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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM INTERNATIONAL GMBH and
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00409
Patent 8,889,135 B2

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges.*

MITCHELL, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

Determining Claims 1–5 Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–5 (collectively, "the challenged claims") of U.S. Patent No. 8,889,135 B2 (Ex. 1001, "the '135 patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner demonstrates, by a preponderance of evidence, that claims 1–5 are unpatentable.

A. Procedural History

Boehringer Ingelheim International GMBH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Petitioner") filed a Petition (Paper 3, "Pet.") requesting an *inter partes* review pursuant to 35 U.S.C. § 311. On July 7, 2016, we instituted trial to determine whether claims 1–5 of the '135 patent are unpatentable under 35 U.S.C. § 103 as obvious over the following combinations: (1) Kempeni 1999[1] and van de Putte 1999,[2] and (2) Rau 1998,[3] Schattenkirchner 1998,[4] and van de Putte 1999. Paper 9 ("Decision on Institution" or "Inst. Dec.").

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[1] Joachim Kempeni, *Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7*, 58 (Supp. I) ANN. RHEUM. DIS. 170 (1999) (Ex. 1011, "Kempeni 1999").

[2] L.B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42 (Supp.) ARTHRITIS & RHEUM. S400 (1999) (Ex. 1008, "van de Putte 1999").

[3] Rolf Rau et al., *Long-term Efficacy and Tolerability of Multiple I.V. Doses of the Fully Human Anti-TNF-Antibody D2E7 in Patients with Rheuma[t]oid Arthritis*, 41 (Supp.) ARTHRITIS & RHEUM. S55 (1998) (Ex. 1006, "Rau 1998").

[4] Manfred Schattenkirchner et al., *Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNF-Antibody D2E7 in*

AbbVie Biotechnology Ltd. ("Patent Owner") filed a Response (Paper 24, "Resp."), and Petitioner filed a Reply (Paper 38, "Reply"). Petitioner supports its Petition with the Declarations of Michael H. Weisman, M.D., a rheumatologist, and William J. Jusko, Ph.D., who studies pharmacokinetics. Pet. 2–3; *see* Exs. 1003, 1004. Patent Owner relies on the Declarations of Dr. Allan Gibofsky, a rheumatologist (Ex. 2071), Alexander Vinks, who studies pharmacokinetics (Ex. 2075), Jeffrey Sailstand, who studies anti-drug antibodies (Ex. 2074), Bryan Harvey, a former FDA official who discusses biologic clinical trials (Ex. 2072), and Jerry Hausman, an economist (Ex. 2073). Resp. 1 n.1.

Oral argument was heard on April 4, 2017, and a transcript of the argument has been entered into the record (Paper 45, "Tr.").[5]

B. Related Proceedings

The parties identify an *inter partes* proceeding, IPR2016-00172 ("172 IPR"), in which Coherus BioSciences Inc. petitioned for review of claims 1–5 of the '135 patent. *See Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2016-00172 (PTAB) (*Coherus*); Pet. 4; Prelim. Resp. 1–2; Paper 6, 1. The Board instituted *inter partes* review of claims 1–5 of the '135 patent in the 172 IPR, *see Coherus*, Case IPR2016-00172, slip op. at 22 (PTAB May 17, 2016) (Paper 9), and found claims 1–5

Patien[t]s with Rheumatoid Arthritis – Results of a Phase I Study, 41 (Supp.) ARTHRITIS & RHEUM. S57 (1998) (Ex. 1007, "Schattenkirchner 1998").

[5] Petitioner and Patent Owner filed Objections to Evidence or Exhibits, *see* Papers 11, 12, 27, and 39. We have reviewed these papers and will give the evidence the appropriate weight in light of these objections.

unpatentable in a final written decision issued May 16, 2017, *see Coherus*, Case IPR2016-00172, slip op. at 44 (PTAB May 16, 2017) (Paper 60).

The parties also identify as related IPR2016-00408, an *inter partes* proceeding also involving the '135 patent filed by Petitioner, and two other *inter partes* proceedings involving related patents, U.S. Patent No. 9,017,680 and U.S. Patent No. 9,073,987, IPR2016-00188 and IPR2016-00189, respectively. Paper 36, 1–2.

C. The '135 Patent

The '135 patent, titled "Methods of Administering Anti-TNFα Antibodies," issued on November 18, 2014. The '135 patent discloses methods of treating rheumatoid arthritis ("RA") with a human anti-tumor necrosis factor α ("TNFα") antibody. Ex. 1001, Abstract, 3:4–7. RA is an autoimmune disease with a pathophysiology that is linked to tumor necrosis factor. Ex. 1001, 25:33–37. Specifically, TNFα has been implicated in activating tissue inflammation and causing joint destruction in RA. *Id.* at 1:12–15, 25:33–37. The methods of the claimed invention involve administering an anti-TNFα antibody having the six complementarity determining regions ("CDRs") and heavy chain constant region of D2E7, a known recombinant human anti-TNFα antibody. *Id.* at 3:28–38, 4:36–55, 9:53–67, 12:14–18. The methods further include administering a total body dose of 40 mg of the anti-TNFα antibody subcutaneously every 13–15 days, i.e., biweekly, for a period of time sufficient to treat RA. *Id.* at 3:39–45, 23:18–21, 24:25–29.

D. Illustrative Claim

Claims 1 and 5 are independent claims of the '135 patent. Claim 1 is illustrative of the challenged claims and recites:

> 1. A method for treating rheumatoid arthritis in a human subject, comprising administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13–15 days for a time period sufficient to treat the rheumatoid arthritis, wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDRl having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("V_H") chain region comprising a CDRl having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of SEQ ID NO:6 and a CDR3 having the amino acid sequence of SEQ ID NO:4.

Ex. 1001, 45:11–25. Claims 2–4 depend ultimately from claim 1. Claim 2 specifies that "the V_L chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:1 and the V_H chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:2." *Id.* at 45:26–29. Claim 3 specifies that the anti-TNFα antibody in the method of claim 2 "is administered for a period of at least 24 weeks," and claim 4 specifies that the anti-TNFα antibody in the method of claim 1 "is administered for a period of at least 24 weeks." *Id.* at 45:30–31, 46:11–12. Independent claim 5 recites a method that is similar to the method of claim 1, except that it recites "consisting of" instead of "comprising," and further recites that the antibody is "administered in the form of a pharmaceutically acceptable composition." *Id.* at 46:13–30.

II. DISCUSSION

Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge that claims 1–5 of the '135 patent are unpatentable as obvious over the combination of van de Putte 2000 and Rau 2000 by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). We find that Petitioner has met its burden for all challenged claims 1–5.

A. Level of Ordinary Skill

In our Decision on Institution, we discussed, as described by each party, the level of ordinary skill in the art as of June 8, 2001, the priority date of the '135 patent. Inst. Dec. 9, n.5. Specifically, we stated that

> Petitioner states that the level of skill in the art is a "practicing rheumatologist with a medical degree, roughly 3 years of experience treating RA patients, and some familiarity or experience with anti-TNFα antibodies and clinical trial procedures and design, including familiarity with basic pharmacokinetic concepts such as half-life." Pet. 17 (citing Ex. 1003 ¶ 12, 14–28). Petitioner also includes a Declaration of Dr. Jusko, a pharmacokineticist. *Id*. at 17–18; *see* Ex. 1004. Patent Owner asserts that one of skill in the art includes a Ph.D. pharmacokineticist with at least three years of experience working with biologic agents. Resp. 18.

Id. n.5.

Patent Owner asks that we adopt the definition of the level of ordinary skill in the art utilized by both the Petitioner and Patent Owner in the 172 IPR that includes "the skill sets of both a physician treating RA patients and a pharmacokineticist with experience in monoclonal antibodies." Resp.

17–18; *Coherus*, Case IPR2016-00172, slip op. at 5–6. Petitioner notes that "[t]o the extent that the level of ordinary skill would have included the skills of a pharmacokineticist, this Petition provides that perspective through the Declaration of Dr. Jusko (Ex. 1004), a world-renowned expert in this field." Pet. 17–18. As both parties have applied a definition of the level of ordinary skill that includes a pharmacokineticist, and such a level of ordinary skill in the art is reflected in the sophistication of the technology and the educational level of those working in the field of the invention, we adopt the level of ordinary skill in the art for the '135 patent set forth in the 172 IPR. *See In re GPAC*, 57 F.2d 1573, 1579 (Fed. Cir. 1995) (setting forth factors to be considered in determining the level of ordinary skill in the art); *Coherus*, Case IPR2016-00172, slip op. at 5–6.

B. 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). Under that standard, claim terms generally are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). An inventor may rebut that presumption by providing a definition of the term in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In the absence of such a definition, limitations are not to be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

In our Decision on Institution, we stated that "[a]lthough Petitioner asserts that we need not construe expressly any term for purposes of our institution decision, Petitioner relies on the explanation provided in the petition in IPR2016-00172 for the ordinary meaning of 'method for treating rheumatoid arthritis,' 'every 13-15 days,' and 'pharmaceutically acceptable composition.'" Inst. Dec. 5 (citing Pet. 19 (citing the 172 IPR Petition 14–17)). We found that such reliance was an improper incorporation by reference of arguments asserted in another petition, which we would not consider. *See id.* at 5; 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document.").

We also discussed in our Decision on Institution the claim term "for a time period sufficient to treat the rheumatoid arthritis," which Patent Owner asserted should be construed. Inst. Dec. 6–7. We disagreed with Patent Owner's assertion that "for a time period sufficient to treat the rheumatoid arthritis" means "for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthritis." *See id.* We concluded for purposes of the decision on institution that we did not need to interpret expressly the claim term "for a time period sufficient to treat the rheumatoid arthritis," but noted the claim term when read in light of the Specification of the '135 patent did not require a particular level of efficacy. *Id*. at 7.

In its Patent Owner Response, Patent Owner asserts that Petitioner does not meet its burden to show unpatentability of the challenged claims regardless of the construction of the phrase "for a time period sufficient to treat the rheumatoid arthritis" because the prior art teaches away from the claimed invention and a person of ordinary skill in the art "would have been motivated to pursue an effective treatment regimen, not one that merely

provided baseline functionality." Resp. 18. Patent Owner, nevertheless, reiterates its position that the term should mean "for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthristis." *Id*. at 65.

Patent Owner explains that

> No clinician would consider himself or herself to be "treating" RA if there were no therapeutically meaningful reduction in the patient's signs, symptoms, and disease progression. Ex. 2071 ¶¶ 21, 104–105, *see* Ex. 2025, 3 (fundamental goal as of 2001 was to eliminate disease activity or control it to the fullest extent possible); Ex. 2070, 242:8–245:1. If that were the case, then anything that had any effect on a patient's symptoms, no matter how minimal or short-lived (for example, an analgesic or intoxicant), would constitute "treatment." Ex. 2071 ¶ 104. That is simply not how a physician seeking to reduce the signs, symptoms, and disease progression would understand his or her clinical objective (both then and now). *Id*.

Resp. 64–65.

Tellingly, there is no citation to the Specification of the '135 patent in Patent Owner's proffered support. *See id*. at 64–67; *see also* Reply 27 (stating Patent Owner does not cite any new intrinsic evidence supporting its proposed construction). The best source for determining the meaning of a claim term is the specification. *See In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997) (stating that "the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification").

As we noted in our Decision on Institution, in reviewing the claims in light of the language of the claims and the Specification of the '135 patent, we found:

> In reviewing the claim language of claims 1 and 5, neither claim recites that any particular level of efficacy is required; each of these claims merely recites administering the antibody for a time sufficient to treat RA. Consistent with that claim language, the Specification describes administering the antibody for therapeutic purposes to alleviate the symptoms and/or progression of disorders such as rheumatoid arthritis. *See, e.g.*, Ex. 1001, 24:25–60.

Inst. Dec. 6.

In the companion *inter partes* proceeding involving the '135 patent, the 172 IPR, we discussed the meaning of the term "for a time period sufficient to treat the rheumatoid arthritis" citing extensively to the Specification of the '135 patent. *See Coherus*, Case IPR2016-00172, slip op. at 6–9 (Paper 60). We adopt here the discussion and the findings set forth in that *inter partes* proceeding construing the claim term "for a time period sufficient to treat the rheumatoid arthritis."

The construction of this term, as set forth in the companion proceeding, i.e., "for a time period sufficient to reduce the signs, symptoms, and/or progression of RA," is consistent with our Decision on Institution, where we stated that the claims do not require a particular level of efficacy and with the description in the Specification of the '135 patent of administering the antibody for therapeutic purposes to alleviate the symptoms and/or progression of RA. *See* Ex. 1001, 24:25–60. Nothing in Patent Owner's discussion set forth above concerning its proffered construction alters our view that the claim term does not require a particular level of efficacy.

As we found in the 172 IPR, Patent Owner's proposed construction introduces ambiguity in the claims. Patent Owner discusses "meaningful reduction" in or reducing "significantly" a patient's signs, symptoms, and disease progression without providing any specific measure for achieving such a goal. *See* Resp. 64–65. We agree with the 172 IPR finding that such ambiguity arises because "Patent Owner's construction does not indicate whether reducing 'significantly' the signs and symptoms of RA means that patients self-report better overall health status on a health survey, or that patients must achieve an ACR20 response, or even an ACR70 response, or a combination of all of the reported outcome measures." *Coherus*, Case IPR2016-00172, slip op. at 9 (Paper 60).

Therefore, consistent with our decision in the 172 IPR and with our Decision on Institution, we determine that the phrase "for a time period sufficient to treat the rheumatoid arthritis" does not require any particular level of efficacy and, under the broadest reasonable construction, means "for a time period sufficient to reduce the signs, symptoms, and/or progression of RA."

C. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said 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 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).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1259. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. 398, 421 (2007). "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted ground of unpatentability in accordance with the above-stated principles.

D. Obviousness over van de Putte 1999 and Kempeni 1999

Petitioner contends that claims 1–5 are unpatentable under 35 U.S.C. § 103 as obvious over van de Putte 1999 and Kempeni 1999. Pet. 19–37. Petitioner asserts that van de Putte 1999 expressly teaches each limitation of

claims 1–5 except for every-other-week administration and administration for 24 weeks (which is a limitation in dependent claims 3 and 4). *Id*. at 2, 19. Petitioner asserts that Kempeni 1999 provides the missing teachings. *Id*. Petitioner offers that "a person of ordinary skill in the art would have, at a minimum, tried administering the prior art doses, including the claimed 40 mg dose, subcutaneously on an every-other-week basis." *Id.* (quoting *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir.) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance."), *cert. denied*, 135 S. Ct. 878 (2014)).

Patent Owner counters that "the clinical and pharmacokinetic ("PK") data in the prior art taught away from the claimed invention because a POSA would have believed that the claimed dosing regimen would result in drug concentration levels that were too low to treat rheumatoid arthritis ("RA")." Resp. 1–2. Therefore, the claimed invention would not have resulted from routine optimization or have been obvious to try in light of such a teaching away. *Id.* at 4.

1. van de Putte 1999

van de Putte 1999 describes the results of a dose-finding phase II study that compared three dose levels of D2E7 and placebo over three months in patients with long-standing active RA. Ex. 1008, 7. In the study, patients received "weekly [fixed] doses of either D2E7 at 20, 40, [or] 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." *Id*. van de

Putte 1999 reports the percentage of patients receiving an ACR20[6] response, as well as the median percent improvement in TJC, SWJC, and CRP for each of the dosing regimens and placebo.

The results are reproduced below.

	Placebo	D2E7	D2E7	D2E7
		20 mg	40 mg	80 mg
	(n=70)	(n=71)	(n=70)	(n=72)
% of pts achieving ACR 20 response	10	49	57	56
Median % improvement in TJC	5	57	61	55
Median % improvement in SWJC	16	42	59	61
Median % improvement in CRP	1	55	67	65

Id. The table above shows the results of the clinical study described in van de Putte 1999. Based on the results, van de Putte 1999 concludes that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)" and that "20, 40, and 80 mg/week were nearly equally efficacious when given s.c. in patients with active RA." *Id.*

2. Kempeni 1999

Kempeni 1999 teaches that D2E7 is a class of fully human, anti-TNFα antibody that "may have advantages in minimizing antigenicity in humans"

[6] ACR20 is short hand for the American College of Rheumatology improvement criteria. Ex. 1011, 4. "[T]o be classified as a responder according to ACR20 criteria, patients must demonstrate: (1) greater than or equal to 20% improvement in swollen joint count ("SWJC"); (2) greater than or equal to 20% improvement in tender joint count ("TJC") and; (3) at least 20% improvement in three of five other measures (patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, an acute phase reactant (for example, erythrocyte sedimentation rate (ESR) or C reactive protein ("CRP")), and a measure of disability . . . ." *Id.*; *see* Ex. 1003 ¶ 19; Ex. 2071 ¶ 41.

compared to biologic TNF antagonists that are not fully human. Ex. 1011, 3. Kempeni 1999 further describes the results of several clinical studies investigating the use of D2E7 to treat RA patients. *Id*. at 3–5. During the clinical trials, efficacy was assessed using the ACR20 criteria. *Id*. at 3–4.

In the first described study, each patient received a single dose of D2E7 (from 0.5 to 10 mg/kg) or placebo by intravenous injection. *Id*. Patients were evaluated for four weeks to determine the pharmacokinetics of D2E7 and to evaluate the safety and efficacy of the compound in terms of onset, duration, and magnitude of response. *Id*.

Kempeni 1999 describes the results of the study as "encouraging," noting that the "therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1–2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." *Id*. Pharmacokinetic parameters were calculated for patients from all dose groups and the estimated mean terminal half-life of D2E7 was determined to be 11.6 to 13.7 days. *Id*.

Patients who continued in the study were given a second blinded dose that was identical to the first and, subsequently, given active drug every two weeks until a "good" response was achieved. *Id*. Patients who did not respond well after 0.5 or 1 mg/kg dosing, however, received higher doses of up to 3 mg/kg. *Id*. Kempeni 1999 discloses that 86% of patients continued to receive treatment with D2E7 after six months, "indicating that long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." *Id*.

In a second study that evaluated the safety and efficacy of weekly subcutaneous 0.5 mg/kg weight-based administration of D2E7, patients were

given either D2E7 or placebo weekly for a period of three months. *Id*. at 4–5. The dose was increased to 1 mg/kg subcutaneously weekly for non-responders or patients losing responder status. *Id*. at 5.

According to the preliminary data, "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." *Id*. Further, up to 78% of patients achieved an ACR20 response after three months of treatment, leading to the conclusion that "D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery." *Id*.

In a third clinical study that evaluated the safety of 1 mg/kg single subcutaneous or intravenous injections, it was determined that the safety profile of single dose D2E7 administration was "comparable to that of placebo." *Id*.

Kempeni 1999 teaches that the data from these studies collectively suggest D2E7 "is safe and effective as monotherapy . . . when administered by single and multiple intravenous and subcutaneous injections. Additional studies are underway to further define optimal use of this novel treatment." *Id*.

3. Analysis

In reviewing the parties' arguments and evidence as set forth in the complete record before us in light of the principles of law set forth above, we determine that Petitioner has shown by a preponderance of evidence that claims 1–5 are unpatentable.

a. The prior art discloses or suggests each and every element of the challenged claims

Petitioner asserts that the combined teachings of van de Putte 1999 and Kempeni 1999 disclose or suggest each element of the challenged claims. Pet. 19–40 (mapping the language of the claims to the disclosures of van de Putte 1999 and Kempeni 1999). In particular, Petitioner argues that "van de Putte 1999 expressly teaches each of the claimed features except for the every-other-week dose and administration for 24 weeks (which is a limitation in dependent claims 3 and 4). But an every-other-week subcutaneous dose and administration for 24 weeks (and longer) would have been obvious in view of the teachings of these references including Kempeni." Pet. 19 (citing Ex. 1003 ¶¶ 31–44; Ex. 1004 ¶¶ 15–23).

Patent Owner does not challenge Petitioner's showing that the prior art discloses each element of claims 1–5. *See generally* Resp.; Reply 1, 3 (citing Resp. 19–52). Based on the full trial record, we determine that van de Putte 1999 and Kempeni 1999 collectively disclose each limitation of the challenged claims. First, we agree with Petitioner that van de Putte 1999 discloses all of the elements of all challenged claims 1–5, except for biweekly dosing and administration for 24 weeks. As explained above, van de Putte 1999 discloses a study in which RA patients received weekly doses of 20, 40, or 80 mg of D2E7 via subcutaneous self-administration over the course of three months. Ex. 1008, 7.[7] The D2E7, therefore, was administered in a pharmaceutically acceptable composition.

[7] Placebo was also given in a fourth arm of the study for the first three months. Ex. 1008, 7.

van de Putte 1999 also specifically reported on the efficacy of each of the doses, including the 20 mg dose, for the three month time period of treatment meeting the "for a time period sufficient to treat the rheumatoid arthritis" requirement. van de Putte states:

> For all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$). 20, 40 and 80 mg/week were nearly equally efficacious when given s.c. in patients with active RA.

Ex. 1008, 7; *see* Pet. 36 (citing Kempeni 1999 also to show similar results from other clinical studies, including that "[t]he therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1-2 weeks"); Ex. 1003 ¶¶ 32–34 (stating that in van de Putte 1999 "39 to 47% of patients receiving D2E7 achieved an ACR20 response compared to the placebo group," and thus, "each dose, including the 20 mg dose, would have been viewed as effective by a person or ordinary skill in the art"); *id*. ¶ 34 n.6 (confirming this understanding of the data from the DE007 study in a contemporaneous publication) (citing Ex. 1029, 4); Ex. 1004 ¶¶ 15–23.

Petitioner also provides evidence, which we credit, that "the increase in ACR20 responses for each dose reported in van de Putte 1999, relative to ACR20 placebo responses, would have demonstrated the clinical effectiveness of each dose to a person of ordinary skill in the art." Pet. 22 (citing Ex. 1003 ¶¶ 33–34). Petitioner supports this conclusion with evidence from FDA's approval of infliximab where the ACR20 response ranged from 30 to 38%. *See id*. at 23; Ex. 1015, 26; Ex. 1003 ¶ 33.

Further, D2E7 is a known recombinant human anti-TNFα antibody having the six CDRs and heavy chain constant region recited in claims 1 and

5, and the amino acid sequences for the variable light and variable heavy chain regions recited in claim 2. Ex. 1001, 3:28–38 (explaining that D2E7 is "described in U.S. Pat. No. 6,090,382, incorporated in its entirety herein by reference"); *see* Ex. 1025, 2:59–67.

Petitioner also shows, by a preponderance of the evidence, that Kempeni 1999 accounts for the differences between van de Putte 1999 and the recited biweekly dosing frequency required by all of the challenged claims, as well as the dosing period of at least 24 weeks that is recited in claims 3 and 4. Specifically, Kempeni 1999 describes a study in which patients received D2E7 via intravenous injection every two weeks for at least 6 months (i.e., 24 weeks). Ex. 1011, 4; *see* Ex. 1003 ¶ 38. We also agree with Petitioner that "Kempeni 1999 reports, based on the DE004 study, that 'plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration' and that '[u]p to 78% of patients achieved a DAS/ACR 20 response after three months of treatment with subcutaneous D2E7,'" Pet. 27 (citing Ex. 1011, 5), leading one of skill in the art to reasonably expect ever-other-week subcutaneous administration "to produce clinical results similar to those achieved with every-other-week intravenous administration," Pet. 28 (citing Ex. 1003 ¶ 39; Ex. 1004 ¶¶ 19–23).

b. Motivation to dose 40 mg every 13–15 days subcutaneously and reasonable expectation of success in treating RA

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of

ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

Petitioner states that one of skill in the art at the time of the invention would have combined the teachings of van de Putte 1999 and Kempeni 1999 to arrive at the claimed invention because

> *First*, a person of ordinary skill in the art would have been motivated to optimize the van de Putte 1999 subcutaneous dosing regimens because each dosing regimen was determined to be effective for treating RA. *Second*, Kempeni 1999 would have provided motivation to optimize the van de Putte 1999 doses to a less frequent dosing interval. *Third*, the claimed dosing regimen was at a minimum one of a finite number of options that a person of ordinary skill in the art would have considered pursuing, and therefore would have been obvious to try.

Pet. 21 (citations omitted); *see* Ex. 1008, 7 (stating "[a]ll doses of D2E7 were statistically significantly superior to placebo"); Ex. 1003 ¶¶ 32–36.

Petitioner asserts that the

> efficacy of the weekly 20 mg dose reported in van de Putte 1999 would have at least suggested that an analogous, every-other-week 40 mg dose would have been an option worth investigating. And a person of ordinary skill would have been particularly attracted to pursuing an every-other-week equivalent (*i.e.*, 40 mg) of the lowest weekly dose (*i.e.*, 20 mg) that was shown to be efficacious in the prior art.

Pet. 25 (citing Ex. 1003 ¶¶ 41–43).

Petitioner points out that Kempeni 1999 teaches that an every-other-week subcutaneous administration of D2E7 is effective for treating RA, as well as a preferred dosing frequency for treating RA at the disclosed doses.

Id. at 26 (citing Ex. 1003 ¶¶ 37–39; Ex. 1011, 4). Petitioner also asserts that this conclusion is supported by D2E7's linear pharmacokinetics. *Id.* at 29–30 (citing Ex. 1004 ¶¶ 19–23). Petitioner concludes that, given the finite number of options, administering 40 mg every 13–15 days to treat RA would have been obvious to try with a reasonable expectation of success in view of the three fixed doses disclosed in van de Putte 1999. Pet. 30–31 (citing Ex. 1003 ¶¶ 41–44).

Patent Owner responds that a person of skill in the art would not have been motivated to optimize the dosing regimens in the prior art to arrive at the claimed invention, nor would one of skill have expected that the claimed dosing regimen would work, because the prior art teaches away from the claimed invention, and "a POSA would have been motivated to pursue an effective treatment regimen, not one that merely provided baseline functionality." Resp. 1, 4, 18 (citing *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (expectation that modification of compound would have achieved "baseline level" of functionality insufficient to show motivation)). To show such lack of motivation or reasonable expectation of success, Patent Owner points to the study where "*every single patient* receiving the 0.5 mg/kg dose was switched to a higher dose by 12 weeks after the trial began (or withdrew from the study altogether) because the 0.5mg/kg dose did not work." *Id*. at 2; *see also id*. at 21–33 (providing additional arguments why the art teaches away).

Patent Owner also refutes Petitioner's reliance on a comparison between the drug concentrations resulting from the weekly doses disclosed in van de Putte 1999 and the claimed 40mg every-other-week dose stating "Petitioner's oversimplification of the amount of D2E7 antibody in the body

after two weeks is incorrect and ignores the multiple, complex PK parameters involved in predicting drug concentration at steady state." *Id*. at 3. According to Patent Owner, such oversimplification ignores lower troughs of drug concentration for an every-other-week dose that would have raised both efficacy and safety concerns. *Id*. at 3, 34–41; *see also id*. at 49–51 (discussing doubling dose and interval between doses can result in ineffectiveness regardless of linear pharmacokinetics of D2E7). Patent Owner also questions the importance that Petitioner places on the half-life of D2E7 in its obviousness analysis. *Id*. at 45–48. Patent Owner posits that "in the absence of additional PK or PD data, designing a dosing regimen to be the same [interval] as a drug's half-life ensures substantial fluctuations of drug concentrations, which are often undesirable." *Id*. at 47–48.

Patent Owner further asserts that a person of ordinary skill in the art would have been concerned about under-dosing producing anti-drug antibodies ("ADAs"). *Id*. at 3–4, 41–45. Patent Owner also presents evidence of commercial success, satisfaction of a long-felt need for new RA therapies, and unexpected results. *Id*. at 4–5. Specifically, Patent Owner states that "HUMIRA® also satisfied the need for an anti-TNFα therapy that could be safely self-administered at home, that did not require weight-based calculations of dose amount, and that maximized patient comfort and convenience by limiting the number of injections." *Id*. at 15. Patent Owner supports its position with testimony from several declarants, including Dr. Gibofsky and Dr. Vinks.

(1) Fixed, subcutaneous dosing

With respect to type of dose and administration, Petitioner asserts that van de Putte 1999's dosing regimen reflects the well-known advantages of

subcutaneous administration over other forms of administration (e.g., intravenous dosing), and fixed dosing over weight-based dosing. Pet. 20–21 (citing Ex. 1008, 7; Ex. 1011, 5; Ex. 1003 ¶¶ 26–27, 31–34; Ex. 1004 ¶¶ 15–23). Petitioner also states:

> Administering D2E7 subcutaneously to human subjects was well know. Kempeni 1999 reported that D2E7 "given subcutaneously was safe and as effective as when administered intravenously[,] demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery' for treatment of RA. In the van de Putte 1999 study, patients suffering from "long standing active rheumatoid arthritis" were given doses of "either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection" for three months.

Id. (citations omitted).

Patent Owner does not challenge Petitioner's showings in this regard, *see generally* Resp.,[8] and we agree with Petitioner that the record establishes by a preponderance of the evidence that the ordinarily skilled artisan would have had a reason to select subcutaneous, fixed dosing and a reasonable expectation of success in achieving a subcutaneous fixed dose. For example, Petitioner points to evidence that subcutaneous dosing would have been more convenient and less expensive for patients because they can self-administer the dose in a short amount of time. Pet. 12–13; Ex. 1003 ¶ 29–30, 34, 37–47; Ex. 2081, 7 (stating that "[i]n general, subcutaneous administration is more desirable for doctors and patients than intravenous

[8] Patent Owner does question the expected drug levels for subcutaneous administration of a 40 mg fixed dose as compared to intravenous administration of a 0.5mg/kg dose as disclosed in Kempeni 1999 because of the loss of drug through absorption. Resp. at 22–23, 23 n.6.

administration" because subcutaneous administration "can be accomplished in minutes" and "can be performed practically anywhere without catheterization" (i.e., it does not require hospital visits like intravenous administration does)).

Dr. Weisman testifies that fixed subcutaneous doses would have been desirable and considered in designing a dosing regimen because of well-known clinical considerations. Ex. 1003 ¶ 47. Specifically, Dr. Weisman states:

> Once properly instructed, a patient can self-administer a fixed subcutaneous dose in the privacy of their own home. Subcutaneous administration avoids complications that can occur with intravenous administration (e.g., thrombosis or problems at the site of administration). As the '135 patent acknowledges, subcutaneous administration of D2E7 was known in the relevant time period to be "advantageous" because it "is convenient for both patient and the health care provider." (Ex. 1001, 2:66–3:2). In addition, at-home subcutaneous administration costs significantly less than receiving intravenous administration in a doctor's office or clinic. Finally, a fixed dose is preferred over a weight-based dose because fixed doses avoid the need to calculate dosage for each patient and the potential for dosing errors. Even Patent Owner acknowledged during prosecution, through the declaration of Dr. Janet Pope, that "patients' ability to self-administer a one-size-fits-all dose by subcutaneous injection using a pre-filled syringe at home was a game changer." (Ex. 1002 (Pope Decl.) 1161 ¶ 52.)

Id.; *see also* Ex. 1025, 22:65–23:1 ("[I]t is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage."). Finally, we note that patients in the clinical study described in van de Putte 1999 were receiving subcutaneous fixed doses, and Kempeni 1999 concluded:

> Based on preliminary data, plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration. . . . The investigators concluded that D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery.

Ex. 1011, 5; Ex. 1008, 7; *see* Ex. 1003 ¶¶ 26, 31–36; Ex. 1004 ¶¶ 15, 19; Ex. 2069, 78:9–81:5 (explaining advantages of subcutaneous dosing).

(2) Biweekly administration of a 40 mg dose

With respect to dose selection and dosing interval, Petitioner presents several arguments why a skilled artisan would have had a reason to modify the van de Putte 1999 dosing regimen to administer a 40 mg dose on a biweekly schedule and expect success in treating RA with that regimen. These arguments include the efficacy determination for all subcutaneous dosing regimens set forth in van de Putte 1999, and the express teaching of Kempeni 1999 of a two-week interval for dosing. Pet 20–21 (citations omitted). Petitioner also supports its obviousness assertion stating that "the claimed dosing regimen was at a minimum one of a finite number of options that a person of ordinary skill in the art would have considered pursuing, and therefore would have been obvious to try." *Id.* at 21 (citations omitted).

One question before us then, is whether a person of ordinary skill in the art would have had a reason to modify van de Putte 1999's 20 mg weekly dose to a 40 mg biweekly dose based on the express teaching of Kempeni 1999 of a two-week interval for dosing. As with other factual questions, Petitioner bears the burden of proving that the skilled artisan would have been motivated to modify the dosing regimen of van de Putte 1999 to arrive at the claimed invention. *In re Magnum Oil Tools Int'l*, 829

F.3d 1364, 1375 (Fed. Cir. 2016) (burden-shifting "does not apply in the adjudicatory context of an IPR"). As explained below, we are persuaded by Petitioner's arguments that it has carried this burden.

After reviewing the entire record developed during trial, we find that Petitioner has carried its burden to show that a person of ordinary skill in the art would have been so motivated. Petitioner asserts that one of skill in the art would have arrived at the claimed dosing regimen as the result of routine optimization because "[t]he efficacy of the weekly 20 mg dose [of D2E7] reported in van de Putte 1999 would have at least suggested that an analogous, every-other-week 40 mg dose would have been an option worth investigating" regardless of whether it was the most efficacious dose tested or not. Pet. 25 (citing Ex. 1003 ¶¶ 41–43). Petitioner further asserts that Kempeni 1999 teaches that every-other-week subcutaneous administration of D2E7 is effective for treating RA, *id*. at 26 (citing Ex. 1003 ¶¶ 37–39), as evidenced by Kempeni 1999's report that therapeutic effects were evident within 24 hours to one week after administration, reaching a maximum effect after 1–2 weeks, and that the mean terminal half-life was 11.6 to 13.7 days. *Id*. (citing Ex. 1011, 4; Ex. 1003 ¶ 37; Ex. 1004 ¶¶ 17–22).

Petitioner also points to Kempeni 1999's description of DE003 where investigators determined how long it would take for a disease flare up after achieving a "good" EULAR response with every-other-week dosing. *Id*. at 26–27. Petitioner states: "[t]his treatment protocol resulted in a 'mean dosing interval of 2.5 weeks,' indicating that, on average, RA symptoms reappeared 2.5 weeks after the last 'good' EULAR response was achieved." *Id*. at 27 (citing Ex. 1011, 4; Ex. 1003 ¶¶ 20, 38).

Petitioner concludes that based on the roughly two-week half-life as described in Kempeni 1999, "a person of ordinary skill in the art would have understood that the every-other-week equivalent of the lowest 20 mg van de Putte [1999] dose was 40 mg." *Id*. at 28 (citing Ex. 1004 ¶ 19–22). Petitioner explains this conclusion as follows:

> This is because the approximate amount of D2E7 circulating in the body two weeks after administering a 40 mg dose would have been roughly one half that dose (*i.e.*, approximately 20 mg). Because this amount of D2E7 remaining after two weeks would have been considered clinically effective in light of van de Putte 1999, a person of ordinary skill would have been motivated to pursue a 40 mg every-other-week subcutaneous dose.

Id. (citing Ex. 1004 19–22; Ex. 1003 ¶¶ 32–34, 37–39).

We agree with Petitioner's analysis that one of skill in the art would have been motivated to modify van de Putte 1999's 20 mg weekly dose to a 40 mg biweekly dose based on the express teaching of Kempeni 1999 of a two-week interval for dosing, in addition to Kempeni 1999's teaching of D2E7's 11.6 to 13.7-day half-life.

Patent Owner asserts that the prior art teaches away from the claimed invention. Specifically, Patent Owner argues that one of ordinary skill in the art would not have relied on the clinical studies disclosed in Kempeni 1999 to teach every-other-week dosing for van de Putte 1999's 20 mg dose because the data from studies upon which Petitioner relies "show[] that every-other-week administration of 0.5 mg/kg dose (the weight-based dose Petitioner contends is equivalent to a fixed 40 mg does) was insufficient to treat RA across a patient population." Resp. 21–22. Patent Owner relies on statements in Kempeni 1999 about the DE003 trial where "patients who did not respond well after 0.5 or 1 mg/kg received higher doses of up to a

maximum of 3 mg/kg." Resp. 23 (quoting Ex. 1011, 4). Patent Owner points out that Kempeni also states that, in the DE004 trial, the "dose of D2E7 [of 0.5mg/kg] was increased to 1 mg/kg subcutaneously weekly for non-responders or those losing their responder status." *Id*. (quoting Ex. 1011, 5).

Patent Owner further relies on two figures in Rau 2000,[9] another prior art reference that reports two outcome measures for the DE003 study described in Kempeni—Figure 4 reporting Disease Activity Score ("DAS") and Figure 5 reporting the erythrocyte sedimentation rate ("ESR"). *Id*. at 24–25.[10] Figures 4 and 5 are reproduced below.

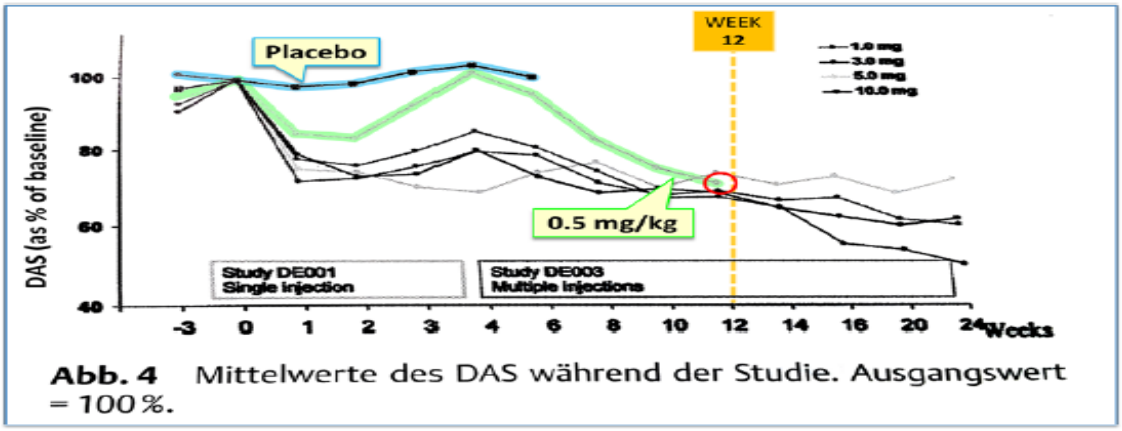


Abb. 4 Mittelwerte des DAS während der Studie. Ausgangswert = 100 %.

Fig. 4 (Rau 2000)

[9] R. Rau et al., *Experience with D2E7*, 25 RHEUM. TODAY 83 (June 2000) (English Translation) (Ex. 2040, "Rau 2000").

[10] The Disease Activity Score or DAS measures disease activity as a composite score of tender joints, swollen joints, erythrocyte sedimentation rate or ESR, and the patient's assessment of health as measured on a visual analogue scale. Ex. 1011, 4; Ex. 2071 ¶ 42.

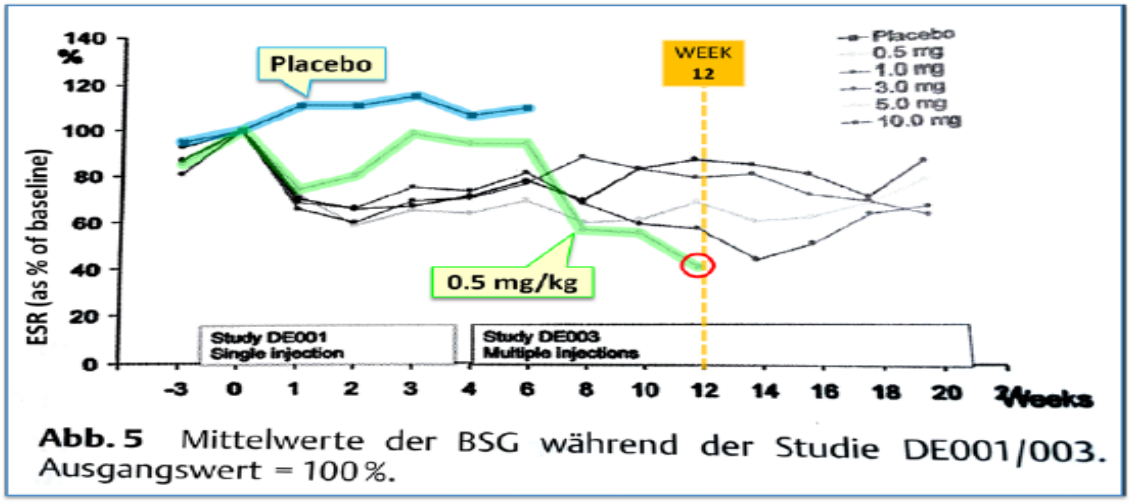


Abb. 5 Mittelwerte der BSG während der Studie DE001/003. Ausgangswert = 100 %.

Fig. 5 (Rau 2000)

Resp. 25 (annotated by Patent Owner). Figure 4 set forth above shows the mean value of DAS for which the baseline value is 100 percent, and Figure 5 set forth above shows the mean value of ESR during Study DE001/003 for which the baseline value is 100 percent. Ex. 2040, 6–7.

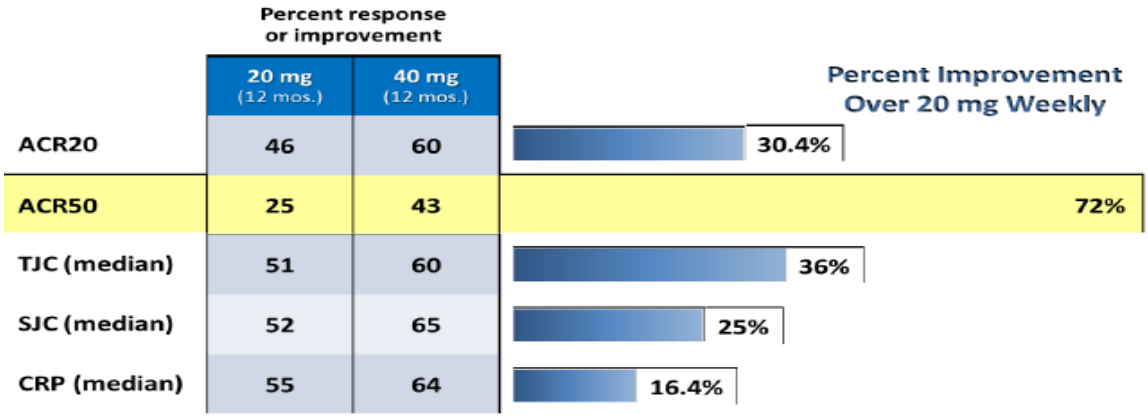
Patent Owner states that one of skill in the art would have understood the following about the 0.5mg/kg dose set forth in both Figures 4 and 5.

> Although the graphs extend beyond 12 weeks, in both Figures 4 and 5, the data for the 0.5mg/kg line ***ends at 12 weeks*** (unlike all of the other administered doses). Ex. 2158, 6-7, Figs. 4-5; Ex. 2071 ¶64; *see* Ex. 2070, 65:17-67:21, 69:11-17, 70:1-17 (acknowledging that termination of the 0.5mg/kg line in Figures 4 and 5 "indicates that ***nobody*** received the .5mg/kg dose after week 12") (emphasis added). A POSA reviewing the prior art would have understood that ***all*** of the patients in the DE003 study were up-dosed after 12 weeks (or withdrew from the study altogether) because the 0.5mg/kg dose was insufficient. Ex. 2071 ¶64; Ex. 2075 ¶86. Consistent with this data, Rau 2000 unambiguously states that only doses greater than 1mg/kg (i.e., greater than an 80mg fixed dose) provided longterm efficacy. Ex. 2040, 4.

Resp. 25–26. Patent Owner concludes that "[g]iven its burden of proof, Petitioner's case fails because the prior art shows that the 0.5mg/kg dose is ineffective." *Id*. at 27.

Patent Owner also asserts that Kempeni 1999's biweekly dose actually teaches away from the claimed invention because the 2.5 week figure was calculated after 12 months of dosing D2E7, after Rau 2000 shows the discontinuation of the 0.5 mg/kg dose as discussed above. Resp. 30–31. Patent Owner also asserts that the 2.5 week figure is the average dosing time across all tested doses, indicating the dosing interval for the 0.5 mg/kg dose would have been less than 2.5 reported for all doses that range up to 10 mg/kg. *Id*. at 31–32. Also, the minimum two-week dosing interval regardless of relapse reported in Kempeni 1999 would skew the mean dosing interval higher than the average period during which relapse would occur. *Id*. at 32.

Finally, Patent Owner also states that the data in the van de Putte abstracts reporting 6 and 12-month data showed that the 20 mg/kg dose was sub-optimal. Resp. 32–33 (citing Ex. 1008, 7; Ex. 2086, 2; Ex. 2090, 5; Ex. 2075 ¶¶ 93–94; Ex. 2071 ¶¶ 49–51, 81–82). Patent Owner provides the following graph to illustrate its point.



Resp. 33 (citing Ex. 2071 ¶ 82).

Patent Owner's declarant, Dr. Gibofsky, states that the graph set forth above shows the following.

> The difference between 20 mg and the higher doses becomes even more evident at 12 months, where the percentage of patients receiving 40 and 80 mg weekly doses was numerically superior for every clinical measure outcome compared to 20 mg weekly. Ex. 2090 (van de Putte 2000b), 5. Significantly, the patients in the 40 mg weekly group showed a 72% improvement in ACR 50 values compared to patients in the 20 mg weekly group. *See id.* This means that ***more*** patients receiving the 40 mg weekly dose achieved a ***greater*** extent of improvement (i.e., at least 50% as measured by the ACR improvement criteria), compared to patients receiving the 20 mg weekly dose.

Ex. 2071 ¶ 82.

We do not agree with Patent Owner's assessment of what the art teaches one of skill in the art. We agree with Petitioner that Patent Owner's response to Petitioner's assertions of obviousness, at bottom, relies on an interpretation of the claim phrase "for a time period sufficient to treat the rheumatoid arthritis" with which we do not agree, namely, that this claim phrase requires a *significant* reduction in the signs and symptoms of RA. *See* Reply 2 (stating Patent Owner "overlooks that neither obviousness nor the claims require the single most effective dose"). As we have stated, *see supra* Section II.B., the claims do not require a particular level of efficacy, but only reduction of the signs, symptoms, and/or progression of RA; therefore, we do not agree with Patent Owner's arguments that the art teaches away from the claimed invention because other doses could be deemed of superior efficacy to the claimed dose.

A reference teaches away from the claimed invention if it criticizes, discredits, or would have discouraged a person of ordinary skill in the art

from "following the path set out in the reference," or if a person of ordinary skill "would [have been] led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). The mere disclosure of alternative designs, however, does not teach away. *In re Mouttet*, 686 F.3d 1322, 1333–34 (Fed. Cir. 2012).

Patent Owner fails to view what the references as a whole teach one of skill in the art. First, van de Putte 1999 teaches subcutaneous administration of fixed doses, 20/40/80 mg doses, of D2E7. Ex. 1008, 7; Ex. 1037, 159:10–160:20. Patent Owner attempts to make efficacy comparisons between these doses as explained above, *see* Resp. 32–33, but as Dr. Weisman testifies and Dr. Gibofsky and Patent Owner agree, these studies were "not powered to provide statistically meaningful comparisons between doses." Resp. 11–12; Ex. 2071 ¶ 79 (stating a "POSA would have known that the study was not designed to provide statistically meaningful comparisons between doses, a point Dr. Weisman does not appear to dispute"); Ex. 1037, 155:11–160:20; Ex. 1003 ¶ 35 (stating "the data in van de Putte 1999 suggests that each dose was superior to placebo, but not that any dose was better or worse than another dose").

Kempeni 1999 discloses several clinical studies that utilized different dosing protocols. DE003 was one of those clinical studies. In the DE003 study, patients received 0.5 to 10 mg/kg of D2E7 intravenously "*every two weeks*" until DAS (Disease Activity Score) responses could be rated as "good." Ex. 1011, 4 (emphasis added). Thus, far from criticizing, discrediting, or discouraging the person of ordinary skill from pursuing a biweekly regimen, Rau 2000 and Kempeni 1999 expressly disclose such

dosing frequency. By the same token, Rau 2000's conclusion that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously" does not specify any particular dosage level, much less exclude any dosage level described in Rau 2000 to provide a teaching away. *See* Ex. 2040, 8. Also, Kempeni 1999 does not criticize or disparage the effectiveness of the 0.5 mg/kg biweekly dose. Rather Kempeni 1999 expressly concludes that the biweekly treatment of D2E7 "in the dose range from 0.5 to 10 mg/kg was well tolerated." Ex. 1011, 4; *see* Ex. 1037, 167:9–168:2; 170:8–19.

Also, Rau 2000 describes the DE001/DE003 clinical study reported in Kempeni 1999 and results of that study. Ex. 2040, 5–7, Figs. 2–5. Rau 2000 discloses that, in DE001, patients received an initial dose of 0.5 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg of D2E7, or placebo intravenously. Ex. 2040, 5. Patients then entered the open label phase of the study, DE003, and received a second injection four weeks after the first injection. *Id.*; *see* Ex. 1011, 4 (Kempeni 1999 describing the transition from DE001 to DE003). Patients subsequently were administered injections when disease activity increased, at a minimum interval of two weeks. Ex. 2040, 5. In the abstract, Rau 2000 describes the DE003 study as a clinical trial in which "D2E7 was given in doses of 0.5–10 mg/kg [intravenously] over 3–5 minutes every two weeks over a time period of now 1½ years." *Id*. at 4.

We do note, as Patent Owner points out, that in discussing the DE001/003 studies, Rau 2000 states that one and a half years of treatment every two weeks intravenously with D2E7, which included a 0.5 mg/kg D2E7 dose, "resulted in an impressive statistically significant and long-lasting reduction of disease activity (moderate DAS response in 80%,

decrease in the number of swollen and tender joints and the ESR > 50%) with all doses > 1 (3) mg/kg body weight." Ex. 2040, 4; *see* Resp. 26 (citing Ex. 2071 ¶ 64; Ex. 2075 ¶ 86). Again, Patent Owner asks us to infer a conclusion that one of skill in the art would read this statement to mean that a 40 mg fixed-dose of D2E7 would be insufficient to treat RA from the absence of this dose in this statement in Rau 2000. *See* Ex. 2071 ¶¶ 64–65; Ex. 2075 ¶ 86. We do not agree with such a conclusion.

First, a later prior art study, Weisman,[11] tested a biweekly 0.5 mg/kg dose of D2E7 (and even a 0.25mg/kg dose), given in combination with methotrexate, and concluded that D2E7 "is well tolerated, safe and efficacious when given in combination with MTX in patients with longstanding RA." Ex. 1014, 5. It appears counterintuitive to test a dosage that previously had been determined to be ineffective, as was done in Weisman. We also agree with Petitioner that the prior art as a whole does not support a conclusion by one of skill in the art that the 0.5 mg/kg biweekly dose of D2E7 was ineffective. *See* Reply 6–7 (citing Ex. 1011, 4; Ex. 2040, 6–7, Figs. 4-5, Ex. 2070, 61:20–64:17, Ex. 1037, 61:9–15; 122:18–125:7; Ex. 1023; Ex. 1006, 5; Ex. 1029, 3; Ex. 1056); *see also* Reply 6, n.5 (stating this statement in Rau 2000 "is therefore a positive report of efficacy at that time point [1 ½-year data], but is not expressly or impliedly reporting inefficacy for 0.5 mg/kg, whose efficacy data was reported through 12 weeks").

[11] Michael Weisman et al., *A Dose Escalation Study Designed to Demonstrate the Safety, Tolerability and Efficacy of the Fully Human Anti-TNF Antibody, D2E7, Given in Combination with Methotrexate (MTX) in Patients with Active RA*, 43 ARTHRITIS & RHEUM. S228 (2000) (Supp.) (Ex. 1014, "Weisman").

Also, Patent Owner's assertion that *all* patients receiving a 0.5 mg/kg dose in Rau 2000 were up-dosed because such a dose was ineffective is not supported by any affirmative statement in Rau 2000 to that effect. *See* Ex. 2040, 6–7 (showing 0.5mg/kg dose was effective at treating RA through 12 weeks); Ex. 2070, 63:13–64:17; Ex. 1037, 122:18–125:7. Kempeni 1999 states that up-dosing was provided to patients "who did not respond well," i.e., a response that could be rated as "good." Ex. 1011, 4. Thus, those patients who achieved a moderate response may have been up-dosed, which would not mean that the lower dose was ineffective. *See* Ex. 1055, 29 (showing Remicade may be up-dosed for certain patients); Ex. 1038, 197:1–204:14. Further, Kempeni 1999 concludes that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." Ex. 1011, 2; *see also* Ex. 1005 (describing the DE010 study, in which patients received 1 mg/kg intravenous or subcutaneous initial doses of D2E7, followed by an open label phase of subcutaneous injections of 1 mg/kg D2E7 and explaining that "[s]ubcutaneous as well as intravenous injections of D2E7 at a dose of 1 mg/kg were safe and efficacious when given with standard, stable doses of [methotrexate] in patients with active RA"). Accordingly, we determine that a preponderance of the evidence supports Petitioner's position that the person of skill in the art would not have been discouraged from pursuing a 40 mg biweekly dosing regimen in view of the up-dosing disclosed in Kempeni 1999 or the DE001/DE003 study results that Rau 2000 describes.

As counsel for Patent Owner notes, Rau 2000 reports that "after the lower doses (0.5 or 1 mg per kg of body weight), the number of swollen joints gradually increased again." Ex. 2040, 6, Fig. 2; *see* Tr. 61:1–5.

Rau 2000 also reports that there was a worsening in ESR (erythrocyte sedimentation rate) after one week in the 0.5 mg/kg group. Ex. 2040, 6. Patent Owner relies on these statements in Rau 2000 as support for its argument that the 0.5 mg/kg dose was ineffective. Tr. 61:1–13. Although Patent Owner's argument has some merit, we do not find that Rau 2000 indicates that the 0.5 mg/kg dose was "ineffective," as Patent Owner argues. For example, Rau 2000's description of the patients' swollen joints notes improvement after administration of all doses, and Figure 2 shows a decrease in the number of swollen joints from week 0 (i.e., the beginning of the study) to week 2. Ex. 2040, 6, Fig. 2; Ex. 2158, 6, Fig. 2 (high resolution version of Rau 2000 that depicts the figures with better clarity). We acknowledge that Rau 2000 discloses an increase in the number of swollen joints when the dosing interval was extended beyond two weeks, but find that such a teaching would not have counseled against a dosing regimen in which D2E7 is administered every two weeks.

We also acknowledge that Rau 2000 reports an ESR in the 0.5 mg/kg group that was "worsening again already after one week." Ex. 2040, 6. But that is only one of the ACR20 criteria. *See id*. at 2. And, despite that disclosure, Rau 2000 reports that "[o]bservation of an ACR-20 . . . response was determined, at any point in time, with about 42% of patients" in the 0.5 mg/kg dosing group and about 65% of patients in the 1 mg/kg dosing group achieving an ACR20 response. *Id*. at 6. Thus, Rau 2000 indicates that the 0.5 mg/kg dose was effective in treating patients (i.e., reducing the signs, symptoms, and/or progression of RA). That the 0.5 mg/kg dose was not the most effective dose is of no moment because, as explained above, the

claims do not require superior efficacy or treatment with the most effective dose. *See supra* § II.B.

(3) Concerns about anti-drug antibodies, therapeutic range of D2E7, and efficacy generally

Patent Owner argues that the available PK data and clinical data for D2E7 would have discouraged a person of ordinary skill from pursuing the claimed dosing regimen in view of the risk of developing ADAs. Resp. 21–45. With respect to the PK data, Patent Owner argues the data suggest that, at steady-state, the trough concentrations (i.e., C_{min}[12]) would have been expected to be too low and the fluctuations between C_{min} and C_{max}[13] greater than those of the 20 mg weekly van de Putte dose, thereby teaching away from the claimed dosing regimen. *Id.* at 34–41. Patent Owner contends that the lower C_{min} values of a subcutaneous 40 mg biweekly dose would have triggered concerns about the risk of developing anti-drug antibodies, and that the greater C_{min} and C_{max} fluctuations would have triggered concerns about the safety of that dosing regimen. *Id.* at 41–45. To illustrate those points, Patent Owner directs us to modeling performed by Dr. Vinks using the available PK data and, where the data were not available, assumptions based on data for similar proteins. *Id.* at 38–41; *see* Ex. 2075.

Even assuming that the C_{min} and C_{max} values from Dr. Vinks's modeling are correct, however, we agree with Petitioner that the conclusions

[12] Dr. Jusko testifies that "[t]he C_{min} is the minimum blood, plasma, or serum concentration of a drug that is observed after administration of a dose and prior to the administration of the next dose." Ex. 1004 ¶ 26 n.6.
[13] Dr. Vinks testifies that "C_{max} is the highest concentration of drug reached at the site of measurement. It is determined by the rate of absorption, bioavailability, and the volume of distribution." Ex. 2075 ¶ 36.

Dr. Vinks draws from the modeling are not entitled to much weight because the minimum effective dose of D2E7 "was undefined in June 2001." Ex. 2003 ¶ 53 n.2; Reply 11–12. Thus, comparing the C_{min} of a 40 mg biweekly dose to the C_{min} of van de Putte 1999's 20 mg weekly dose does not suggest that persons of ordinary skill in the art would have been discouraged from selecting a 40 mg biweekly dose of D2E7 out of concern for the potential of developing ADAs.

Moreover, the available information regarding D2E7 suggests that, although the potential for developing ADAs was known, such potential would not have discouraged a skilled artisan from pursuing a 40 mg biweekly dose of D2E7. In contrasting D2E7 with other biological anti-TNF treatments, Kempeni 1999 discloses that one would have expected the fully human D2E7 antibody to be less immunogenic (i.e., there would have been less of a concern with developing ADAs). Ex. 1011, 1; *see* Ex. 1036, 30:13–32:16. That is, Kempeni 1999 explains that the therapeutic efficacy of infliximab (REMICADE®), a chimeric antibody that is part human and part mouse, and etanercept (ENBREL®), a human fusion protein, "may be limited by an immune response to their non-human elements or artificially fused human sequences." Ex. 1011, 3. Kempeni 1999 further states that the fully human D2E7, "may have greater therapeutic potential" and "advantages in minimising antigenicity in humans." *Id.*; *see also* Ex. 1012, 8 ("Since D2E7 consists only of human sequences, allergic reactions are less probable than with non-human monoclonal antibodies."). Neither Patent Owner's arguments nor Dr. Vinks's testimony regarding ADAs accounts for the differences between D2E7, which is fully human, and other biological

anti-TNF treatments, which are not.[14] *See* Resp. 41–45; Ex. 2075 ¶¶ 62–75, 160–166.

We also do not find the evidence of record sufficient to show that fluctuations in C_{min} and C_{max} for a 40 mg biweekly treatment would have raised safety issues such that one of ordinary skill in the art would have been discouraged from using that dosing protocol. Dr. Vinks testifies that "'large fluctuations between C[$_{max}$] and C[$_{min}$] can be hazardous,' particularly if the drug 'has a narrow therapeutic range.'" Ex. 2075 ¶ 42 (citing Ex. 2112, 11); *see also id.* ¶ 148 ("It was reported in the prior art that 'the magnitude of fluctuations between the maximum and minimum stead-state plasma concentrations are an important consideration for any drug that has a *narrow therapeutic range*'" (emphasis added)). Nothing in the record, however, suggests that D2E7 has a narrow therapeutic range. Rather, as Petitioner explains, D2E7 has a wide therapeutic window and a relatively long half-life. Reply 12, 16–17; *see* Ex. 1011, 2 (reporting that D2E7 has a half-life of

[14] We also note that Kempeni 1999 reports D2E7 was safe and efficacious over a wide range of doses (i.e., from 0.5 mg/kg to 10 mg/kg). Ex. 1011, 3. And Rau 2000, although recognizing that "idiotypical epitopes can represent a theoretical potential for allergic reactions" (i.e., reactions due to the development of ADAs), explains that that theoretical potential was not borne out in the data from the D2E7 clinical trials because "reactions which were described as allergic . . . did not recur in the same patients with continuation of the treatment" and "did not require any therapeutic intervention." Ex. 2040, 8. Further, the evidence suggests that an anti-TNFα treatment can be effective and safe even when some patients develop ADAs. As Petitioner explains, REMICADE® and ENBREL® are approved for the treatment of RA, even though some patients using those products develop ADAs. Reply 15.

11.6 to 13.7 days, and that the drug was safe and efficacious in clinical trials when dosed over a range of 0.5 mg/kg to 10 mg/kg).

Finally, Patent Owner asserts that half-life alone does not provide sufficient information to design a dosing regimen and points to several biologics that do not dose according to a single half-life. Resp. 35–48. Petitioner does not rely on half-life alone, however, to suggest the biweekly 40 mg total body dose. As Petitioner points out, the prior art correlated D2E7's half-life with clinical data supporting the safety and efficacy of biweekly dosing. Reply 16–17 (citing Ex. 1011, 4; Ex. 2040, 8). Although we agree with Patent Owner that half-life alone may not be enough of a predictor for a dosing interval, the clinical data coupled with D2E7's half-life is.

In sum, we are not persuaded that the available PK data and clinical data for D2E7 would have taught away from selecting a 40 mg biweekly dose. That does not end our inquiry, however, because Patent Owner presents arguments and evidence regarding objective indicia of nonobviousness that we must consider before reaching our conclusion on obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). We consider those arguments and evidence below.

c. Objective Indicia of Nonobviousness

Patent Owner argues that objective evidence of a long-felt, but unmet, need for new RA therapies, unexpected results, and commercial success ("secondary considerations") supports the nonobviousness of the challenged claims. Resp. 57–61. "For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the *claimed invention*." *In re Huai-*

Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). We apply "a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP*, 829 F.3d at 1329 (citations omitted). That presumption, however, is rebuttable. *Id.*

As explained further below, we are not persuaded that Patent Owner's arguments and evidence support the nonobviousness of the challenged claims.

(1) Commercial success

Patent Owner offers evidence of the success of HUMIRA®, a commercial formulation of the claimed subject matter, to support the nonobviousness of the challenged method claims. Resp. 60–61.

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *WBIP*, 829 F.3d at 1829. That presumption of nexus, however, is rebuttable, as "a patent challenger may respond by presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *WBIP*, 829 F.3d at 1329.

There is no dispute in this case that HUMIRA® is commercially successful. Resp. 60; Reply 23–24 (discussing impact of sales of HUMIRA®); *see* Ex. 2073 ¶¶ 8–9 (Dr. Hausman testifying that HUMIRA® "has become a top-selling TNF inhibitor for the treatment of rheumatoid

arthritis"). Patent Owner asserts that the success of HUMIRA® is attributable to "the claimed invention as a whole—a regimen that specifies the biological agent (D2E7), the method of administration (subcutaneous), the dose (40 mg fixed dose) and the dosing interval (13-15 days)." Resp. 60.

Petitioner, on the other hand, contends that any presumption of nexus has been rebutted because the features leading to any commercial success of HUMIRA® are not due to the claimed dosing regimen, but to prior art attributes such as the fully humanized D2E7 antibody itself. Reply 23–24; Pet. 56–58. To support its position, Petitioner directs us to Patent Owner's patent directed to the D2E7 antibody itself and other uses of HUMIRA®. Pet. 57; Reply 26; Ex. 1025.

Petitioner correctly notes that Patent Owner does not account for the other patents covering HUMIRA® in its efforts to establish commercial success. *See* Tr. 33:60–35:20; Ex. 1034, 5–10 (Dr. Hausman testifying that he did not investigate whether the active ingredient versus the dosing regimen drove the commercial success of HUMIRA®). Further, some of the record evidence attributes HUMIRA®'s commercial success to the fully human D2E7 anti-TNFα antibody, rather than the recited dosing regimen. Ex. 2031, 3 ("The scientific idea was to see if they could develop an antibody drug candidate against the TNF target that was 'fully human' . . . By using only human DNA in the drug, it was supposed to help the treatment circumvent immune-system surveillance, and therefore avoid triggering immune-system reactions that might cause additional side effects."). And, as explained above, the D2E7 antibody was known and patented. Ex. 1001, 3:28–38; *see generally* Ex. 1025. "Where market entry by others was precluded [due to blocking patents], the inference of non-

obviousness of [the asserted claims], from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013).

On this record, it is not clear whether the sales of HUMIRA® are due to the dosing regimen recited in the '135 patent or the known and patented fully human D2E7 antibody. Consequently, we cannot conclude from the evidence before us that the commercial success of HUMIRA® was due to the merits of the invention recited in in the '135 patent. Accordingly, we determine that Petitioner presents sufficient evidence to rebut the presumption of nexus between the commercial success of HUMIRA® and the claimed dosing regimen. We, therefore, are not persuaded that Patent Owner's evidence of commercial success supports the nonobviousness of the challenged claims.

(2) Long-felt need

Patent Owner contends there was a long-felt need for new RA therapies supporting the nonobviousness of the challenged claims. Resp. 57–58. Specifically, Patent Owner argues that, as of June 2001, there was a need for new treatments for RA to address the clinical disadvantages associated with then-existing treatments. *Id.* In particular, Patent Owner asserts that although two anti-TNFα agents were approved as of 2001 (i.e., REMICADE® and ENBREL®), "[a] need thus existed for additional biologics with more advantageous dosing regimens," and HUMIRA® satisfied that need where biologics from other companies failed. *Id.* at 58.

We are not persuaded that Patent Owner demonstrates that the claimed dosing regimen satisfied a long-felt, but unmet need for RA treatment. For example, although Patent Owner presents some evidence that

there may have existed a need for RA treatments with a less frequent dosing schedule, (i.e., ENBREL® required twice weekly administration), the prior art already disclosed biweekly D2E7 dosing regimens. *See* Ex. 1011, 4 (Kempeni 1999 describing biweekly dosing of D2E7); Ex. 2040, 6–7, Figs. 4, 5. Likewise, Patent Owner contends that there was a need for subcutaneous dosing (i.e., REMICADE® was administered intravenously), but the prior art disclosed subcutaneous dosing of anti-TNFα agents generally, as well as subcutaneous dosing of D2E7. *See* Ex. 2099, 5 ("The recommended dose of ENBREL for adult patients with [RA] is 25 mg given twice weekly as a subcutaneous injection"); Ex. 1008, 7 (van de Putte 1999[15] describing subcutaneous dosing of D2E7). Similarly, Patent Owner fails to tie its evidence of long-felt need to the 40 mg dose recited in the claims.

Further, Patent Owner contends that D2E7 succeeded where other anti-TNFα agents did not, but does not sufficiently connect that success to a subcutaneous dose of 40 mg administered biweekly. Rather, it appears from the evidence that the driving force behind the satisfaction of a long-felt need and success where others had failed was the introduction of the first fully human anti-TNFα antibody, not the claimed dosing regimen. *See* Ex. 1011, 3 (explaining that the therapeutic duration of chimeric antibodies and human fusion proteins "may be limited" by an immune response, and that fully human D2E7 "may have advantages in minimising antigenicity in humans"); Ex. 2074 ¶ 100 (Dr. Gibofsky's testimony that prior art anti-TNFα inhibitor TNFbp dimer failed because a "'significant antibody response' was reported

[15] L.B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 Ann Rheum. Dis. (Supp.) S269 (2000) (Ex. 1008, "van de Putte 1999").

that 'affected the half-life and clearance of the TNFbp *at each dose group*'" tested (internal citation omitted and emphasis added)). Accordingly, we are not persuaded that Patent Owner's evidence of long-felt need supports the nonobviousness of the challenged claims.

(3) Unexpected results

Patent Owner argues that despite the lower predicted C_{min} of the claimed dosing regimen and concern about formation of ADAs that would have followed from the lower C_{min}, the claimed dosing regimen is unexpectedly effective. Resp. 58–60. Patent Owner does not direct us to sufficient evidence showing that the efficacy of a subcutaneous 40 mg biweekly dosing regimen would have been unexpected. Nor does Patent Owner compare that dosing regimen to the closest prior art. *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) ("when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art" (internal quotations and citation omitted)); *See generally* Resp. 58–60. Rather, Patent Owner simply reiterates its teaching away arguments. We reject those arguments in the context of unexpected results for the same reasons provided above with respect to Patent Owner's teaching away arguments. That is, we determine that a preponderance of the evidence suggests that a subcutaneous 40 mg biweekly dosing regimen would have been expected to be safe and effective at treating RA.

4. Conclusion as to obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*,

676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we conclude that Petitioner has satisfied its burden of demonstrating, by a preponderance of the evidence, that the subject matter of claims 1–5 of the '135 patent would have been obvious over the combination of van de Putte 1999 and Kempeni 1999.

E. Obviousness over Rau 1998, Schattenkirchner 1998, and van de Putte 1999

Petitioner alleges that claims 1–5 also would have been obvious over Rau 1998, Schattenkirchner 1998, and van de Putte 1999. Pet. 40–56.

1. Rau 1998

Rau 1998, like Kempeni 1999, describes the DE003 study in which patients were treated with multiple intravenous doses of D2E7 every two weeks until the patient reached a good response according to European League Against Rheumatism ("EULAR") response criteria of an absolute Disease Activity Scale ("DAS") value of <2.4.[16] Ex. 1006, 5. After achieving a good EULAR response, a patient was retreated only when the DAS value increased to above 2.4 again. *Id*. Patients treated with 0.5 and 1 mg D2E7/kg body weight were offered the possibility of a dose escalation. *Id*. The mean dosing interval for the study was 2.5 weeks. *Id*. Rau 1998 concluded that "D2E7 has been shown to be safe and efficacious in patients with active RA over 12 months." *Id.*

[16] EULAR response criteria use the DAS that indexes RA activity. A DAS value is determined by a physician examining 28 joints in the shoulders, arms, hands, and knees, counting the number of joints that are swollen or tender. Ex. 1003 ¶ 20. Dr. Weisman testifies that a "'good' EULAR response is a reasonably stringent measure of treatment efficacy." *Id*.

2. Schattenkirchner 1998

Schattenkirchner 1998 examined "the efficacy and tolerability of weekly s.c. administrations of new, fully human anti-TNF-alpha antibody D2E7." Ex. 1007, 5. Patients received weekly doses of 0.5 mg/kg D2E7 as s.c. injections, but non-responders or patients who lost their responder status received s.c. injections at a dose of 1 mg/kg. *Id*. Based on data from up to six months of administration of D2E7, Schattenkirchner 1998 found that "plasma concentrations of D2E7 after multiple s.c. injections are comparable with those after i.v. injections of D2E7." *Id*. Schattenkirchner 1998 concluded that "[t]he s.c. administration of D2E7 has been shown to be safe and efficacious." *Id*.

3. Analysis

Petitioner asserts that a "40 mg subcutaneous dose is the only element that is not expressly disclosed by Rau 1998. This element, however, would have been suggested by Schattenkirchner 1998 and van de Putte 1999." Pet. 40. Petitioner points out that Schattenkirchner 1998 demonstrates that "plasma concentrations of D2E7 after multiple s.c. injections are comparable with those after i.v. injections of D2E7," and that s.c. administration of D2E7 has been shown to be safe and efficacious. Pet. 43–44 (citing Ex. 1003 ¶ 49). Petitioner also relies on van de Putte 1999's disclosure of a 40 mg dose of D2E7. *Id*. at 41–42. Petitioner concludes that selecting the dose and route of administration would have been a "routine optimization" of Rau 1998 yielding predictable results. *Id*. at 42 (citing Ex. 1003 ¶¶ 41–51).

In contesting Petitioner's showing, Patent Owner offers arguments similar to those presented in the van de Putte 1999 and Kempeni 1999 combination. Resp. 62 (stating "Ground 2 is entirely redundant of

Ground 1" and "Ground 2 is contrary to the evidence for the same reasons as Ground 1 and is otherwise factually erroneous"). First, Patent Owner asserts that the DE003 trial discussed in Rau 1998 (and Kempeni 1999 as discussed above) would not have demonstrated that every-other-week dosing of D2E7 is effective or desirable; second, neither Rau 1998 nor Schattenkirchner demonstrates the efficacy of a 40 mg every-other-week dose, suggesting this dose would be inadequate; and third, a POSA would not have equated subcutaneous and intravenous routes of administration based on undisclosed, "preliminary data" from the DE004 trial discussed in Schattenkirchner, which used weight-based dosing, and would have had safety and efficacy concerns including the formation of ADAs. *Id*. at 62–63 (referring to arguments presented in §§ II.A.1, 3, II.A.3, 4, IV.A.1.a, and IV.A.2.c). Patent Owner also relies on the same objective evidence of nonobviousness as for the van de Putte 1999 and Kempeni 1999 combination. *Id.* at 54.

For the reasons that we discussed concerning those arguments for the first combination of references, van de Putte 1999 and Kempeni 1999, we are persuaded that Petitioner establishes a reasonable likelihood of prevailing at trial on claims 1–5 of the '135 patent.

III. MOTION TO SEAL

Patent Owner filed a Combined Motion to Seal and Motion for Protective Order. Paper 25. In its motion, Patent Owner seeks entry of the the Board's default protective order, filed as Exhibit 2218. *Id.* at 1. Patent Owner moves to seal Exhibits 2217 and 2073A, and asserts that these exhibits contain non-public proprietary market data that was provided to Patent Owner by a non-party subject to Patent Owner's obligation to maintain the confidentiality of the information. *Id*. at 2. Petitioner did not

file an opposition to Patent Owner's Combined Motion to Seal and Motion for Protective Order.

Upon review, good cause exists to enter the proposed Protective Order and seal the above exhibits.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner establishes, by a preponderance of the evidence, that claims 1–5 of the '135 patent are unpatentable;

FURTHER ORDERED that the Default Protective Order (Ex. 2218) is hereby entered and shall govern the conduct of this proceeding unless otherwise modified;

FURTHER ORDERED that Patent Owner's Motion to Seal (Paper 25) is *granted*;

FURTHER ORDERED that the following documents shall be sealed as "Board and Parties Only," and will be kept under seal unless and until we refer to material in the papers or exhibits in a final written decision: Exhibits 2217 and 2073A; and

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

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