. Ex. 1029, 13:31–40. Rather, Bodor describes tailoring the administration/treatment "to the particular exigencies specific to a given mammal," as Bodor's treatment method is intended for use with human and non-human subjects, e.g., domesticated animals. *Id.* at 13:35–37; 14:54–57. Bodor explains that "[t]herapeutically effective amounts may be easily determined, for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect." *Id.* at 14:54–57. Bodor further explains that the methods "are to be used in concomitance with continuous clinical evaluations by a

skilled practitioner (physician or veterinarian) to determine subsequent therapy. Such evaluation will aid and inform in evaluating whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.” *Id.* at 14:43–50. There again, Bodor’s disclosure regarding a treatment dose does not include any consideration of a patient’s weight. Thus, Bodor does not support Petitioner’s assertion that a patient’s weight is considered in Bodor’s method of treating MS with a cladribine complex, or that a skilled artisan would have inferred such a teaching from Bodor.

To the extent that Petitioner provides examples to show that under certain very specific circumstances, Bodor’s total dose of cladribine could reach an amount that equals about 1.7 mg/kg at the end of a treatment period for a particular patient, we do not find that showing persuasive in terms of establishing a reasonable likelihood of prevailing on an anticipation challenge. It is apparent to us that Petitioner’s examples involve a strategic selection of patient weight and treatment duration that support a calculation that yields a 1.7 mg/kg total dosage for the treatment period. We agree with Patent Owner that such a strategy is insufficient to establish inherency as it demonstrates only the total dose that is possible for some patients. It is a long-standing principle that inherent anticipation requires the missing descriptive element to be “necessarily present,” and not merely possibly present. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

Further, we determine that Petitioner has not identified disclosures in Bodor that adequately support Petitioner’s assertion that a subsequent round of Bodor’s therapy, during what Petitioner refers to as the maintenance period, would necessarily be at the same dosage administered in the first round. According to Petitioner, a skilled artisan would infer that the same

dosages would be administered to the patient in both the first and second rounds of treatment, because Bodor did not teach different dosages for a subsequent cladribine administration round. Pet. 38. However, as noted above, Bodor provides an instruction that its methods are to be used with continuous clinical evaluations for beneficial effect to determine any need for adjusting a particular treatment dose. Ex. 1029, 14:43–57. In other words, the dosage amount administered is not necessarily a static one. Rather, dosage may require adjustments in view of ongoing and continuous clinical evaluation. Moreover, for the same reasons discussed regarding Bodor’s initial or induction therapy, Petitioner has not persuasively identified disclosures in Bodor that a subsequent round of Bodor’s therapy would be based on the weight of the patient or that the total dose of cladribine reached at the end of that period would necessarily be about 1.7 mg/kg.

For at least the foregoing reasons, we find that Petitioner has not shown a reasonable likelihood of prevailing on its assertion that independent claim 17, or its dependent claims, claims 19, 20, and 22–29, are anticipated by Bodor.

D. Obviousness over Bodor and Knowledge in the Art

Petitioner asserts that claims 17, 19, 20, and 22–29 would have been obvious over the combined teachings of Bodor and the common knowledge of one of ordinary skill in the art. Pet. 42–50. Patent Owner disagrees. Prelim. Resp. 41–54. We incorporate our description of Bodor in Section II.C.1. here.

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

“An obviousness determination requires finding both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

1. Discussion

As in its anticipation challenge, Petitioner asserts here also that Bodor alone discloses every limitation of the challenged claims. Pet. 42. According to Petitioner, even if we are not persuaded that a skilled artisan would have made the inferences regarding Bodor’s treatment method alleged by Petitioner for the anticipation ground, the challenged claims are still unpatentable as obvious over Bodor and in view of the common knowledge of a PHOSITA. *Id.*

We begin by focusing on the total dosage limitations recited in independent claim 17 and Petitioner’s assertion that it would have been obvious to arrive at a total dosage of 1.7 mg/kg at the end of the induction period and at the end of a maintenance period. *Id.* at 45–48. According to Petitioner, Bodor’s disclosure of treating patients with 10 mg daily for ten to fourteen days in a first round of treatment, i.e., a total dosage of 100 mg – 140 mg, amounts to about 1.7 mg/kg “for numerous patients and a large section of the patient population.” *Id.* at 45.

Petitioner contends, to the extent that Bodor's 10 mg/day dosing does not always amount to a total dosage of about 1.7 mg/kg dosage at the end of the induction and maintenance period, "it would have been obvious to a PHOSITA to make the total dosage at the end of the induction period and at the end of the maintenance period to be 1.7 mg/kg because a PHOSITA would be motivated to fine tune dosages to arrive at a therapeutically effective amount," as Bodor suggests fine tuning dosages with concurrent evaluation of beneficial effect. *Id.* (citing Ex. 1029, 13:31–40). According to Petitioner, the skilled artisan would have been motivated to "start with previously suggested dosage amounts in the medical literature, which Bodor specifically acknowledges." *Id.* (citing Ex. 1029, 12:65–13:8).

Specifically, Petitioner asserts that a skilled artisan would have been motivated to begin by "adjusting for bioavailability" the subcutaneous cladribine dosage of 0.7 mg/kg disclosed in Rice, a journal article incorporated by reference in Bodor. *Id.* at 45–46 (citing Ex. 1008, 1–2, 9); *see* Ex. 1029, 13:5–8. Petitioner contends that the skilled artisan would have been motivated to then "evaluate the beneficial effect of this initial dosage and raise the dosage up to 1.7 mg/kg, as suggested by Bodor . . . to find the therapeutically effective amount." *Id.* (citing Ex. 1029, 13:37–40; Ex. 1005 ¶¶ 161–164).

Petitioner acknowledges that Rice also discloses a higher (subcutaneous) dosage of 2.1 mg/kg, Pet. 46 (citing Ex. 1008, 1–2, 9), however, Petitioner contends that a skilled artisan would have known that "a lower dosage is preferable to a higher dose," especially because Rice describes both doses as effective, *id.* (citing Ex. 1005 ¶ 164). Petitioner contends that a skilled artisan "could adjust" Rice's suggested dosage, through "trial and error," as Bodor provides motivation to pick a low dosage

and adjust that dosage. *Id.* (citing Ex. 1029, 13:31–40). Petitioner also relies on Bodor’s teaching to adjust dosages to support its position that a skilled artisan would have had a reasonable expectation of success in finding a therapeutically effective dosage. *Id.*

Additionally, Petitioner contends that it would have been obvious to administer the same dosage during both the induction and maintenance periods because “it was common practice in the medical arts to prescribe the same dose of an immunosuppressant (and other drugs) during a second phase as a first phase, absent some compelling reason not to.” *Id.* at 48–49 (citing Ex. 1005 ¶¶ 168–170). According to Petitioner, “a PHOSITA would have expected success in doing so for the same reason – the medical community had studied this dosing regime and found it effective for many drugs, including immunosuppressants like cladribine.” *Id.*

Patent Owner argues, among other things, that Bodor does not teach or suggest weight-based dosing, and that Petitioner has not established any motivation to modify Bodor’s teaching to arrive at a method for treating MS comprising a total induction period dose of about 1.7 or 1.7–3.5 mg/kg, and a maintenance period total dosage of about 1.7 mg/kg, as required by the challenged claims. Prelim. Resp. 41, 50. In particular, Patent Owner asserts that “Petitioner’s suggestion to ‘fine tun[e]’ by ‘trial and error’ is plagued by hindsight.” *Id.* at 48. According to Patent Owner, “[a]bsent a suitable starting point in Bodor, Petitioner relies on Rice but fails to identify what would have motivated a POSA to choose Rice from among the various cladribine studies as a starting point.” *Id.* at 48. Patent Owner asserts also that Petitioner’s reliance on Rice in this single-reference ground challenge is improper. *Id.* at 43.

Patent Owner continues that Petitioner's reliance on knowledge in the art is unavailing because, "nothing in the prior art taught a POSA how the combination of the different variables—dose, length and number of dosing period or drug-free periods—would impact the treatment of MS or what specific combination (if any) would result in a safe and effective MS treatment method." *Id.* at 48. According to Patent Owner, Petitioner's obviousness challenge involves "merely throw[ing] metaphorical darts at a board in hopes of arriving at a successful result [when] the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" and should be rejected as improperly relying on hindsight. *Id.* 48–49 (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012)).

Having considered the arguments and the evidence on the current record, we determine that Petitioner has not shown sufficiently for institution that Bodor discloses each limitation of the challenged claims expressly or inherently for the reasons discussed regarding the anticipation ground. It is only by employing a strategy that exemplifies treatment of patients having specifically selected weights and specifically selected treatment durations that Petitioner is able to show that Bodor's method of treating MS with 10 mg of the cladribine complex daily arrives at about a total dosage of 1.7 mg/kg at the end of a treatment period. Indeed, Petitioner recognizes that Bodor's teachings do not always arrive at that total dosage. Pet. 45.

Insofar as Petitioner relies on Bodor, in view of the asserted common knowledge of a skilled artisan at the time of the invention, to demonstrate that "it would have been obvious for a PHOSITA to make the total dosage at the end of the induction period and at the end of the maintenance period to

be 1.7 mg/kg,” *id.* at 45, we determine that showing is also insufficient for institution. In particular, we agree with Patent Owner that Petitioner’s obviousness challenge relies improperly on hindsight, rather than only upon the teachings of Bodor and the asserted knowledge in the art, to reach the total dosage limitations in the challenged claims. Petitioner urges that a skilled artisan would have modified Bodor’s method of treating MS based upon a flat daily oral dosage of its cladribine-cyclodextrin complex to instead depend upon a dosing scheme based upon the patient’s weight. *Id.* In support of that contention, Petitioner asserts that “[a] PHOSITA would have been motivated to start with previously suggested dosage amounts in medical literature, which Bodor specifically acknowledges.” *Id.* Specifically, Petitioner refers to Rice and its disclosure of a study wherein patients were administered a subcutaneous dosage of cladribine as a treatment for MS. *Id.*

What is missing from Petitioner’s argument is why, apart from hindsight, a skilled artisan would have exchanged Bodor’s flat dosing method for oral administration of a cladribine complex with the weight-based method disclosed in Rice for use with subcutaneous administration of cladribine. Instead, Petitioner focuses its discussion on a skilled artisan’s motivation to “fine tune” the weight-based dosages in Rice “to arrive at a therapeutically effective amount.” Pet. 45. Petitioner asserts that a skilled artisan would have been motivated to evaluate the beneficial effect of Rice’s 0.7 mg/kg dosage (adjusted for bioavailability) and then “raise the dosage up to 1.7 mg/kg, as suggested by Bodor . . . to find the therapeutically effective amount.” *Id.* (citing Ex. 1029, 13:37–40; Ex. 1005 ¶¶ 161–164).

Bodor, however, does not teach or suggest switching to a weight-based dosage or fine tuning a weight-based dosage. Rather, Bodor suggests

fine tuning its daily flat dosage of 10 mg, apart from any consideration of a patient's weight. Ex. 1029, 13:31–35. Bodor explains that such fine tuning involves increasing or decreasing that daily dosage, and/or administering the cladribine composition with another active ingredient to achieve a beneficial effect. *Id.* at 13:31–40. Petitioner has not shown, nor do we find, that Bodor's teaching of increasing or decreasing the daily dose means shifting to a weight-based dosing method or arriving at a total dosage based on a patient's weight. Indeed, Bodor recognized methods involving weight-based dosing in the prior literature and expressly disclosed a different method of treating MS orally with a flat daily dosage of its cladribine complex, independent of a patient's weight. *See id.* at 12:55–13:40.

Thus, it is apparent that Petitioner's contention that a skilled artisan would have modified Bodor's method of dosing its cladribine-complex to depend upon a patient's weight or to provide a total dosage that is about 1.7 mg/kg at the end of the induction period and at the end of the maintenance period, as recited by the challenged claims, is improperly guided by hindsight and not the teachings of Bodor, or in view of the knowledge in the art.

Accordingly, we determine that Petitioner has not shown a reasonable likelihood of prevailing in its obviousness challenge of independent claim 17, or its dependent claims, claims 19, 20, and 22–29 over Bodor and in view of the asserted knowledge in the art.

E. Obviousness over Bodor and Rice

Petitioner asserts that claims 17, 19, 20, and 22–29 would have been obvious over the combined teachings of Bodor and Rice. Pet. 50–57. Patent Owner disagrees. Prelim. Resp. 54–63. We incorporate our description of Bodor in Section II.D.1 here.

1. Rice

Rice is a journal article that describes a study “[t]o evaluate the safety and efficacy of two doses of cladribine in patients with progressive MS.”

Ex. 1008, 1. Rice describes the study as administering a “placebo or cladribine 0.07 mg/kg/day for 5 consecutive days every 4 weeks for either two or six cycles (total dose, 0.7 mg/kg or 2.1 mg/kg, respectively), followed by placebo, for a total of eight cycles.” *Id.* The doses of cladribine and placebo were administered via subcutaneous injection. *Id.* at 2.

Rice states that:

After all patients at a study site completed the 12-month double-blind phase, the blind was broken, and patients who fulfilled the hematologic dosing criteria were permitted to receive open-label cladribine treatment during the long-term extension phase of the study, provided at least 12 months had elapsed since the last dose of cladribine and there was evidence of disease progression. Patients treated with open-label cladribine were evaluated monthly for 12 months following initiation of the drug, and then quarterly.

Id. at 2. Rice also states that some patients entered retreatment during a follow-up phase. *Id.* at 5.

2. Discussion

Petitioner contends that if we are not persuaded that a skilled artisan would have made the inferences regarding Bodor’s treatment method alleged by Petitioner for the anticipation ground, the challenged claims are still unpatentable as obvious over Bodor and Rice. Pet. 50. In particular, for the total dosage limitations recited in independent claim 17, Petitioner asserts that it would have been obvious to arrive at a total dosage of 1.7 mg/kg at the end of the induction period and at the end of a maintenance period in view of Bodor’s teachings. *Id.* at 52. According to Petitioner, Bodor’s

disclosure of treating patients with 10 mg daily for ten to fourteen days in a first round of treatment, i.e., a total dosage of 100 mg–140 mg, amounts to about 1.7 mg/kg “for numerous patients and a large section of the patient population.” *Id.* at 52–53.

Additionally, Petitioner contends that “it would have been obvious to a PHOSITA to make the total dosage at the end of the induction period and at the end of the maintenance period to be 1.7 mg/kg in view of Rice.” *Id.* at 53. Specifically, Petitioner relies on Rice’s disclosure that a total dosage of 0.7 mg/kg of cladribine was administered to MS patients via subcutaneous injection. *Id.* at 53 (citing Ex. 1008, 1; Ex. 1005 ¶¶ 181–185). Petitioner asserts that “Bodor taught orally administered cladribine with a lowered bioavailability (41.9%) compared to subcutaneous administration of cladribine.” *Id.* (citing Ex. 1029, 19:45–67; Ex. 1005 ¶ 186). Based on that teaching, Petitioner asserts that “a PHOSITA would have arrived at about 1.7 mg/kg by simply adjusting Rice’s recommended dosage by the bioavailability of orally administered cladribine.” *Id.* (citing Ex. 1005 ¶ 186). From there, Petitioner asserts that “a PHOSITA would be motivated to select the number of days or 10 mg tablets to administer after accounting for patient weight, as instructed by Rice.” *Id.* at 53–54 (citing Ex. 1008, 1; Ex. 1005 ¶ 187).

According to Petitioner, the skilled artisan “would have been motivated to use Rice’s 0.7 mg/kg recommended dosage because Rice’s study demonstrated positive effects on patients receiving that dosage.” *Id.* at 54 (citing Ex. 1005 ¶¶ 188–189). Additionally, Petitioner asserts that the skilled artisan would have been “motivated to consult Rice because Bodor specifically mentions Rice as a source of inspiration for dosing.” *Id.* at 54 (citing Ex. 1029, 13:5).

Petitioner contends that, in view of Rice’s success at a subcutaneous dosage of 0.7 mg/kg (translated by Petitioner to an oral dose of 1.67 mg/kg), “a PHOSITA would be motivated to start with this dosage and confirm that it was therapeutically effective for oral administration as well.” *Id.* at 54–55 (citing Ex. 1005 ¶¶ 190–193). Petitioner continues that “[o]nce confirmed, a PHOSITA would not be motivated to adjust the dosage amount.” *Id.* at 55.

According to Petitioner, “Rice’s efficacy would have also given a PHOSITA a reasonable expectation of success in using that total dosage. *Id.* (citing Ex. 1005 ¶ 192). Further, Petitioner asserts that a skilled artisan would have been motivated, with a reasonable expectation of success, to administer the same dosage during Bodor’s first and second phases because Rice’s used the same dosage during all of its phases and the trial proved promising. *Id.*

Patent Owner argues, among other things, that Petitioner fails to establish any motivation to combine Rice’s weight-based dosage with Bodor’s flat dosing treatment method. Prelim. Resp. 54–55. Referring to its arguments for the anticipation and prior obviousness grounds, Patent Owner asserts that Bodor does not disclose or suggest the total dose limitations of the challenged claims. *Id.* at 55. Patent Owner argues further that “Rice does not remedy Bodor’s deficiencies.” *Id.*

Patent Owner asserts that, despite the beneficial results reported in Rice that are highlighted by Petitioner, Rice used “EDSS scores as an outcome measure” and Rice explains that “no significant treatment effects were found” based on those scores, and that “clinical efficacy was not shown.” *Id.* at 57 (quoting Ex. 1008, 8–9). According to Patent Owner, a skilled artisan seeking to improve Bodor’s method would not have looked to Rice’s “reportedly ineffective cladribine study.” *Id.*

Having considered the arguments and evidence on the current record, we determine that Patent Owner has the better position. To begin, to the extent that Petitioner relies on Bodor as disclosing each limitation of the challenged claims expressly and through the asserted inferences a skilled artisan would have made from the reference, *see, e.g.*, Pet. 41–42, 44–45, we determine that Petitioner’s showing is insufficient for institution for at least the reasons discussed in the anticipation ground.

Next, for its combination of Bodor and Rice, Petitioner contends that “it would have been obvious for a PHOSITA to make the total dosage at the end of the induction period and at the end of the maintenance period to be 1.7 mg/kg.” Pet. 52–53. Based on our consideration of the arguments and evidence, we determine that showing is also insufficient for institution. Here again, we find that Petitioner’s obviousness challenge relies improperly on hindsight, rather than upon the combined teachings of Bodor and Rice, to reach the total dosage limitations in the challenged claims. Specifically, Petitioner’s proposed combination of Bodor and Rice involves modifying Bodor’s method of treating MS with a 10 mg daily oral dosage of its cladribine-cyclodextrin complex to instead depend upon a patient’s weight to determine an oral dosage amount, in view of the weight-based dosage disclosed in Rice for a subcutaneous cladribine treatment. *Id.* at 51–52. According to Petitioner, “[a] PHOSITA would have been motivated to use Rice’s 0.7 mg/kg recommended dosage because Rice’s study demonstrated positive effects on patients receiving that dosage.” Pet. 54 (citing Ex. 1005 ¶¶ 188–189; Ex. 1008, 9).

As noted above, Patent Owner challenges Petitioner’s characterization of Rice as demonstrating clinical efficacy at that dosage. Prelim. Resp. 57. However, even if certain study results indicated some beneficial effects upon

administering a weight-based dosage, that manner of determining a dosage amount in Rice and the results observed from it involved treating MS via subcutaneous administration of cladribine. Petitioner has not persuasively identified any teaching or suggestion in Rice or Bodor to convert Rice's subcutaneous weight-based dosage to an orally administered weight-based dosage. Rather, as Petitioner asserts, Bodor already considered Rice prior to envisioning its orally administered flat dosage. Indeed, according to Petitioner, Rice was a "source of inspiration for dosing" in Bodor. Pet. 54. As a result, Bodor disclosed an oral dosage of 10 mg/day for periods of 10–14 days for its cladribine-complex. Bodor explains that its compositions "optimize the bioavailability of cladribine following oral administration." Ex. 1029, 13:11–13.

In view of Bodor's consideration of Rice and the bioavailability of cladribine when teaching a 10 mg daily oral dosage, Petitioner has not explained sufficiently why a skilled artisan would be motivated to follow all aspects of Bodor's treatment method, including administering a cladribine-complex according to Bodor's schedule of 10–14 days for an induction period and for a maintenance period, *except* Bodor's 10 mg/day dosage amount. In other words, the motivation to modify Bodor's method of dosing to a weight-based dosage or to achieve a total dose based on weight remains missing.

Thus, it is apparent that Petitioner's contention that a skilled artisan would have modified Bodor's method of dosing its cladribine-complex to depend upon a patient's weight or to provide a total dosage that achieves 1.7 mg/kg at the end of the induction period and at the end of the maintenance period, as recited by the challenged claims, is improperly guided by hindsight and not the combined teachings of Bodor and Rice.

Accordingly, we determine that Petitioner has not shown a reasonable likelihood of prevailing in its obviousness challenge of independent claim 17, or its dependent claims, claims 19, 20, and 22–29, over the combination of Bodor and Rice.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established a reasonable likelihood of prevailing in its assertion that at least one challenged claim of the '903 patent is unpatentable. Accordingly, we deny the Petition and decline to institute the requested *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

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