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Paper: 109
Entered: July 11, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. and APOTEX CORP.,
ARGENTUM PHARMACEUTICALS LLC, ACTAVIS ELIZABETH LLC,
TEVA PHARMACEUTICALS USA, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., SUN PHARMACEUTICAL INDUSTRIES, INC.,
and SUN PHARMA GLOBAL FZE,
Petitioners,

v.

NOVARTIS AG,
Patent Owner.

Case IPR2017-00854[1]
Patent US 9,187,405 B2

Before CHRISTOPHER M. KAISER, ROBERT A. POLLOCK, and KRISTI L. R. SAWERT,[2] *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Claims 1–6 Not Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined with this proceeding.
[2] Replacing Judge Lora M. Green, who has left the Board.

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–6 of U.S. Patent No. US 9,187,405 B2 (Ex. 1001, "the '405 patent"). We have jurisdiction under 35 U.S.C. § 6.

For the reasons that follow, we determine that Petitioners have failed to show, by a preponderance of the evidence, that claims 1–6 of the '405 patent are unpatentable.

A. Procedural History

Apotex Inc. and Apotex Corp. ("Apotex") filed a Petition requesting an *inter partes* review of claims 1–6 the '405 patent. Paper 2 ("Pet."). Novartis AG[3] ("Novartis"), filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). We instituted *inter partes* review of each of the challenged claims. Paper 11, 27 ("Dec.").

Three parties filed Petitions substantially the same as Apotex's Petition along with requests for joinder: 1) Argentum Pharmaceuticals LLC ("Argentum") (IPR2017-01550, Papers 1 and 3); 2) Actavis Elizabeth LLC and Teva Pharmaceuticals USA, Inc. (collectively, "Teva") (IPR2017-01946, Papers 2 and 3); and 3) Sun Pharmaceutical Industries, Ltd., Sun Pharmaceutical Industries, Inc., and Sun Pharma Global FZE (collectively, "Sun") (IPR2017-01929, Papers 2 and 3). We granted each Petition and

[3] According to Patent Owner, "Novartis AG has assigned its rights in U.S. Patent 9,187,405 to Novartis Pharmaceuticals Corporation (*see* Assignment at Reel 043314/Frame 0800). The real party in interest is Novartis Pharmaceuticals Corporation. Novartis AG and other Novartis subsidiaries may also have an interest." Paper 22.

associated requests for joinder to IPR2017-00854. *See* IPR2017-01550, Paper 10; IPR2017-01946, Paper 9; IPR2017-01929, Paper 7, respectively. Because our grants of joinder were conditioned on Apotex taking the lead role in the joined proceeding, we refer to Apotex, Argentum, Teva, and Sun, collectively, as "Petitioners."

After institution of trial and our grants of joinder, Patent Owner filed a Patent Owner Response (Paper 26, "PO Resp."); Petitioners filed a responsive Reply (Paper 49, "Pet. Reply"); and Patent Owner filed an authorized Sur-Reply (Paper 63, "PO Sur-Reply").

Patent Owner also filed a Corrected Contingent Motion to Amend. Paper 61. Petitioners opposed (Paper 51), and Patent Owner responded with a Reply in support of its motion (Paper 64).

Petitioners rely on the declaration of Dr. Barbara S. Giesser (Ex. 1002), first submitted with Apotex's Petition, and on the later-submitted Reply Declaration of Leslie Z. Benet, Ph.D. (Ex. 1047).

Patent Owner relies on the declarations of Fred D. Lublin, M.D. (Exs. 2003, 2025, 2107, 2097), William J. Jusko, Ph.D. (Exs. 2005, 2024, 2095), Lawrence Steinman, M.D. (Exs. 2022, 2096), and Jerold Chun, M.D., Ph.D, (Ex. 2098). Patent Owner further relies on the declaration of named inventor Christian Schnell. Ex. 2026.

Petitioners filed motions for observations on depositions of Drs. Lublin, Jusko, Steinman, and Chun (Papers 77, 79, 76, and 78, respectively); Patent Owner filed responses to each of those motions (Papers 90, 93, 91, 92, respectively).

We heard oral argument on May 11, 2018. A transcript of that proceeding is entered as Paper 108 ("Tr.").

The parties filed the following motions. Petitioners filed a motion to exclude evidence (Paper 82); Patent Owner opposed (Paper 89); and Petitioners submitted a reply in support of its first motion to exclude (Paper 98). Patent Owner filed a first motion to exclude evidence (Paper 80); Petitioners opposed (Paper 94); and Patent Owner submitted a reply in support of its first motion to exclude (Paper 97). Patent Owner filed a supplemental motion to exclude evidence (Paper 102); Petitioners opposed (Paper 101); and Patent Owner submitted a reply in support of its supplemental motion to exclude (Paper 103). The parties have also filed six motions to seal. (Papers 36, 50, 83, 99 (by Petitioners); Papers 29, 37 (by Patent Owner)).

B. Related Proceedings

According to Patent Owner, there are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Paper 4, 2. Petitioners note that in IPR2014-00784, the Board issued a Final Written Decision relating to U.S. Patent No. 8,324,283 B2, and that "[a]lthough not from the same patent family as the '405 patent, the '283 patent included claims to pharmaceutical compositions of fingolimod, or a pharmaceutically acceptable salt thereof, that is suitable for oral administration, as well as claims directed to the treatment of multiple sclerosis using S1P receptor agonists." Pet. 20; *see id.* at 13–14; Paper 49, 7. We are not persuaded, however, that the Board's prior decision with respect to the '283 patent is probative of the instant proceeding.

C. The '405 Patent and Relevant Background

The '405 patent, titled "S1P Receptor Modulators for Treating Relapsing-Remitting Multiple Sclerosis," issued to Peter C. Hiestand and

Christian Schnell from U.S. Application No. 14/257,342 ("the '342 application"), filed April 21, 2014. Ex. 1001, at [21], [60], [71], [72]. The '342 application is a divisional of Application No. 13/149,468 ("the '468 application") (now U.S. Pat. No. 8,741,963). *Id.* at [60]. The '468 application, in turn, is a continuation of Application No. 12/303,765 ("the '765 application."), which is the U.S. entry of PCT/EP2007/005597, filed June 25, 2007. *Id.*; Ex. 1009, 21, 40. PCT/EP2007/005597 claims priority to foreign application GB0612721.1 (Ex. 1012), filed on June 27, 2006. Ex. 1001, at [30]; *see* Ex. 1009, 57–58.

The instant "invention relates to the use of an S1P[4] receptor modulator in the treatment or prevention of neo-angiogenesis associated with a demyelinating disease, e.g. multiple sclerosis." Ex. 1001, 1:5-8. "Characteristic pathological features of demyelinating diseases include inflammation, demyelination and axonal and oligodendrocyte loss. In addition[,] lesions can also have a significant vascular component. A firm link has recently been established between chronic inflammation and angiogenesis and neovascularization seems to have a significant role in the progression of disease." *Id.* at 9:6–12. According to the inventors, "[i]t has now been found that S1P receptor modulators have an inhibitory effect on neo-angiogenesis associated with demyelinating diseases, e.g. MS." *Id.* at 9:13–15.

"Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with chronic inflammatory demyelination leading to progressive decline of motor and sensory functions and permanent

[4] S1P refers to sphingosine-1 phosphate, a natural serum lipid. Ex. 1001, 1:13–14.

disability." Ex. 1001, 8:61–64. The inventors state that S1P receptor agonists or modulators may be useful in the treatment of MS, including the Relapsing-Remitting form (RR-MS), which accounts for 85% of patients' initial experience with the disease and is the precursor to the more debilitating Secondary-Progressive form (SPMS). *Id.* at 9:64–10:21; *see also id*. at 10:3–5 (noting that within 10 years of onset about half of RR-MS patients will develop SPMS); Ex. 1005,[5] 159–60, Fig. 1 (discussing the pathophysiology, classification, and clinical course of MS).

"S1P receptor agonists or modulators are known as having immunosuppressive properties or anti-angiogenic properties in the treatment of tumors . . . ." Ex. 1001, 8:56–60. Preferred compounds stimulate lymphocyte homing, thereby "elicit[ing] a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression." *Id.* at 2:17–23. "A particularly preferred S1P receptor agonist . . . is FTY720, i.e., 2-amino-2-[2-(4-octyphenyl)ethyl] propane-1, 3-diol . . . ." *Id.* at 8:17–30. This compound, also known as fingolimod, is the active ingredient in Novartis's Gilenya product (fingolimod hydrochloride) approved for the treatment of RR-MS. *See* Ex. 2040, 11; Ex. 2024 ¶ 38.

D. The Challenged Claims

Illustrative claim 3 recites (paragraphing added):

> 3. A method for treating Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising

[5] Thomson, "*FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value,*" 1(3) CORE EVIDENCE 157-167 (2006). Ex. 1005.

orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1, 3-diol, in free form or in a pharmaceutically acceptable salt form,

at a daily dosage of 0.5 mg,

absent an immediately preceding loading dose regimen.

The remaining independent claims differ only in the language of the preamble, such that the "treating" language of claim 3 is replaced with "reducing or preventing or alleviating relapses" (claim 1) or "slowing progression" of RR-MS (claim 5).

Depending from claims 1, 3, and 5, respectively, claims 2, 4, and 6 specify that the 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1, 3-diol is the hydrochloride salt form—i.e., fingolimod hydrochloride.

E. Grounds of Unpatentability

We instituted trial to review the patentability of the challenged claims on each of the three grounds asserted in the Petition:

Ground	Claims	References	Basis
1	1–6	Kovarik[6] and Thomson[7]	§ 103
2	1–6	Chiba,[8] Kappos 2005,[9] and Budde[10]	§ 103

[6] Kovarik and Appel-Dingemanse, WO 2006/058316, published June 1, 2006. Ex. 1004. ("Kovarik").
[7] Thomson, "*FTY720 in Multiple Sclerosis: The Emerging Evidence of its Therapeutic Value,*" 1(3) Core Evidence 157-167 (2006). Ex. 1005. ("Thomson").
[8] Chiba et al., US 6,004,565, issued Dec. 21, 1999. Ex. 1006. ("Chiba").
[9] Kappos et al., "*FTY720 in Relapsing MS: Results of a Double-Blind Placebo-Controlled Trial with a Novel Oral Immunomodulator,*" 252 (Suppl 2) J. Neurology Abstract O141 (2005). Ex. 1007. ("Kappos 2005").
[10] Budde, et al., "*First Human Trial of FTY720, a Novel Immunomodulator, in Stable Renal Transplant Patients,*" 13 J. Am. Soc. Nephrology 1073-1083 (2002). Ex. 1008. ("Budde").

Ground	Claims	References	Basis
3	1–6	Kappos 2010[11]	§ 102

Paper 11, 27.

II. ANALYSIS

A. Legal Principles

To anticipate a claim under 35 U.S.C. § 102,[12] "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented 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 that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

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[11] Kappos et al., "*A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis*," 362(5) N. Engl. J. Med. 387–401 (2010). Ex. 1038. ("Kappos 2010").

[12] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '405 patent have an effective filing date before the effective date of the applicable AIA amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show 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." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted); *see also Belden Inc. v. Berk–Tek LLC,* 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

B. Person of Ordinary Skill in the Art

Petitioners propose that a person of ordinary skill in the art as of the date of the invention

> would typically include a person with a medical degree (M.D.) and several years of experience treating multiple sclerosis patients. . . . would be familiar with administering therapeutic agents for the treatment of multiple sclerosis, including RR-MS, and dosing regimens of the various therapeutic agents available for treating RR-MS. . . . [and] would be knowledgeable about the

> multiple sclerosis medical literature available at the relevant time.

Pet. 18–19 (citing Ex. 1002 ¶¶ 39–40). Petitioners' proposal is consistent with the definition offered during prosecution that, "[t]he relative skill of those in the art is high, generally that of an M.D. or Ph.D. with expertise in the area of neurology." Ex. 1009, 13. We further note, in focusing on the MS disease state and the conduct of a prophetic clinical trial of fingolimod ("Compound A") in treating RR-MS, the Specification suggests that one of ordinary skill in the art would possess a medical or related doctoral degree and have experience in the field of MS treatment and clinical research. *See, e.g.*, Ex. 1001, 8:61–9:12, 9:64–10:16, 11:4–12:13.

In the Preliminary Response, Patent Owner argues that Apotex's proposed definition "is plainly incorrect" because "a person of skill in other dosing patent cases almost always includes a pharmacologist," the '405 Patent and relevant references include pharmacologists as "essential contributing authors," and "[p]harmacologists would have to interpret that data before reaching any conclusions about the obviousness of a 0.5 mg daily dose." Prelim. Resp. 39–43.

In our Decision instituting trial, we agreed with Patent Owner that in the context of this proceeding, expertise in pharmacology would be useful in determining obviousness. Dec. 8. We further noted that it was not necessary to decide between the hypothetical medical doctor proposed by Petitioners and the pharmacologist proposed by Patent Owner, as courts and tribunals have frequently identified the hypothetical person of ordinary skill as a composite or team of individuals with complementary backgrounds and skills. Dec. 8–9 (citing *AstraZeneca Pharm. LP v. Anchen Pharm., Inc.*, No.

10-CV-1835 JAP TJB, 2012 WL 1065458, at *19, *22 (D.N.J. Mar. 29, 2012), *aff'd*, 498 F. App'x 999 (Fed. Cir. 2013) (collecting cases); *Helsinn Healthcare S.A. v. Dr. Reddy's Labs. Ltd.*, No. CV 11-3962 (MLC), 2016 WL 832089, at *72 (D.N.J. Mar. 3, 2016) (reversed on other grounds by *Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc.*, 855 F.3d 1356 (Fed. Cir. 2017), *cert. granted*, --- S. Ct. ----, 2018 WL 1142984 (June 25, 2018)); *Merial, Inc. v. Fidopharm Inc.*, IPR2016-01182, Paper 11 at 9 (PTAB Nov. 7, 2016)).

Accordingly, we determined that one of ordinary skill in the art could be part of a multi-disciplinary research team including 1) a Ph.D. with expertise in the area of neurology and/or an M.D. having several years of clinical experience treating multiple sclerosis patients, and who would be knowledgeable about the multiple sclerosis medical literature, and 2) a pharmacologist with experience in drug development. *Id.* at 9.

Neither party argues that this determination is incorrect. Nor, upon consideration of the complete record, do we find reason to modify our prior determination.

C. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812

F.3d 1056, 1062 (Fed. Cir. 2016). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

i. Whether the Preambles are Limiting

The preambles of the independent claims recite methods for "reducing or preventing or alleviating relapses in" (claim 1), "treating" (claim 3), and "slowing progression of" (claim 5) RR-MS "in a subject in need thereof." This "subject in need thereof" is then reflected in the body of each claim as it recites the step of orally administering fingolimod "to said subject."

Petitioners argue that the preambles of the independent claims should be accorded no patentable weight as they "at most merely describe[] the intended purpose of the method and that the subject receiving fingolimod is a subject with RR-MS." Pet. 24–25; Ex. 1002 ¶¶ 43–45. As we understand the argument, Petitioners propose that "said subject" is any subject with RR-MS, as such persons inherently are, or will be, "in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS." *Id.* at 22–23; Ex. 1002 ¶¶ 43–45. Thus, Petitioners argue, the preambles "are not required to breathe life into the claim[s]." *Id.* at 24.

Petitioners' argument, however, conflates the etiology and progression of multiple sclerosis with the plain language of the claims. Thus, for example, Petitioners may be correct that because patients accrue neurologic disability with each relapse episode, "an RR-MS patient is in need of a treatment that reduces, prevents or alleviates relapses and slows the progression of RR-MS," depending on that patient's disease state. *See* Pet. 23. But "[i]n the absence of any evidence to the contrary, we must presume that the use of these different terms in the claims connotes different

meanings." *CAE Screen Plates, Inc. v. Heinrich Fiedler GMBH & Co. KG*, 224 F.3d 1308, 1317 (Fed. Cir. 2000). In the present case, Petitioners do not direct us to sufficient evidence that "reduc[ing], prevent[ing] or alleviat[ing] relapses," as set forth in claim 1, is necessarily the same as the arguably broader language, "treating," recited in claim 3.

In contrast to Petitioners' position, Patent Owner contends that the preambles of independent claims 1, 3, and 5, limit the scope of the challenged claims, and are necessary to provide understanding to what the inventors actually invented. Prelim Resp. 29–35. Relying on the testimony of its expert, Dr. Lublin, Patent Owner presents evidence that "a person of skill would not understand reducing relapses, treating the disease, and slowing its progression to mean the same thing." *Id*. at. 32–33 (citing Ex. 2003 ¶¶ 5–7, 43–55). As noted above, we do not ascertain where, on this record, Petitioners or Petitioners' experts argue or present evidence that these three terms are synonymous.

Patent Owner also points out that failing to accord meaning to the differences in the preambles "would eliminate any differences among claims 1–2, 3–4, and 5–6." *Id.* at 30–31. On balance, we agree with Patent Owner that the presumption against claim redundancy weighs against Petitioners' proposed construction.

We also find persuasive Patent Owner's argument that the words in the preambles inform the scope of "said subject" in the body of each claim. Prelim. Resp. 29–35. In particular, the preambles of claims 1, 3 and 5:

> provide[] an antecedent basis for terms used in the body of each claim, specifying the needs of the "subject" alluded to later. This is a classic example of the preamble defining a term—the "subject in need" of certain effects—which then is subsequently used in the body of the claim—"to said subject."

Id. at 34.

Because the three preamble terms, "reducing or preventing or alleviating relapses in" (claim 1), "treating" (claim 3), and "slowing progression of" (claim 5) RR-MS have different meanings, and each informs the scope of the "subject" in the body of the claims, we concluded that the preambles give life and meaning to the balance of the claim. *See Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). Accordingly, we construed the preambles of claims 1, 3, and 5 as limiting, and accord the ordinary and customary meaning to the claim language "reducing or preventing or alleviating relapses in," "treating," and "slowing progression of" RR-MS "in a subject in need thereof." Dec. 12. We further construed the terms "reducing or preventing or alleviating relapses" and "slowing progression" as subsumed within the genus of "treating" RR-MS.[13] *Id.* Upon consideration of the complete record, we find no reason to modify our construction.

ii. Whether the Preambles Invoke an Efficacy Element

The parties do not appear to argue that our construction of the preambles is incorrect, but disagree as to whether they invoke an efficacy element. According to Patent Owner, we should construe the claims to require that administering 0.5 mg fingolimod daily provides the effects recited in the preambles or, in the alternative, require that the drug "be given for the 'intentional purpose for which the method must be performed.'" PO Reply 9; Sur-Reply 3–4 (quoting *Janssen v. Rexall Sundown, Inc.*, 342 F. 3d

[13] Unless specifically indicated otherwise, we refer herein to the more generic "treating" as a matter of convenience.

1329, 1333 (Fed. Cir. 2003)); Ex. 2095 ¶¶ 9–17. Petitioners, by contrast, contend that the preambles do not create an efficacy requirement but merely inform the scope of "said subject" in the body of the claims, or "describe the intended purpose of the method." Pet. 24–25; Pet. Reply 7–8 (citing *In re Montgomery*, 677 F.3d, 1375, 1380 (Fed. Cir. 2012)); Opp. 5–6.

Consistent with our determination in section II(C)(i), above, administration of fingolimod to "said subject" in the claim body clearly refers to "a subject in need" of treatment of RR-MS in the preambles. Accordingly, at a minimum, we agree with Patent Owner that the claims require that the 0.5 mg daily dosage of fingolimod is given for the purpose of treating RR-MS. Although an understanding that the claims refer to the administration of fingolimod for the purpose of treating RR-MS provides context for understanding Grounds 1–3, counsel for Patent Owner points out that whether the preambles further demand that the orally administered dosage is efficacious is "more important for the motion to amend." Tr. 45:5–10. We agree with Patent Owner. And, as we do not reach the substance of Patent Owner's motion to amend (*see* section II(A), below), we need not further construe the preambles. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

iii. Daily Dosage

Illustrative claim 3 recites a method for treating RR-MS in a subject comprising "orally administering to said subject [fingolimod] . . . at a daily

dosage of 0.5 mg." The parties disagree as to whether "daily dosage" requires administration over a course of treatment for more than one day.

Relying on the testimony of Dr. Benet, Petitioners argue that "the broadest reasonable construction of a 'daily dosage of 0.5 mg' includes a total dose of 0.5 mg in 24 hours regardless of what unit doses are used or whether the same dose is repeated on consecutive days." Pet. Reply 8–9 (citing Ex. 1047 ¶¶ 107–116).

According to Patent Owner, considered in context, "'daily' does not mean 'once.' It means 0.5 mg per day for more than one day . . . . [because] therapies like fingolimod require continuous administration to be effective. Giving the drug only once would be meaningless." PO Sur-Reply 3–4. As Dr. Steinman explains, "[a] person of skill with any familiarity with RRMS or disease-modifying therapies like fingolimod would understand that these [disease modifying therapies] are never proposed as a single-dose cure, but are always envisioned to be taken on a regular basis over an extended period." Ex. 2089 ¶ 22; *see* Ex. 2024 ¶ 114. Thus, "[a] skilled person would understand 'daily dosage' to refer to once a day for a number of days." Ex. 2096 ¶ 21; *see also id.* (further noting that "[a] single, one-time dose can be referred to by the phrase 'a dosage' and the word 'daily' is not needed.").

Consistent with Dr. Steinman's testimony, the Specification states that "[d]aily dosages required in practicing the method of the present invention . . . will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition treated . . . . [and] may alternatively be administered intermittently, e.g., at a dose of 0.5 to 30 mg every other day or once a week." Ex. 1001, 11:20–38; *see* Ex. 2089 ¶ 23. Accordingly, the Specification presents intermittent

dosing (i.e., not every day) as an alternative to daily dosing and, in so doing, indicates that either regimen entails administration for more than one day.

As an initial matter, we credit Dr. Benet's testimony that a daily dosage need not be administered as a single unit dose and, thus, refers to the total dose administered in 24 hours. *See* Ex. 1047 ¶¶ 110–111; Ex. 1001, 11:24–25 ("daily dosage" includes "as a single dose or in divided doses"). On balance, however, we find that Patent Owner has the better position with respect to the length of treatment implicit in the claim term. The '405 Patent is directed to the treatment of a chronic and progressively debilitating disease. *See* Ex. 1001, 8:61–9:5, 9:64-10:5; Ex. 1005, 159; *see generally* Ex. 1023, 193–202.[14] As Dr. Steinman indicates, such patients are in need of treatment "on a regular basis over an extended period of time." Ex. 2089 ¶ 22. This is consistent with our reading of the Specification as disclosing daily or intermittent treatment for more than one day. *See* Ex. 1001, 11:20–38; *see* Ex. 2089 ¶ 23.

Moreover, with respect to Petitioners' argument in their Reply brief that the claim language is broad enough to encompass both single administration and administration on consecutive days (*see* Pet. Reply 8–9), we conclude that, in the context of the '405 patent, Petitioners' proposed definition renders the word "daily" superfluous. Accordingly, we construe "daily dosage of 0.5 mg" as referring to the amount of fingolimod administered per day over the course of a multi-day treatment.[15]

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[14] MCALPINE'S MULTIPLE SCLEROSIS, 4th Ed., Compston, ed. (Elsevier, Inc., December 2005).

[15] Although our construction of "daily dosage" is helpful to understanding the claims as a whole, our determination with respect to Petitioners' obviousness grounds would be the same under either construction.

D. Ground I: Obviousness in view of Kovarik and Thomson

Petitioners challenge claims 1–6 under 35 U.S.C. § 103 as obvious in view of Kovarik and Thomson. Pet. 21, 32–48. Patent Owner opposes. We begin with an overview of the asserted references.

i. Overview of Kovarik

Kovarik relates to an improved loading dosage regimen of S1P receptor modulators or agonists for the treatment of transplant patients suffering from autoimmune diseases or disorders, including multiple sclerosis. Ex. 1004, 1, 14. Preferred S1P receptor modulators or agonists "elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression." *Id.* at 2. In a particularly preferred embodiment, the S1P receptor agonist is FTY720 (i.e., fingolimod). *Id.* at 13.

Kovarik teaches that S1P receptor modulators or agonists are used in combination with cyclosporine A and everolimus in transplantation experiments and "[d]ue to their immune-modulating potency . . . are also useful for the treatment of inflammatory and autoimmune diseases." *Id.* at 1. According to Kovarik, "[i]t has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide further unexpected benefits." *Id.* In particular, an "S1P receptor modulator or agonist . . . is administered in such a way that during the initial 3 to 6 days . . . of treatment the dosage of said S1P receptor modulator or agonist is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage of said S1P receptor modulator or agonist is administered and thereafter the treatment is continued with the standard or a lower daily dosage . . . ." *Id.* at

13–14. "[T]he standard daily dosage (also called maintenance dose) refers to the dosage of an S1P receptor modulator or agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment." *Id.* at 14.

According to Kovarik:

> A particularly preferred dosage of . . . the preferred S1P receptor modulator FTY720, is e.g. 2-5, 5-10, 10-15 and 15-20 mg, e.g. a regimen of 2.5mg/5mg/7.5mg/10mg or 5mg/10mg/15mg/20mg, respectively, during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 2.5 mg or 5 mg, or at a lower daily dosage, e.g. 0.1 to 0, 5 [sic] mg.
>
> In a further embodiment of the invention, a preferred loading regimen of . . . the preferred S1P receptor modulator FTY720, may also be e.g. 0.5mg/1 mg/1.5mg/2mg during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 0,5 [sic] mg.

Id. at 15.[16] Kovarik further discloses: "A method for treating an autoimmune disease in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg." *Id.* at 17.

[16] In our Decision instituting *inter partes* review, we interpreted these passages in Kovarik as teaching the administration of a nominal loading dose of 0.5 mg of fingolimod followed by "maintenance therapy" at the same daily dose. Dec. 18 (citing Ex. 1004, 15). For the reasons set forth on pages 50–51 of the Patent Owner Response, we are persuaded that Patent Owner sufficiently establishes that Kovarik does not teach the administration of a nominal loading dose of 0.5 mg of fingolimod followed by "maintenance therapy" at the same daily dose.

ii. Overview of Thomson

Thomson teaches that "[fingolimod] elicits lymphocyte sequestration by facilitating a reversible redistribution of lymphocytes from the circulation to secondary lymphoid tissues. This is a unique immunomodulation mechanism whereby T lymphocytes are effectively directed away from inflammatory sites toward the lymphatic system." Ex. 1005, 162; *see also id*. at Abstract ("There is good evidence that FTY720 achieves immunomodulation as shown by a reversible redistribution of peripheral blood lymphocytes after oral administration."). According to Thomson:

> FTY720 has shown promising results in preclinical models of EAE, which in part has led to its clinical evaluation in multiple sclerosis. There is moderate evidence from two meeting abstracts of a phase II study that FTY720 (administered orally once daily for up to 12 months) improved the patient-oriented outcomes of relapse rate and the likelihood of remaining relapse-free. In addition, there is moderate evidence that disease-oriented outcomes were also improved by FTY720 in that inflammatory disease activity (both new and existing) was reduced as determined by MRI.

Id. at 166–167.

In reviewing the emerging clinical evidence for fingolimod as a treatment for multiple sclerosis, Thomson reports that "[t]wo meeting abstracts have been published showing results obtained with FTY720 in a 12-month phase II clinical trial in patients with active relapsing multiple sclerosis." Ex. 1005, Abstract. These publications disclosed the benefits of fingolimod as compared to placebo at doses of 1.25 and 5 mg per day.[17] *See id*. at 164–65, Table 4.

[17] We note that one of the referenced studies is Kappos 2005 (Ex. 1007).

Thomson also reviews a number of shorter-term clinical trials relating to pharmacodynamic and pharmacokinetic outcomes of fingolimod administration. *Id.* at 162–164, Table 3. With respect to one multi-dose study, Thomson notes that "[p]eripheral blood lymphocyte counts decreased from baseline to nadir (range 3–7 d after first dose) by 80 and 88% in subjects receiving FTY720 1.25 and 5 mg, respectively." *Id.* at Table 3.

With respect to another study involving single doses of 0.25, 0.5, 0.75, 1, 2, or 3.5 milligrams of FTY720, Thomson states: "All FTY720 groups showed a temporal pattern of relative lymphocyte sequestration, seen at the latest 6 h postdose. No clear dose response, but the highest doses showed a more pronounced reduction in lymphocyte numbers." *Id.* (referencing, in part, Budde 2002 (Ex. 1008)); *see also id.* at 163 ("Although the higher doses of FTY720 produced a more rapid and sustained lymphocyte sequestration, the actual degree of this property was similar across the range of doses used in the study and no clear dose–response relationship was detected.").

With respect to yet another study involving renal transplant patients co-administered cyclosporine and 0.25, 0.5, 1, or 2.5 mg doses of fingolimod for twelve weeks, Thomson reports that "lymphocyte sequestration was seen as early as w 1, nadir was reached at w 4 and was fully reversed 4-8 w after cessation of treatment. The pharmacodynamics were not dose-linear over the 10-fold dose range." *Id.* at Table 3; *see id*. at 164.

iii. Analysis of Ground 1

In short, Petitioners argue that the challenged claims would have been obvious over Kovarik and Thomson, because Kovarik teaches a 0.5 mg daily dose of fingolimod for the treatment of multiple sclerosis, whereas Thomson

teaches a range of doses, including 0.5 mg, which result in the lymphocyte homing effect then thought to underlie fingolimod's efficacy in treating RR-MS. In particular, Petitioners contend that "Kovarik discloses that the oral administration of a 0.5 mg daily dose of FTY720 provides effective treatment of multiple sclerosis . . . ." Pet. 36; *see* Ex. 1002 ¶¶ 119, 126; 1047 ¶¶ 25–30. According to Petitioners:

> A person of skill in that art would have read Kovarik's teachings as readily applicable to a patient with the RR-MS form of the disease because RR-MS is by far the most common form of the disease at onset and accounts for approximately 85% of cases. Also, a skilled artisan would have known that inflammation is the driver of relapses in RR-MS and that fingolimod hydrochloride was taught to treat MS by reducing inflammation through the accelerated lymphocyte homing mechanism taught by Kovarik.

Pet. 41–42 (internal citations omitted).

Petitioners argue that, "Thomson provides additional motivation to administer 0.5 mg FTY720 to a patient with RR-MS . . . [by] present[ing] an array of evidence supporting the efficacy of FTY720 in treating RR-MS by reducing relapse rates and slowing progression of RR-MS associated with inflammation." Pet. 42 (citing Ex. 1002, ¶ 109). According to Petitioners,

> [t]he skilled artisan would have had a reasonable expectation that the daily oral dose of 0.5 mg FTY720 taught by Kovarik would be therapeutically effective for patients suffering from RR-MS because Thomson describes clinical trials of FTY720 that tested doses in the range of 0.25 mg to 3.5 mg, in which it was found that "the actual degree of this property [lymphopenia] was similar across the range of doses used."

Pet. 43 (citing Ex. 1005, 162–63; Ex. 1002 ¶¶ 112–13).

In response, Patent Owner argues that Kovarik does not sufficiently link the treatment of RR-MS to the administration 0.5 mg daily dosages of

fingolimod, but instead is directed to loading dose rates and ratios—elements expressly excluded by the challenged claims. PO Resp. 4, 36–37; Sur-Reply 13–14. We find that Patent Owner has the better position.

Kovarik generally discloses the use of S1P receptor modulators or agonists, such as fingolimod, at daily dosages ranging from 5 mg to 0.1 mg after a loading dose regimen, for a host of conditions, including prolonging allograft survival rates in transplant patients and treating patients suffering from autoimmune diseases, exemplified by "multiple sclerosis, lupus nephritis, rheumatoid arthritis, inflammatory bowel diseases or psoriasis." Ex. 1004, 14. On page 15 of the reference, Kovarik discloses administration of a loading dose regimen followed by maintenance therapy at a daily dosage of, e.g., 0.5 mg of fingolimod per day, without specifying the disease or condition treated. At best, we find that Kovarik teaches that, after a loading dose regimen, an unspecified autoimmune disease may be treated with a daily dosage of "about 0.1 to 0.5mg" of fingolimod." *See id*. at 17 ("A method for treating *an autoimmune disease* in a subject in need thereof, comprising administering to the subject, after a loading regimen, a daily dosage of FTY720 of about 0.1 to 0.5mg." (emphasis added)).

Kovarik is directed to the use of loading doses, which, as Dr. Giesser testified and supports with evidence, "are not today, and were not in June 2006, part of the accepted MS or RR-MS treatment protocols. Ex. 1002 ¶ 67; PO Resp. 4, 36–37, 63–64. Ex. 2022 ¶ 8; *see also* Ex. 1047 ¶ 36 ("loading doses are merely to increase the rate at which steady state is achieved"); Ex. 1002 ¶¶ 67, 72, 119, 121–22; Ex. 2024 ¶ 130–133. Considering the testimony of the parties' experts, we credit Patent Owner's argument that Kovarik merely illustrates how a loading dose might be used

for an unspecified autoimmune disease, but would have had little relevance to the treatment of RR-MS, and provides no guidance as to dosing for RR-MS with, or without, a loading dose. *See* PO Resp. 36 ("The example did not cover 'any' or 'all' autoimmune disease(s), only one unspecified condition. RRMS is just one of dozens if not over 100 autoimmune diseases.") (citing Ex. 2022 ¶¶ 145–146); PO Reply 13–14 (citing Ex. 2096 ¶¶ 56–69); Ex. 2024 ¶¶ 141–151. Petitioners have not shown sufficiently how Kovarik links the treatment of RR-MS to the administration of 0.5 mg daily dosages of fingolimod with, or without, a loading dose. Accordingly, Petitioners have not demonstrated that one of ordinary skill in the art would have been motivated to administer 0.5 mg daily dosages of fingolimod to persons in need of treatment for RR-MS.

Petitioners further rely on Thomson as evidence that one of ordinary skill in the art would have recognized that a 0.5 mg daily oral dose of fingolimod would be effective in the treatment of RR-MS. *See* Pet. 42–46. We do not find Petitioners' arguments persuasive. Thomson discloses that fingolimod was effective for the treatment of RR-MS at 1.25 and 5 mg per day—substantially higher than the 0.5 mg daily dosage set forth in the challenged claims. *See* Ex. 1005, 164–165. Although Thomson also references a 0.5 mg dose, this is only in connection with single-dose safety data in renal transplant patients. *Id.* at 163 (discussing Budde, Ex. 1008 (*see* section II(E)(iii), below)). On this record, we agree with Drs. Steinman and Jusko that Thomson, like Kovarik, fails to teach or suggest the administration of 0.5 mg daily dosages of fingolimod to persons in need of treatment for RR-MS. *See* Ex. 2022 ¶¶ 161–162; Ex. 2024 ¶¶ 152–156.

For at least these reasons, we conclude that Petitioners have not demonstrated by a preponderance of evidence claims 1–6 would have been obvious under 35 U.S.C. § 103(a) in view of Kovarik and Thomson.

In section II(E), below, we discuss Patent Owner's arguments and evidence with respect to teaching away. Although not necessary to our determination with respect to Ground 1, our determination that the prior art teaches away from the claimed invention supports our conclusion that Petitioners have not demonstrated by a preponderance of evidence claims 1–6 would have been obvious under 35 U.S.C. § 103(a) in view of Kovarik and Thomson.

E. Ground 2: Obviousness in view of Chiba, Kappos 2005, and Budde

Petitioners assert that claims 1 and 5 would have been obvious under 35 U.S.C. § 103(a) over the combination of Chiba, Kappos 2005, and Budde. Pet. 48–57. Patent Owner opposes. We begin with an overview of the asserted references.

i. Overview of Chiba

Chiba discloses that fingolimod hydrochloride and related compounds are capable of suppressing the immune response of mammals through accelerated lymphocyte homing ("ALH-immunosuppression"). Ex. 1006, Abstract, 2:35–44, 4:63–5:7. "For example, the compound FTY720 specifically directs lymphocytes to the peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches. By reversibly sequestering lymphocytes in these tissues, the compounds can inhibit an immune response in a mammal." *Id.* at Abstract; *see id.* at 2:38–40, 17:38–40. Such ALH-immunosuppressive compounds "are useful in for the prevention or treatment of resistance to transplantation or transplantation rejection . . .

[and] autoimmune diseases such as . . . multiple sclerosis" (*id.* at 6:26–49) and may be administered "to an adult daily by 0.01-10 mg (potency) in a single dose or in several divided doses." (*id*. at 8:28–34).

ii. Overview of Kappos 2005

According to Kappos 2005, "FTY720 is an oral immunomodulator (sphingosine-1 phosphate receptor (S1P) modulator) that reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes. FTY720 has demonstrated both preventive and therapeutic efficacy in several animal models of MS." Ex. 1007, O141. Kappos discloses the clinical and MRI results of a double-blind, placebo-controlled study to evaluate efficacy, safety and tolerability of 1.25 mg and 5.0 mg daily doses of FTY720 in the treatment of RR-MS. *Id.* According to Kappos 2005, the study "demonstrated efficacy of FTY720 on MRI and relapse-related endpoints" and "strongly suggest[s] that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration." *Id*.

iii. Overview of Budde

Budde discloses a randomized, double-blind, placebo-controlled clinical trial designed to measure safety, single-dose pharmacokinetics, and pharmacodynamics of single oral doses of fingolimod in stable renal transplant patients. Ex. 1008, Abstract. Budde shows that single oral doses of 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, and 3.5 mg of the drug induced decreased lymphocyte counts as compared to placebo with a nadir of 4.7–8 hours after administration. *Id*. at 1078; *see id*. at 1079 ("All FTY-randomized groups manifested a temporal pattern of relative lymphopenia,

detected at the latest by 6 h postdose."); *id.* at 1082 ("Single oral doses of FTY in doses ranging from 0.5 mg to 3.5 mg caused a dose-dependent, reversible lymphopenia."). According to Budde:

> At FTY doses ranging from 0.5 mg to 3.5 mg, no clear dose response relationship was detected, but the two highest dose groups exhibited a more pronounced decline in lymphocyte numbers. FTY doses of ≥2.0 mg were associated with a more rapid onset of lymphopenia (31 to 43% decrease after 2 h). The three subjects treated with 3.5 mg FTY manifested the most prolonged and intensive lymphopenia.

Id.

With respect to safety, "single oral doses of FTY were well tolerated with transient asymptomatic bradycardia as the most common adverse event." *Id.* at 1082. "Higher doses of FTY were more frequently associated with bradycardia: 9 out of 12 subjects randomized to ≥0.75 mg of FTY developed bradycardia; however, only 1 of 12 subjects receiving 0.25 to 0.5 mg of FTY." *Id.* at 1075.

iv. Analysis of Ground 2

Petitioners argue that claims 1–6 would have been obvious "[b]ecause Chiba teaches oral administration of fingolimod hydrochloride for the treatment of multiple sclerosis, with Kappos 2005 confirming its utility in RRMS patients and Budde confirming the efficacy of a 0.5 mg daily dose of FTY720." Pet. 54. In particular, Petitioners state:

> In view of Kappos 2005 and Budde, the skilled artisan would have a reasonable expectation that the 0.5 mg daily dose, a dose within the range taught by Chiba and specifically used by Budde, would induce the desired pharmacological effect (lymphopenia) in RR-MS patients. EX1002, ¶¶58, 60-61, 64, 84, 139, citing EX1022 at 309, EX1018 at 237-39, EX1019 at 684, EX1031 at 1081, EX1028 at 440, and identifying lymphopenia as being "often used as a clinical end-point in dose response studies" and

> "relevant for relating dosage to lymphopenia for MS." Thus, a skilled artisan would have had reason to use the 0.5 mg dose identified in these clinical trials because there was no substantial pharmacological detriment to using the lower 0.5 mg dose and because Budde teaches that the 0.5 mg dose was associated with a decreased risk of adverse effects such as bradycardia when compared to higher doses. EX1008 at 1075-76; EX1002, ¶139.

Id. at 53–54.

In opposing Petitioners' arguments, Patent Owner contends, *inter alia*, that one of ordinary skill in the art would not have been motivated to combine the cited references to arrive at the claimed invention because the art as a whole taught away from administering daily dosages as small as 0.5 mg for the treatment of RR-MS.[18] *See* PO Resp. 33–39; PO Reply 5–8. A reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken" in the claim. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Whether the prior art teaches away from a reference may be dispositive of a challenge set forth in an *inter partes* review. *See generally, Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017).

[18] Patent Owner further provides evidence of unexpected results and skepticism by those of ordinary skill in the relevant field. *See id.* at 39–41. Because our conclusions with respect to teaching away are sufficient to our determination with respect to Petitioners' obviousness grounds, we need not consider this additional evidence.

Patent Owner's teaching away argument relies primarily on the combination of Webb, Kahan 2003,[19] and the Park references, Park 2003[20] and Park 2005,[21] which we discuss below.

1. Webb, Kahan 2003, and the Park References

Webb, a prior art article published by researchers at Merck in the respected, peer-reviewed Journal of Neuroimmunology, provides the lynchpin of Patent Owner's teaching away argument. *See* Ex. 2014;[22] Ex. 2096 ¶ 26. Webb studied the effects of fingolimod and its phosphorylated active metabolite, FTY-P, in a mouse model of RR-MS, experimental autoimmune encephalitis, or EAE. Ex. 2014, Abstract, 118. Webb initiated EAE by immunizing SLJ mice with a peptide based on the mouse proteolipid protein, PLP. *Id.* at 109, 110. The mice were then exposed to fingolimod, FTY-P, or control preparations. *Id.* at 110. Noting that "the effects of [fingolimod] are a result of the generation of the metabolite FTY-P," Webb focused on FTY-P "to examine the dose response

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[19] Kahan, et al., *Pharmacodynamics, Pharmacokinetics, and Safety of Multiple Doses of FTY720 in Stable Renal Transplant Patients: A Multicenter, Randomized, Placebo-Controlled, Phase I Study*, Transplantation, 76(7): 1079-1084 (2003). Ex. 1031.

[20] Park et al. "*Peripheral Blood FTY720 Pharmacokinetic/ Pharmacodynamic (PK/PD) Modeling in Renal Transplanted Recipients*," Abstract #707, Kidney: Pharmacogenetics, Kinetics and New Drug, p. 333-334 (2003). Ex. 2048.

[21] Park, et al., *Pharmacokinetic/Pharmacodynamic Relationships of FTY720 in Kidney Transplant Patients*, Brazilian J. Med. Biol. Res., 38: 683-694 (2005). Ex. 1019.

[22] Webb et al., *Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice*, 153 J. Neuroimmunology 108–21 (2004). Ex. 2014.

for clinical efficacy and peripheral lymphopenia, and the relationship between these two phenomena." *Id.* at 114.

In Figure 5B, Webb shows the cumulative clinical scores of mice immunized with the PLP peptide alone, or with increasing amounts of FTP-Y. *Id.* at 115; *see* Ex. 2024 ¶ 73. Although the scores for each of the FTP-Y pools is numerically lower than that of the PLP control, Webb indicates that only the results for the 1 mg/kg and 0.3 mg/kg treatments were statistically significant. *Id.* In Figure 6B, Webb shows that increasing amounts of FTP-Y cause increasing amounts of lymphocyte suppression (lymphopenia), which was considered a marker for therapeutic efficacy. *Id.; see* Ex. 2022 ¶ 41; Ex. 2024 ¶ 74. Figure 6C plots the cumulative clinical scores versus percent lymphopenia for the various pools. *Id.; see Ex. 2024* ¶ 74.

In discussing these experiments, Webb observed

> a dose-dependent and reversible lymphopenia on treatment with FTY720 or FTY-P. This reached a maximum of about 70–80% depletion at the highest doses used. . . . Because EAE is known to be a T cell-dependent disease, such sequestration, by preventing the entry of T cells with specificity for myelin components into the CNS, would account for the therapeutic efficacy.
>
> * * *
>
> In dose response experiments, we found that a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy, and thereafter, the dose response relationship between clinical benefit and lymphopenia was very steep.

Id. at 118.

According to Patent Owner, "EAE studies like those in Webb are an important 'predictive index for clinical therapeutic application' for MS treatment and thus useful in establishing dosing." PO Resp. 34 (citing Ex. 2022 ¶¶ 68, 72). Patent Owner further argues that, absent evidence to

the contrary, one of ordinary skill in the art would have understood Webb's threshold of about "about 70% depletion of peripheral lymphocytes" to apply across species. *Id.* (citing Ex. 2024 ¶ 75) (further noting that more than 80% lymphocyte suppression was known to be required to achieve a clinical effect in human transplant patients).

Patent Owner further points to Kahan 2003 and the Park references as evidence of the degree of lymphocyte depletion seen in humans dosed with 0.5 mg of fingolimod. *See* PO Resp. 9–14 (citations omitted). Kahan 2003 monitored 65 stable renal transplant patients receiving once-daily doses of 0.125, 0.25, 0.5, 1.0, 2.5, or 5.0 mg fingolimod, or placebo for 28 days. Ex. 1031, Abstract. Kahan 2003 reported that fingolimod "doses greater than or equal to 1.0 mg/day produced a significant reduction in peripheral blood lymphocyte count by up to 85%," with no "major increase in adverse events or a change in renal function" as compared to placebo. *Id.* Doses less than 1.0 mg/day produced materially lower reductions in peripheral lymphocyte blood counts. *Id*. at 1081-82; Ex. 2022 ¶ 56. As shown in Figure 1 of the reference, at the end of the administration period, the 1.0 mg daily dose resulted in about 70% lymphocyte suppression, whereas the 0.5 mg daily dose resulted in about 50% lymphocyte suppression. *Id.* at 1081; *see* Ex. 2022 ¶ 57.

Park 2003 monitored peripheral blood lymphopenia in 23 kidney transplant patients receiving 0.25, 0.5, 1.0 or 2.5 mg daily doses of fingolimod over the course of 12 weeks. Ex. 2048. Park reports that "EC_{50} was achieved at FTY720 doses of 0.5 mg and blood concentrations of 0.6 ng/mL. Since FTY720 PK are dose-linear and effective doses of FTY720 are 2.5 and 5 mg/day, the immunosuppressive effect of FTY720

may depend upon induction of high degree of lymphopenia (~80%)." *Id.* According to Dr. Steinmann, this indicates that for fingolimod, "0.5 mg was the 'EC50,' *i.e.*, the 'effective concentration' that reduced lymphocyte counts by half fingolimod's maximum level of about 88%. . . . In other words, 0.5 mg daily suppressed lymphocytes by about 44%." Ex. 2022 ¶ 59.

Dr. Steinmann further points to Park 2005, a follow-on to Park 2003. *Id.* at ¶¶ 61–66, 140–141 (citing Ex. 1019). Figure 7A of Park 2005 plots levels of lymphocyte suppression among patients administered daily doses of fingolimod over the course of 12 weeks. Ex. 1019, 690. Dr. Steinmann testifies that: "Patients in the 0.5 mg group range from less than 20% to less than 60% suppression; the 1.0 mg group range from 40% and 70%; and the 2.5 mg group between 70% and 80%. Thus, dose drove not only the average amount of suppression but also the degree of variation among patients. Lower doses had far more variation than higher doses." Ex. 2022 ¶ 62. Further interpreting Figure 7, Dr. Steinmann calculates that "the EC50 level—the level that achieves half the maximum effect, or about 44% suppression—is 0.48 mg daily, +/- 0.08 mg." *Id.* ¶ 63; *see also id.* at ¶ 64 (interpreting Park Table 3 as showing that 0.5 mg daily doses result in about 42% lymphocyte suppression with substantially more week-to-week variation than higher dose regimens).

Contrasting Webb's 70% threshold with Kahan 2003's and Park's teachings that 0.5 mg daily doses of fingolimod resulted in 50% or less depletion of lymphocytes, and greater variability than higher doses, Patent Owner argues that the prior art teaches away from administering 0.5 mg daily dosages of fingolimod for the treatment of RR-MS. PO Resp. 33–39;

see Ex. 2024 ¶¶ 124–127; Ex. 2022 ¶¶ 78, 115, 124–142; Ex. 2003 ¶ 39; Ex. Tr. 35:3–36:21.

Dr. Steinman explains that

> RRMS is a life-long condition. Relapses occur roughly 1.5 times per year. With each relapse (or even without), the disease progresses. More lesions develop on the CNS. Often, baseline function worsens with a relapse; that is, the effects of an attack can linger after the relapse is done. Disability thus accumulates over time. As a result, MS doctors focus on sustained, consistent relapse prevention and slowing progression of the disease. Even with some side-effects, the benefits of such sustained prevention are likely to outweigh the costs.

Ex. 2096 ¶ 43 (citing Ex. 2022 ¶¶ 29–30, 118). Accordingly, Dr. Steinmann testifies, "[s]ubstantial inter-patient variability would be unacceptable in a MS Drug." Ex. 2022 ¶ 144. Moreover, prior art studies showed that fingolimod was generally well tolerated such that any serious "side effects would have been manageable in comparison to the risks associated with submaximal therapeutic efficacy." *Id.* at ¶ 141. Thus, a 0.5 mg daily dosage regimen of fingolimod would have held promise as a treatment for RR-MS only if it could provide consistent, sustained benefits to patients. *See* Ex. 2096 ¶ 43.

With this background, we understand Patent Owner to argue that one of ordinary skill in the art would have been dissuaded from treating patients with doses of fingolimod that were likely to provide ineffective, sub-optimal, or variable clinical efficacy. Whereas Webb teaches that at least about 70% lymphocyte depletion provides a surrogate or marker for optimal efficacy, Kahan 2003 and the Park references show that 0.5 mg daily doses will not provide that level of lymphocyte depletion and, moreover, result in greater variability in this indicia of clinical efficacy.

Responding to Patent Owner's teaching away argument, Petitioners first address Webb's statement that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy." Pet. Reply 12–14. Focusing on Webb's 0.3 mg/kg dose—the lowest dose shown to have statistically significant clinical efficacy—Petitioners argue that the underlying data show that 0.3 mg/kg dose did not achieve at least 70% lymphopenia but "only about 60%, the same level of lymphopenia that 0.5 mg achieved in humans in Kahan 2003 and Park after 4 weeks," thus "suggest[ing] that the 0.5 mg daily dose would be clinically effective." *Id.* at 12 (citations omitted). Petitioners also contend that one of ordinary skill in the art "would not have been dissuaded from the 0.5 mg dose for RR-MS because of week-to-week or interpatient variability in lymphopenia or because higher lymphopenia (80%) was correlated with 'best efficacy' for preventing transplant rejection." *Id.* (citing Ex. 1047 ¶¶ 56–62).

We do not find Petitioners' arguments persuasive. First, we credit Dr. Steinman's testimony that one of ordinary skill in the art would have read Webb to mean what it says: "In dose response experiments, we found that a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy." *See* Ex. 2096 ¶¶ 26–40; *see also* Ex. 2095 ¶ 10 n.2; Ex. 2024 ¶¶ 65–80. We note for example, Dr. Steinman's testimony that, as compared to the summary data presented in the article, the Webb authors would have had access to more detailed information about their experiments from which to draw their conclusions, and that those conclusions were the result of the authors' collective judgment that had withstood rigorous peer review. *See id.* at ¶¶ 33–40.

Dr. Steinman's testimony is underscored by that of Dr. Chun, a co-author of Webb, which we likewise find persuasive. Ex. 2098 ¶¶ 2–9, 17–35. Dr. Chun testifies that:

> Our conclusion that 70% suppression was needed for "any efficacy" was the product of our collective judgment based on a totality of data presented in our paper. The average effect of one dose in one group of mice was just one piece of data. We also assessed the effects of different doses in individual mice; the ability of a dose to produce sustained clinical improvement; and other facts to reach our conclusions. As those with experience running EAE experiments know, the model has a subjective aspect that requires judgment-calls when interpreting results.

Id. at ¶ 7; *see also* Ex. 1063, 186:2–25, 275:11–18 (explaining that "any" efficacy in Webb could have been written as "most consistent," "predominant," or "reproducible"). According to Dr. Chun:

> Some mice would respond to lower doses with higher suppression, and vice versa. These differences in how individual mice responded to FTY-P were thus obscured by statistical use of standard error of the mean.
>
> * * *
>
> However, those individual observations did inform our overall conclusion that "a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]" (*Id.* at 118.) It is common in academic papers to report conclusions like this in the Discussion. Practical constraints imposed by journals prevent the publication of all the underlying data, such as data from each individual mouse. We thus highlighted the basic conclusion of "about 70%" in the Discussion to inform the readers.

Id. at ¶¶ 33–34.

Pointing to the testimony of Dr. Steinmann, Patent Owner also contends that Petitioners' expert incorrectly relied on maximum suppression data in Kahan 2003 and Park 2005 to conclude that 0.5 mg daily doses of

fingolimod would have resulted in levels of lymphopenia likely to be effective against RR-MS. PO Sur-Reply 6–7 (citing Ex. 2096 ¶¶ 41–54). According to Dr. Steinmann, Dr. Benet is also "mistaken in arguing that the inter-patient and week-by-week variability for 0.5 mg in Park 2005 would not be of independent concern to a person of skill designing a fingolimod dose." Ex. 2096 ¶¶ 50–52. Having considered the opposing arguments and the respective backgrounds of Drs. Bennet and Steinmann, we credit the testimony of Dr. Steinmann.[23]

2. Kataoka

Patent Owner further contends that Kataoka supports its position that lower doses of fingolimod would have been expected to provide sub-optimal clinical benefits. *See* PO Resp. 15, 19; PO Sur Reply 7–8, 12. Kataoka teaches that:

> Prophylactic administration of FTY720 at 0.1 to 1 mg/kg almost completely prevented the development of EAE, and therapeutic treatment with FTY720 significantly inhibited the progression of EAE and EAE-associated histological change in the spinal cords of LEW rats induced by immunization with myelin basic protein. Consistent with rat EAE, the development of proteolipid protein-induced EAE in SJL/J mice was almost completely prevented and infiltration of CD4+ T cells into spinal cord was decreased by prophylactic treatment with FTY720.

Ex. 1029, Abstract. Referencing the rat data in Kataoka Figure 1, Patent Owner argues that "[d]oses of 0.1 and 0.3 mg/kg reduced clinical

[23] Although Dr. Benet presents impressive credentials in drug development and the pharmaceutical sciences generally (*see*, *e.g.*, Ex. 1047 ¶¶ 1–11; Ex. 1048), Dr. Steinmann's background in researching MS and other autoimmune diseases (*see*, *e.g.*, Ex. 2022 ¶¶ 1, 12–21) is more pertinent to the issues before us.

scores and lymphocyte infiltration, although to a lesser extent than 1.0 mg/kg did. So, like the studies before it, Kataoka pointed to doses of 0.1 mg/kg or higher." PO Resp. 19 (citing Ex. 1029 ¶ 441; Ex. 2022 ¶¶ 86-89; Ex. 2024 ¶¶ 81-82). According to Dr. Steinmann, "Kataoka's lowest dose was more than three times higher than Webb's lowest dose," such that Kataoka "did not explore the boundary between effective and ineffective doses." Ex. 2022 ¶ 89.

We do not find Patent Owner's initial argument persuasive as it relies on rat data without adequately explaining how the dosages of fingolimod in rats correlates to the results reported by Webb using a mouse model.

Petitioners argue that mouse data in Kataoka confirms the efficacy of 0.5 mg fingolimod, thereby negating Patent Owner's teaching away argument. *See* Pet. Reply. 15; Ex. 1047 ¶¶ 64–78. According to Dr. Benet, Kataoka demonstrates that 0.1 mg/kg doses of fingolimod alleviated EAE symptoms in the mouse model. Ex. 1047 ¶¶ 64–65. Then, applying a conversion from the July 2005 FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (Ex. 1049), Dr. Benet calculates that a mouse dose of 0.1 mg/kg translates to approximately 0.5 mg in humans, and would have had substantially the same efficacy as a 1.25 mg dose or 5 mg dose. *Id.* at ¶¶ 67–74; *see also id*. at ¶ 77 (applying conversion factor from FDA Guidelines to Kataoka's rat data).

The FDA Guidance provides "a process (algorithm) for deriving the maximum recommended starting dose (MRSD) for *first-in-human* clinical trials of new molecular entities in adult healthy volunteers . . . . The purpose of this process is to ensure the safety of the human volunteers." Ex. 1049, 1

(italics in original). Fingolimod, however, had already been examined in healthy adult volunteers and, moreover, was used to treat human transplant patients and those suffering from MS. These existing studies provided substantial evidence of fingolimod's safety and side effects profile in humans. *See e.g.*, Ex. 1005, 157 (stating that fingolimod is "[w]ell tolerated. No serious adverse events noted. Most common adverse event is asymptomatic, mild, and transient reduction in heart rate"); Ex. 1006, 317 ("FTY720 is well tolerated and not associated with the side effects commonly observed with immunosuppressant therapy.); Ex. 1007 ("Treatment was generally well tolerated . . . with the most frequently reported (> 15 % patients) being mild headaches and nasopharyngitis."); Ex. 1008, 1075 ("No serious adverse events were reported during or after the administration of FTY. . . . The most common of the 28 reported adverse events were bradycardia *(n* = 10) and headache."); Ex. 1018, 241 ("Transient, asymptomatic bradycardia was observed after fingolimod administration, but overall the drug was well tolerated with no serious adverse events.").

Accordingly, and notwithstanding Dr. Benet's statement that it was "standard practice for pharmacologists to use the multipliers provided in FDA Guidance to translate animal doses from preclinical studies into doses for use in human clinical studies" (Ex. 1047 ¶ 68), the FDA Guidance on its face, indicates that it is not intended to apply to the dosing of well-established compounds such as fingolimod. Consistent with the teachings of the FDA Guidance, Patent Owner argues that one of ordinary skill in the art would not have used the FDA Guidance to extrapolate the mouse and rat data in Kataoka to a human dose. PO Sur-Reply 7–8 (citing Ex. 2095).

Consistent with our independent reading of the FDA Guidance, we find Patent Owner's argument persuasive for the reasons set forth in paragraphs 3–18 of Dr. Jusko's Declaration, Exhibit 2095. Summarizing this testimony, Dr. Jusko explains that,

> a person of skill in June 2006 would not have considered extrapolating from animal to human doses because extensive PK/PD data already existed in humans. The FDA Guidance is expressly designed only to identify a safe first-in-human dose before such data exists. But once human PK/PD data exists, that data would provide far more relevant information for estimating a dose's effects than an estimate based on simple animal dose data. Accordingly, a person of skill would not have used the FDA Guidance to extrapolate a human dose from Kataoka's lowest effective mouse dose.

Ex. 2095 ¶ 4.

Extending his analysis, Dr. Jusko argues that applying clearance data gathered from human and animal studies, a pharmacologist would calculate that Kataoka's 0.1 mg/kg effective dose in rats corresponds to about 1.4 mg in a 75 kg human. Ex. 2095 ¶¶ 19–28.[24]

In view of the above, Petitioners have not demonstrated that Kataoka detracts from Patent Owner's evidence of teaching away. To the contrary,

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[24] Petitioners vigorously challenged the bases for Dr. Jusko's calculations at deposition. Petitioners, for example, challenged Dr. Jusko's decision to use 75 kg as a standard patient weight in his calculation rather than other standard or average patient population weights as low as 60 kg. *See*, *e.g.*, Paper 74 ¶¶ 13–21; Paper 80, 14. Considering the formula Dr. Jusko used in calculating an equivalent human dose ("0.1 mg/kg from Kataoka x 75 kg human weight x 0.19 Conversion Factor = 1.43 mg"), simple arithmetic indicates that the substitution of 60 kg patient for the 75 kg standard used by Dr. Jusko also results in a dose substantially greater than 0.5 mg, i.e., 0.1 mg/kg from Kataoka x 60 kg human weight x 0.19 Conversion Factor = 1.14 mg. *See* Ex. 2095 ¶ 25.

Dr. Jusko's substantially unrebutted calculations using human and animal clearance data provide some support for Patent Owner's teaching away argument.

Considering all the evidence before us, Patent Owner has established that one of ordinary skill in the art would have been dissuaded from administering 0.5 mg daily dosages of fingolimod for the treatment of RR-MS, and that one of ordinary skill in the art would have had no reason to combine the teachings of Chiba, Kappos 2005 and Budde to arrive at the claimed invention. Accordingly, Petitioners have not demonstrated by a preponderance of evidence that claims 1–6 would have been obvious under 35 U.S.C. § 103(a) as asserted in Ground 2.

F. Ground 3: Obviousness in view of Kappos 2010

Petitioners challenge claims 1–6 under 35 U.S.C. § 102 as anticipated by Kappos 2010. Pet. 21, 57–61; *see* Ex. 1002 ¶¶ 144–146. Petitioners' challenge is predicated on the assertion that Kappos 2010 qualifies as prior art because claims 1–6 are not entitled to a filing date earlier than the April 21, 2014 filing date of the '342 application. Pet. 17–18, 57. In particular, Petitioners argue that the claim limitation requiring fingolimod administration "absent an immediately preceding loading dose regimen" first appeared in a preliminary amendment to the '342 application, whereas the originally filed '342 application and all prior applications are "silent regarding loading dose regimens." *Id*. at 57–58 (citations omitted).

Patent Owner does not dispute that Kappos 2010 discloses each element of claims 1–6, but argues: first, that Kappos 2010 is not prior art; and second, that in contravention of 35 U.S.C. § 311(b), Petitioners' "anticipation theory is a ruse to unlawfully smuggle a 112 written

description argument into an IPR." Prelim. Resp. 5, 45–49. We find no merit in the latter argument.

i. Jurisdiction to address Ground 3

Although § 311(b) permits *inter partes* review "only on a ground that could be raised under section 102 or 103," Petitioners have not challenged the instant claims on any ground other than those that could be raised under sections 102 and 103. *See* Pet. 5–8 (overview of Grounds 1–3). Consistent with the grounds set forth in the Petition, we do not address invalidity on any basis other than under sections 102 and 103. Ascertaining whether an asserted reference qualifies as prior art under these sections, however, is integral to our analysis. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (obviousness analysis requires consideration of "the scope and content of the prior art"). Not surprisingly, various panels of the Board have already addressed underlying §112 issues in the context of anticipation and obviousness grounds in *inter partes* reviews. *See, e.g.*, *Bioactive Labs. v. BTG Int'l Inc*., Case IPR2015-01305 (PTAB Dec. 15, 2015) (Paper 19, 8–12) (finding that Petitioner failed to demonstrate that parent application having same specification as challenged patent lacked written descriptive support and enablement for the challenged claims); *Dr. Reddy's Labs. Ltd. et al. v. Galderma Labs. Inc.*, Case IPR2015-01778, (PTAB Feb. 16, 2016) (Paper 11, 7-8); *Coalition For Affordable Drugs VIII, LLC v. Trustees of University of Pennsylvania*, Case IPR2015-01835 (PTAB Mar. 7, 2016) (Paper 7, 8-11) (finding that provisional application lacked sufficient written description to support claim of priority).

Consistent with these prior Board decisions, Patent Owner cites no authority precluding us from conducting analyses where, as in the present

case, the prior art status of a reference turns on whether one or more applications in the chain of priority of the challenged patent satisfy the written description requirement. Patent Owner, nevertheless, argues that:

> "[C]haracterising this issue as a question of" anticipation or obviousness cannot give the Board authority where it has none. The Board "simply cannot evade Congress's limitation upon its jurisdiction by" using Sections 102 and 103 as a back door to a Section 112 challenge.

PO Resp. 59 (citing *Mayfield v. Nicholson*, 499 F.3d 1317, 1320 (Fed. Cir. 2007); *Widdoss v. Sec'y of Dep't of Health & Human Servs.*, 989 F.2d 1170 (Fed. Cir. 1993)).

Patent Owner's citation to *Mayfield* is inapposite. In *Mayfield*, Appellant attempted to challenge a lower court's finding of fact by characterizing it as a matter of statutory interpretation—a question of law. *Mayfield*, 449 F.3d at 1322–23. With respect to Ground 3, however, we address anticipation (resolved on the bases of underlying facts), by ascertaining a factual issue (the scope and content of the prior art) with reference to second factual issue (whether the claims are entitled to a priority date of the '342 application), which necessitates a decision on a third factual issue (whether the '342 application recites sufficient written description to support the claims). *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1369 (Fed. Cir. 2009) (treating as a question of fact whether parent application provided sufficient § 112 support for the challenged claims such that applicants were entitled to an earlier priority date); *see also Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017) (reiterating that anticipation is a question of fact). Nowhere does our analysis invoke the question of law Patent Owner seeks to inject (i.e., whether we have the authority to address a ground of invalidity under

§ 112). Patent Owner's citation to *Widdoss v. Sec'y of Dep't of Health & Human Servs.*, 989 F.2d 1170 (Fed. Cir. 1993), is also inapplicable insofar as it refers to whether a court may waive a jurisdictional statutory time period and has no bearing on the present case.

In sum, we conclude that the panel is not jurisdictionally barred from addressing the merits of Petitioners' anticipation challenge, including the underlying question of whether Kappos 2010 qualifies as prior art with respect to the '405 patent.

ii. Whether Kappos 2010 qualifies as prior art

Patent Owner relies on the testimony of Drs. Steinman and Jusko in addressing the substance of Petitioners' contention that Kappos 2010 qualifies as prior art because the claim limitation requiring fingolimod administration "absent an immediately preceding loading dose regimen" is not supported in the text of the '405 patent or any of the substantially identical applications in its chain of priority. PO Resp. 62 (citing Ex. 2022 ¶¶ 10, 182–185; Ex. 2024 ¶¶ 19–21, 171–176). As set forth in the cited testimony, Patent Owner's experts explain why a person of ordinary skill in the art would understand that the specification of the '405 patent and its priority documents show possession of the full scope of the invention claimed. For example, pointing to Clinical Trial section in column 11 of the Specification, Dr. Jusko states:

> An ordinarily skilled person in this art would know that the dosing instructions "daily dosage" in this context are complete and that no loading dose is to be included. Further, a person of skill would know it would be ill-advised to alter the dosing regimen set forth in the instructions because changes in safety and efficacy could result. A person of skill in the art would know not to add in a loading due to the risk of the adverse effect of

> first-dose bradycardia. Also, MS is a chronic disease and as such would likely not require a loading dose to reach an effective dose quickly in a patient, as was shown in Kappos 2005 using daily doses of 1.25 mg or 5.0 mg. Given these considerations, the recitation in the patent of a daily dosage of 0.5, 1.25, or 2.5 mg p.o. would be understood as clear and complete by a person of ordinary skill in the art, and that the absence of an immediately preceding loading dose would be understood.

Ex. 2024 ¶ 174.

Dr. Jusko further explains that, because the Specification describes intermittent dosing without mentioning a loading dose, "[a] person of skill would understand the daily or intermittent doses to be the full and complete dosing regimen, and thus would understand the patent to mean that there should be no immediately preceding loading dose in the dosing regimen." *Id.* ¶ 175.

Dr. Steinmann sets forth similar opinions (*see* Ex. 2022 ¶¶ 10, 182–185) emphasizing, for example, that because initial doses of fingolimod were associated with bradycardia, one of ordinary skill in the art would interpret the Specification's silence with respect to loading doses as indicating the administration of only a daily dose. *See* Ex. 2022 ¶¶ 186–187.

Considering their respective backgrounds and experience, Drs. Jusko and Steinman are both well-qualified to testify as to the understanding of one of ordinary skill in the relevant art. *See e.g.*, Ex. 2005 ¶¶ 1, 7–13; Ex. 2006 (Jusko); Ex. 2022 ¶¶ 1, 12–21; Ex. 2023 (Steinman). We find their testimony on this matter credible and substantially unrebutted by Petitioner or Petitioners' experts. *See, e.g.*, Pet. Reply 24–25; Ex. 1002 ¶ 144 (Dr. Giesser stating that she "understood" the Specification lacked support for a loading dose, but evincing no independent analysis from the view point of

one of ordinary skill in the art). Their testimony is also consistent with the Specification and comports with our construction of "daily dosage."

"[A] patentee bears the burden of establishing that its claimed invention is entitled to an earlier priority date than an asserted prior art reference." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016). Considering the record as a whole, Patent Owner has demonstrated that the claims of the '405 patent are supported by the '342 application and the substantially similar disclosures of its predecessor applications, such that Kappos 2010 does not qualify as prior art.

Accordingly, we conclude that Petitioners have not demonstrated by a preponderance of evidence that Kappos 2010 anticipates claims 1–6 under 35 U.S.C. § 102(a).

III. MOTIONS

A. Motion to Amend

In its Corrected Contingent Motion to Amend, Patent Owner requests that we consider certain substitute claims if any one of the original claims of the '405 patent are found unpatentable. Paper 61, 1. As Petitioners have not shown by a preponderance of the evidence that any claim of the '405 patent is unpatentable, we deny Patent Owner's motion as moot.

B. Petitioners' Motion to Exclude

Petitioners filed a motion to exclude evidence (Paper 82); Patent Owner opposed (Paper 89); and Petitioners submitted a reply in support of its first motion to exclude (Paper 98).

i. Exhibits 2057 and 2070

Petitioner seeks to exclude Exhibits 2057 and 2070, and expert testimony relying on Exhibit 2057 under F.R.E. 602, 801-803, 805, and 901. Paper 82, 1–5; Paper 98, 1-2. Considering the parties' arguments and evidence, we agree with Patent Owner that Exhibit 2057, together with the signature pages relating to that document (Ex. 2070) comprise a report by inventors of the '405 patent describing work underlying the claimed invention, and intended to support Patent Owner's unexpected results arguments. *See* Paper 89, 1–5. Nevertheless, because we do not rely on the disputed portions of the record in our Decision, we deny this portion of Petitioners' motion as moot.

ii. Exhibits 2063–2066

Petitioner also seeks to exclude Exhibits 2063–2066 and expert testimony relying thereon under F.R.E. 106, 602, 801-803, 805, and 901. Paper 82, 5–11; Paper 98, 2–4. Patent Owner opposes. Paper 89, 6–11. The disputed exhibits relate to Patent Owner's arguments regarding skepticism in the field. Because, as with Exhibits 2057 and 2070, we have not reached the merits of Patent Owner's evidence of secondary considerations of nonobviousness, we dismiss Petitioners' Motion to exclude regarding those exhibits as moot.

iii. Exhibits 2098 and 2096

Petitioner further seeks to exclude under F.R.E. 702 and 703, Exhibit 2098 and Exhibit 2096, paragraphs 28, 31–34. Paper 82, 11–15; Paper 98, 5. Exhibit 2098 comprises Dr. Chun's testimony regarding the facts and circumstances surrounding the publication of Webb, including that the authors' conclusions reflect detailed, underlying and unpublished

experimental data. For example, Dr. Chun states: "We did not report the results from individual mice, nor would the Journal have provided the space needed to do so." Ex. 2098 ¶ 26. "However, those individual observations did inform our overall conclusion that 'a threshold of about 70% depletion of peripheral lymphocytes was required to see any efficacy[.]'" *Id.* at ¶ 34. Summarizing his testimony, Dr. Chun states that, "our conclusion that about 70% reduction in peripheral blood lymphocyte levels was required for any efficacy was not a mistake; it was the result of collective judgment based on multiple data sources and an appreciation of the subjective nature of determining clinical scores in this model." *Id.* at ¶ 8.

In the disputed portions of Exhibit 2096, Dr. Steinman testifies that in interpreting Webb, he took into account, for example, that "a person of skill would have understood that the authors had access to data from individual mice too, and that data would have informed their judgment as well." Ex. 2096 ¶ 31; *id.* at ¶ 33 ("Practical constraints on article length would normally preclude the publication of data like this. Instead, I would expect scientists who observe an important trend in disaggregated data to note their observation in summary form in the discussion section, just as the authors did here.").

Petitioner argues that Dr. Chun's testimony is "speculative and unsubstantiated" and his "memory cannot be relied upon." Paper 82, 13–14. Petitioner further contends that Patent Owner's failure to produce "the data underlying the Webb reference and any descriptions or summaries of the data Dr. Chun relied upon . . . renders the testimony cited above both unreliable and entitled to no weight, justifying exclusion of the testimony from consideration." *Id.* at 12.

As an initial matter, Petitioner does not persuasively argue that Dr. Steinmann relies on either Dr. Chun's testimony, or to Webb's unpublished data. *See id.* at 11–12. Nor do we understand Petitioners' complaint that it is not in possession of the underlying unpublished data as having any bearing on Dr. Steinmann's testimony as to how one of ordinary skill in the art would understand Webb. In addition, we take at face value Patent Owner's explanation that neither it, nor Dr. Chun, is in possession of that data. Paper 89, 13. Rather, "[t]he data belong to Merck, where Dr. Chun was employed while preparing the Webb paper." *Id.* (citing Ex. 2098 ¶ 2). With respect to Dr. Chun's memory and the underlying basis for his testimony, this goes to the weight of his testimony. Assessing the weight of fact and expert testimony is well within the purview of this panel.

Accordingly, and for the reasons set forth at pages 11–15 of Patent Owner's Opposition (Paper 89), which we find persuasive, we deny Petitioners' motion to exclude Exhibit 2098 and paragraphs 28, 31–34 of Exhibit 2096.

C. Patent Owner's First Motion to Exclude

Patent Owner filed a first motion to exclude evidence (Paper 80); Petitioners opposed (Paper 94); and Patent Owner submitted a reply in support of its first motion to exclude (Paper 97).

i. The Testimony of Dr. Giesser

Patent Owner moves to exclude "all or at least the pharmacology opinions" of Dr. Giesser (Ex. 1002), as well as her CV (Ex. 1003). Paper 94, 1. According to Patent Owner, "Dr. Giesser perform[ed] an improper, hindsight-driven analysis" and "strayed far outside her area of expertise." Paper 80 at 1–6. For the reasons set forth in Petitioners' opposition, we do

not agree that Dr. Geisser's analysis was improper. *See* Paper 94 at 1–7. Although we recognize the limitations of Dr. Giesser's expertise in pharmacology, Patent Owner's arguments go to the weight we should accord her testimony, not its admissibility. *See e.g.*, Dec. 9–10; Paper 80, 6; Paper 97, 3. Accordingly, Patent Owner's motion to exclude Ex. 1003 and all or part of Ex. 1002 is denied.

ii. Exhibits relating to IPR2017-01550 and Clinical Trial Protocol

Patent Owner moves to exclude documents relating to IPR2017-01550 (Exs. 1032, 1035, 1037, 1041), and a confidential Novartis clinical trial document obtained during discovery (Ex. 1051). Paper 80, 7–10; Paper 98, 3–4. Petitioners oppose. Paper 94, 7–8. Because we do not rely on Exhibits 1032, 1035, 1037, 1041, or 1051 in our Decision, we deny this portion of Patent Owner's motion as moot.

iii. Dr. Chun's Deposition and Related Exhibits

Patent Owner moves to exclude Exhibits 1055 and 1056, introduced at Dr. Chun's deposition, as well as certain of his responses to questions of fact and opinion Petitioners posed at his deposition. Paper 80, 10–13; Paper 97, 4–5. Petitioners oppose. Ex. 94, 9–13. According to Patent Owner, Exhibits 1055 and 1056 relate to Phase II clinical trials in transplant patients and are thus beyond the scope of Dr. Chun's declaration, which "was limited to reciting facts about his Webb paper." Paper 80, 11. Patent Owner further argues, inter alia, that the introduction of Exhibits 1055 and 1056 was untimely, and that Dr. Chun, by his own admission, lacked the expertise to interpret clinical trial data. *Id.* at 12–13. Although Patent Owner's arguments may have some merit, we do not rely on Exhibits 1055 and 1056

in our Decision. Accordingly, we deny this portion of Patent Owner's motion as moot.

iv. Dr. Jusko's Deposition and Related Exhibits

Patent Owner moves to strike Exhibits 1057–1060, introduced at Dr. Jusko's Deposition, as well as his responses to questions regarding them as "improper impeachment and irrelevant." Paper 80, 13–15; Paper 97, 4–5. As Petitioners' explain, the challenged exhibits were introduced to test Dr. Jusko's opinion that a 75 kg patient would have been used to calculate equivalent human dosages from animal data. Paper 94, 13–15. We agree with Petitioners that this is sufficient reason to introduce Exhibits 1057–1060. Accordingly, we deny Patent Owner's motion with respect to Exhibits 1057–1060 and related testimony, and have considered this information in our analysis.

D. Patent Owner's Supplemental Motion to Exclude

Patent Owner filed a supplemental motion to exclude evidence (Paper 102); Petitioners opposed (Paper 101); and Patent Owner submitted a reply in support of its supplemental motion to exclude (Paper 103). Patent Owner's motion relates to Exhibits 1065–1069, submitted in support of Petitioners' sur-reply to Patent Owner's motion to amend. *See* Paper 102, 1. Because we do not reach the parties' arguments with respect to Patent Owner's motion to amend, or otherwise rely on Exhibits 1065–1069, we deny Patent Owner's motion to exclude these exhibits as moot.

E. Stipulated Protective Order and Motions to Seal

i. Paper 29

In Paper 29, Patent Owner moves for entry of a Stipulated Protective Order (Exhibit 2074), which "differs from the Default Protective Order by

addition of a category of confidential material to be marked "OUTSIDE ATTORNEY'S EYES ONLY – PROTECTIVE ORDER MATERIAL," and that "[a]ccess to such material is restricted to outside counsel, experts, one in-house counsel of a party, and support personnel." Paper 29, 2; *see also* Ex. 2074 (redlined version of the Default Protective Order showing changes). Patent Owner avers that lead Petitioner Apotex agrees to the entry of the stipulated protective order and that "[a]n identical protective order was entered by a similarly constituted panel of the Board in *Torrent Pharms. Ltd. et al v. Novartis AG et al*, IPR2014-00784, Paper 41 (May 7, 2015)." *Id.* at 2–3. The record does not indicate that any other Petitioner objects to the entry of the proposed Stipulated Protective Order. To the contrary, Petitioners collectively submit motions to seal under the Stipulated Protective Order and, thus, acquiesce to its entry. *See* Papers 36, 37, 50, 83, and 99.

Upon review of the motion, we determine that Patent Owner has identified sufficiently how the proposed Stipulated Protective Order departs from the Board's default protective order set forth in the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48769–71 (Aug. 14, 2012). We further find that good cause exists for the proposed modifications from the Board's default protective order and that the proposed Stipulated Protective Order is warranted. Accordingly, we grant Patent Owner's unopposed motion for entry of a Stipulated Protective Order (Exhibit 2074).

We also address the parties' motions to seal. Papers 29, 37 (by Patent Owner); Papers 36, 50, 83, 99 (by Petitioner). Relevant to these motions, the Office Patent Trial Practice Guide states:

> 3. A party intending a document or thing to be sealed may file a motion to seal concurrent with the filing of the document or

> thing. § 42.14. The document or thing will be provisionally sealed on receipt of the motion and remain so pending the outcome of the decision on motion.
>
> 4. *Protective Orders:* A party may file a motion to seal where the motion contains a proposed protective order, such as the default protective order in Appendix B. § 42.54. Specifically, protective orders may be issued for good cause by the Board to protect a party from disclosing confidential information. § 42.54. Guidelines on proposing a protective order in a motion to seal, including a Standing Protective Order, are provided in Appendix B. The document or thing will be protected on receipt of the motion and remain so, pending the outcome of the decision on motion.

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012).

"There is a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an inter partes review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Techs.*, LLC, IPR2012–00001, slip op. at 1–2 (PTAB Mar. 14, 2013) (Paper 34). For this reason, except as otherwise ordered, the record of an *inter partes* review trial shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Motions to seal may be granted for good cause; until the motion is decided, documents filed with the motion shall be sealed provisionally. *See* 37 C.F.R. §§ 42.14, 42.54(a). The moving party bears the burden of showing that there is good cause to seal the record. *See* 37 C.F.R. § 42.20(c).

As set forth in the Board's Trial Practice Guide, confidential information that is sealed subject to a protective order ordinarily will become public 45 days after final judgment in a trial. Office Patent Trial

Practice Guide, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). A party seeking to maintain confidentiality of information may file a motion to expunge the information before it becomes public; however, if the existence of the information is identified in a final written decision following trial, there is an expectation that the information will be made public. *Id.* This rule "balances the needs of the parties to submit confidential information with the public interest in maintaining a complete and understandable file history for public notice purposes." *Id.*

Under the Board's procedures, there is an expectation that all exhibits, including those filed under seal here, will be made part of the public record. Furthermore, the public's interest in understanding the basis for our decision on patentability means that any good cause alleged in a motion to seal must overcome this heightened public interest. Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

In Paper 29, Patent Owner moves to seal Exhibits 2057 and 2063–2066. According to Patent Owner,

> Exhibits 2063-66 represent confidential communications with the FDA and/or disclose proprietary information regarding the design and execution of Novartis clinical trials. Novartis holds the information contained in these exhibits as confidential and takes precaution to prevent their distribution. Additionally, at least Exhibit 2057 contains redactions of specific personal information that is subject to Swiss Privacy Law and may not be distributed outside of Novartis. As a result, public disclosure of these documents could cause competitive business harm and good cause exists to seal them.

Paper 29, 3. We find that Patent Owner has satisfied the good cause requirement with respect to Exhibits 2057 and 2063–2066. Because we do not rely on these exhibits in our Decision, Patent Owner's desire to keep these documents confidential is not outweighed by the public interest in maintaining a complete and understandable record of these proceedings. Accordingly, we grant Patent Owner's motion with respect to Exhibits 2057 and 2063–2066.

Patent Owner further seeks to seal "portions of the Patent Owner's Response [Paper 26] and accompanying declarations of Lawrence Steinman (Ex. 2022), William Jusko (Ex. 2024), Fred Lublin (Ex. 2025), and Christian Schnell (Ex. 2026) containing substantive reference to the above exhibits." Paper 29, 4. Patent Owner does not otherwise identify the portions of those documents subject to its motion. We note, however, that Patent Owner has filed redacted versions of these documents. Accordingly, we grant Patent Owner's request on condition that, within 10 business days of this Decision, Patent Owner certify that the redacted versions of the documents on file, or in the alternative, replacement copies thereof, comport with the grant or denial of any motion to seal in this proceeding.

ii. Paper 37

In Paper 37, Patent Owner moves to seal Paper 38, the unredacted version of its Brief in Opposition to Additional Discovery and unredacted versions of Exhibits 1042 and 1043, submitted by Petitioners. Considering the nature of these documents, and that we do not rely on this information in our Decision, Patent Owner has sufficiently shown good cause for granting this request.

iii. Paper 36

As we understand Paper 36, Petitioners move to seal the unredacted versions of Exhibits 1042 and 1043 and the entirety of Exhibits 1044 and 1045 because Patent Owner has designated each of these documents confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion.

As set forth above, we grant Patent Owner's motion to seal with respect to Exhibits 1042 and 1043, rendering Petitioners' request moot with respect to these Exhibits. With respect to Exhibits 1044 and 1045, because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

iv. Paper 50

As we understand Paper 50, Petitioners move to seal their Reply to Patent Owner's Response (Paper 49), the unredacted version of Exhibits 1047, and the entirety of Exhibits 1050 and 1051 because Patent Owner has designated such information confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion. Because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

v. Paper 83

As we understand Paper 83, Petitioners move to seal their Motion to Exclude (Paper 82) because Patent Owner has designated such information

confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion. Because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

vi. Paper 99

As we understand Paper 83, Petitioners move to seal their Reply in Support of Motion to Exclude (Paper 98) because Patent Owner has designated such information confidential subject to the Stipulated Protective Order. We do not discern that Patent Owner joins the motion. Because the subject information may be confidential to Patent Owner rather than Petitioner, we deny the request. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

IV. CONCLUSION

Having weighed Petitioners' arguments and evidence as to the challenged claims against Patent Owner's countervailing arguments and evidence, we determine that Petitioners have not established by a preponderance of the evidence the unpatentability of claims 1–6 of the '405 Patent.

V. ORDER

For the above reasons, it is

ORDERED that claims 1–6 of the '405 Patent have not been shown to be unpatentable as obvious under 35 U.S.C. § 103 over Kovarik and

Thomson;

FURTHER ORDERED that claims 1–6 of the ’405 Patent have not been shown to be unpatentable as obvious under 35 U.S.C. § 103 over Chiba, Kappos 2005, and Budde;

FURTHER ORDERED that claims 1–6 of the ’405 Patent have not been shown to be unpatentable as anticipated under 35 U.S.C. § 102 over Kappos 2010;

FURTHER ORDERED that Patent Owner’s Corrected Contingent Motion to Amend (Paper 61) is denied as moot;

FURTHER ORDERED that Petitioners’ motion to exclude Exhibits 2057 and 2070, and expert testimony relying on Exhibit 2057 (Paper 82) is denied as moot;

FURTHER ORDERED that Petitioners’ motion to exclude Exhibits 2063–2066 and expert testimony relying thereon (Paper 82) is denied as moot;

FURTHER ORDERED that Petitioners’ motion to exclude Exhibit 2098 and paragraphs 28, 31–34 of Exhibit 2096 (Paper 82) is denied;

FURTHER ORDERED that Patent Owner’s motion to exclude Exhibit 1003 and all or part of Exhibit 1002 (Paper 80) is denied;

FURTHER ORDERED that Patent Owner’s motion to exclude Exhibits 1032, 1035, 1037, 1041, 1051 (Paper 80) is denied as moot;

FURTHER ORDERED that Patent Owner’s motion to exclude Exhibits 1055, 1056, and portions of Exhibit 1063 (Paper 80) is denied as moot;

FURTHER ORDERED that Patent Owner’s motion to exclude Exhibits 1057–1060 and portions of Exhibit 2095 (Paper 80) is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1065–1069 (Paper 102) is denied as moot;

FURTHER ORDERED that Patent Owner's motion for entry of a Stipulated Protective Order (Paper 29) is granted;

FURTHER ORDERED that the Stipulated Protective Order (Exhibit 2074) is hereby entered and shall govern the conduct of this proceeding unless otherwise modified by the Board;

FURTHER ORDERED that Patent Owner's motion to seal Exhibits 2057 and 2063–2066 (Paper 29) is granted. Patent Owner's further request to seal related portions of Paper 26 and Exhibits 2022, 2025 and 2026 is provisionally granted on condition that, within 10 business days of this Decision, Patent Owner certify that the redacted versions of the documents on file, or in the alternative, replacement copies thereof, comport with the grant or denial of any motion to seal in this proceeding;

FURTHER ORDERED that Patent Owner's motion to seal Paper 38, the unredacted version of its Brief in Opposition to Additional Discovery and unredacted versions of Exhibits 1042 and 1043 (Paper 37) is granted;

FURTHER ORDERED that Petitioners' motion to seal the unredacted versions of Exhibits 1042, 1043, and the entirety of Exhibits 1044 and 1045 (Paper 36) is denied. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

FURTHER ORDERED that Petitioners' motion to seal their Motion to Exclude (Paper 82) is denied. To the extent any of this information is not substantively relied on in the final written decision, Patent Owner may file its own motion to seal within 10 business days of this Decision.

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

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