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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00189
Patent 9,073,987 B2

Before TONI R. SCHEINER, JAMES T. MOORE, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges.*

MOORE, *Administrative Patent Judge.*

FINAL WRITTEN DECISION

Determining Claims 1 and 2 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 and 2 of U.S. Patent No. 9,073,987 B2 (Ex. 1001, "the '987 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 and 2 are unpatentable.

A. Procedural History

Coherus BioSciences Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review pursuant to 35 U.S.C. § 311. AbbVie Biotechnology, Ltd. ("Patent Owner") filed a Preliminary Response (Paper 7, "Prelim. Resp."). On June 13, 2016, we instituted trial to determine whether claims 1 and 2 of the '987 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Kempeni[1] and van de Putte.[2] Paper 8 ("Institution Decision or "Inst. Dec."). Patent Owner requested rehearing of the Institution Decision. Paper 12. Rehearing was denied. Paper 27.

Patent Owner subsequently filed a Response (Paper 33, "Resp."), and Petitioner filed a revised Reply (Paper 49, "Reply"). Oral argument was conducted before the panel on February 16, 2017. A transcript of the argument was entered into the record (Paper 55, "Tr.").

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[1] Joachim Kempeni, *Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7*, ANN. RHEUM. DIS., 58 pp. 170–72 (1999) (Ex. 1003).

[2] Leo van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, ARTHRITIS & RHEUM. 42(S9):S400 (abstract 1977) (1999) (Ex. 1004).

Petitioner supports its Petition with the declaration testimony of Dr. Sharon Baughman (Ex. 1006), Dr. James O'Dell (Ex. 1007), and Dr. Brian Reisetter (Ex. 1025). Patent Owner relies on the declaration testimony of, *inter alia*, Dr. Allan Gibofsky (Ex. 2065), Dr. Brian Harvey (Ex. 2066), Dr. Jerry A. Hausman (Ex. 2067), Mr. Jeffrey M. Sailstad (Ex. 2068), and Dr. Alexander A. Vinks (Ex. 2069).

B. Related Proceedings

The parties identify the following U.S. patent applications and U.S. patents as related to the application that issued as the '987 patent: Application No. 14/175,993; Application 14/634,478; Application No. 14/634,530; Application No. 14/715,310; U.S. Patent No. 8,889,135 ("the '135 Patent"); U.S. Patent 9,017,680 ("the '680 Patent"); U.S. Patent 8,911,737; U.S. Patent No. 8,974,790;[3] and U.S. Patent No. 8,992,926. Pet. 2.

Petitioner also filed petitions seeking *inter partes* review of the '135 and '680 patents, IPR2016-00172 and IPR2016-00188, respectively. Paper 5, 1. Patent Owner further identifies two additional petitions, filed by a different petitioner, seeking *inter partes* review of the '135 patent, IPR2016-00408 and IPR2016-00409. Paper 6, 1. A final decision has been rendered in IPR2016-00172 at Paper 60 therein.

We are not aware of any pending litigation.

C. The '987 Patent

The '987 patent, titled "Methods of Administering Anti-TNFα Antibodies," issued on July 7, 2015. The '987 patent describes biweekly dosing regimens for the treatment of TNFα associated disorders, preferably

[3] Misidentified as U.S. Patent Number 8,984,790, a typographical error.

subcutaneously. Ex. 1001, 2:61–63. "TNFα" is a known tumor necrosis factor α which causes necrosis in certain mouse tumors, mediates shock, and is implicated in sepsis, infections, autoimmune diseases, transplant rejection, and graft-versus host disease. *Id*. at 1:15–30.

In order to inhibit some of these ailments, therapeutic strategies were developed to inhibit human TNFα ("hTNFα"). The '987 patent discloses a method of treating with an hTNFα antibody. *Id*. at Abstract.

D. Illustrative Claims

Claims 1 and 2 are the only claims of the '987 patent, and are reproduced below.

> 1. A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising:
>
> administering to said patient a total body dose of 40 mg of a human anti-TNFα antibody,
>
> wherein the dose is administered subcutaneously from a 40 mg dosage unit form once every 13-15 days, and
>
> wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDR1 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 CDR1 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.
>
> 2. The method of claim 1, wherein 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.

Ex. 1001, 59:35–48 and 60:35–46.

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 by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain why Petitioner has met its burden with respect to claims 1 and 2.

A. Level of Ordinary Skill in the Art

We begin our analysis by addressing the level of ordinary skill in the art as of June 8, 2001. The '987 patent is a continuation of the application that issued as the '135 patent, and that the '135 patent claims the benefit of provisional application 60/296,961, filed June 8, 2001. Petitioner and Dr. Baughman explain that a skilled artisan would possess the skill sets of both a physician treating RA patients and a pharmacokineticist with experience in monoclonal antibodies. Pet. 26; Ex. 1006 ¶ 15.

Dr. Baughman describes the ordinarily skilled artisan physician as an M.D. with at least three years of experience treating RA patients, including with one or more anti-TNFα biologic agents. Ex. 1006 ¶ 15; *see* Pet. 26; Ex. 1007 ¶ 12 (Dr. O'Dell agreeing with Dr. Baughman's definition of the skilled physician). Dr. Baughman describes the ordinarily skilled artisan pharmacokineticist as having a Ph.D. in pharmacokinetics or a related field, and at least three years of experience with the pharmacokinetics and pharmacodynamics of biologic agents, either in industry or academia. Ex. 1006 ¶ 15; *see* Pet. 26–27.

Patent Owner's experts Dr. Gibofsky and Dr. Vinks apply Petitioner's and Dr. Baughman's description of the ordinary artisan. Ex. 2065 ¶¶ 53–54; Ex. 2069 ¶¶ 101–103. We adopt that description of the level of ordinary skill in the art, because it is the description that both parties have applied in this proceeding without challenge, and it is consistent with the level of ordinary skill in the art as reflected by the prior art of record.

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).

The Petition sets forth three terms for construction: (1) the preamble phrase "[a] method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis," (2) "every 13–15 days," and (3) "dosage unit form." Pet. 14–16. Patent Owner initially contended that the preamble was in need of no construction, but contended that the administration of D2E7 produces a meaningful improvement in a variety of clinical outcome measures. Prelim. Resp. 18–20.

In the Institution Decision, we determined that, based on the then-existing record, the preamble phrase is not limiting. Inst. Dec. 8–9. We further determined that no other claim term required construction to resolve the parties' dispute. Inst. Dec. 8 (citing *Vivid Techs., Inc. v. Am. Sci. &*

Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy")).

Petitioner does not dispute our preliminary determination that the preamble phrase "[a] method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis" is not limiting. We have reassessed that determination in light of the arguments and evidence adduced at trial, and maintain that determination based on the full record.

Patent Owner argues for reconsideration of our determination. Patent Owner asserts that "[a]s of June 2001, a treating physician who satisfied the definition of a POSA[4] would have understood the claims to require meaningful therapeutic efficacy." Resp. at 61 (citing Ex. 2065 ¶¶ 20, 92–93). As support, Patent Owner points to the '987 patent specification's disclosure that "administration of D2E7 produces a meaningful improvement in a variety of clinical outcome measures" such as ACR20, ACR50, and SJC.[5] *Id*. at 62.

Patent Owner also contends that the specification of the '987 patent provides "clinically meaningful outcome parameters" for the treatment of RA. *Id*. (citing Ex. 2065, ¶¶ 92–93). Patent Owner, therefore, again asserts that we should construe the phrase to mean that the treatment has "meaningful therapeutic efficiency." We again decline to interpret the claim in this manner. Such a construction would add much uncertainty to the

[4] We understand POSA to be used as shorthand for a Person of Ordinary Skill in the Art.
[5] ACR is shorthand for the American College of Rheumatology improvement criteria. SJC stands for swollen joint count. Ex. 1001, 28:23;30:22.

claim. Meaningful is a highly subjective term, depending on the outcome sought by a treating physician and what he or she might regard as meaningful as regards that outcome.

Patent Owner relies upon the testimony of Dr. Gibofsky, who disagrees with the interpretation we have given the claims. Dr. Gibofsky testifies that our interpretation permits that "any drug that had an effect on a patient's RA symptoms, no matter how insignificant or short-lived (for example, an analgesic or intoxicant), would constitute 'reducing signs and symptoms.'" Ex. 2065, ¶ 92. Dr. Gibofsky ignores that the claim requires treatment with a specific antibody, at a particular dosage, over a particular time period. We do not see an interpretation of these claims whereby they could be directed to any analgesic or intoxicant to reduce those signs or symptoms.

Dr. Gibofsky also makes the statement that "[n]o clinician would consider himself or herself to be 'reducing signs and symptoms' of RA if there were no therapeutically meaningful reduction in the patient's signs and symptoms of the disease." *Id.* To us, this narrower interpretation seems inconsistent with the stated therapeutic benefit of slowing the advance of the disease, where all actual measures might nonetheless still be getting worse. Ex. 1001, 24:62–63.

As we explained in the Institution Decision, claims 1 and 2 do not expressly recite any particular level of efficacy. Rather, they require administering the antibody in a particular dosage amount, form, and time period as claim limitations, without regard to any particular effect other than having as a goal reducing signs and symptoms. Inst. Dec. 9. Moreover, the specification describes administering the antibody for therapeutic purposes

to alleviate the symptoms and/or progression of the disorder. Ex. 1001, 24:25–60. There are many possible ways to quantify such alleviation or reduction in progression, and the claims do not recite one. Injecting a choice of potential "meaningful" measures would render the claim's metes and bounds largely indecipherable.

Accordingly, for these reasons, we reaffirm our determination that, under the broadest reasonable construction, the preamble phrase "[a] method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis" only provides context for the invention and is nonlimiting.

C. Obviousness of Claims 1 and 2 over Kempeni and van de Putte

Petitioner argues that the combination of Kempeni and van de Putte would have rendered obvious the subject matter of claims 1 and 2. Pet. 30–41.

The thrust of Patent Owner's contrary position is that one of ordinary skill in the art would not have been motivated to develop a 40 mg, subcutaneous, every other week dosage regimen to treat RA and would not have reasonably expected success in achieving treatment of RA with that dosage regimen given the collective teachings of the art. Resp. 20–63.

Based on our review of the arguments and evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of claims 1 and 2 would have been obvious over the combination of Kempeni and van de Putte, as explained below.

1. Kempeni (Ex. 1003)

Kempeni teaches that D2E7 is a fully human anti-TNFα monoclonal antibody that "may have advantages in minimising antigenicity in humans"

compared to other biologic TNF antagonists that are not fully human or artificially fused human sequences. Ex. 1003, 1. Kempeni further describes the results of several clinical studies investigating the use of D2E7 to treat RA patients. *Id.* at 1–3. Kempeni is prior art under 35 U.S.C. § 102(b), published in 1999. Pet. 22; Ex. 1003, 1.

During the clinical trials, efficacy generally was assessed using, *inter alia*, the ACR20 criteria. *Id.* at 1–2. To be classified as a responder according to ACR20 criteria, a patient 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, including patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, an acute phase reactant (e.g., C reactive protein ("CRP")), and a measure of disability. *Id.* at 2.

In the first described study, each patient received a single dose of D2E7 (from 0.5 to 10 mg/kg)[6] 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 antibody in terms of onset, duration, and magnitude of response. *Id.*

Kempeni 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 ("PK") parameters were calculated for patients from all

[6] The 0.5 to 10 mg/kg refers to the amount of D2E7 that patients received per kilogram of body weight.

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" DAS (Disease Activity Score)[7] 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 (sometimes referred to in this proceeding as "updosing"). *Id.* Kempeni 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 2–3. The dose was increased to 1 mg/kg subcutaneously weekly for non-responders or patients losing responder status. *Id.* at 3.

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.*

[7] The DAS is a composite score of tender joints, swollen joints, erythrocyte sedimentation rate, and a patient's disease activity assessment as measured on a visual analogue scale. *Id.* at 2.

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 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.*

2. Van de Putte (Ex. 1004)

Van de Putte 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. 1004, 1. 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 reports the percentage of patients receiving an ACR20 response, as well as the median percent improvement in TJC, SWJC, and CRP for each of the dosing regimens and placebo.

The results are set forth in the table reproduced below.

	Placebo	D2E7	D2E7	D2E7
	(n=70)	20 mg (n=71)	40 mg (n=70)	80 mg (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. Based on the results, van de Putte 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 [subcutaneously] in patients with active RA." *Id.*

3. Analysis

A patent 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 to a person of ordinary skill in the art at the time the invention was made. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Obviousness is resolved based on 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, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

a. Scope and content/Differences

Petitioner asserts that the combined teachings of van de Putte and Kempeni disclose or suggest each element of the challenged claims. Pet. 20–26, 36–38 (claim chart mapping the language of the claims to the disclosures of Kempeni and van de Putte).

Patent Owner does not challenge Petitioner's showing that the prior art discloses each element of claims 1 and 2. *See generally* Resp.

Based on the full trial record, we determine that van de Putte and Kempeni collectively disclose each limitation of the challenged claims. First, we agree with Petitioner that van de Putte discloses all of the elements of claims 1 and 2, except for biweekly dosing.

As explained above, van de Putte discloses a study in which RA patients received weekly doses of 20, 40, or 80 mg of D2E7, or placebo, via subcutaneous self-administration over the course of three months. Ex. 1004, 1. The D2E7, therefore, was administered in a pharmaceutically acceptable composition. Further, D2E7 is a known recombinant human anti-TNFα antibody having the six CDRs and heavy chain constant region recited in claims 1 and 2, 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. Patent No. 6,090,382, incorporated in its entirety herein by reference"); *see* Ex. 1008, 2:59–67.

Petitioner also shows, by a preponderance of the evidence, that Kempeni accounts for the differences between van de Putte and the recited biweekly dosing frequency required by all of the challenged claims. Specifically, Kempeni describes a study in which patients received D2E7 via intravenous injection every two weeks for at least 6 months (i.e., 24 weeks). Ex. 1003, 2.

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 asserts, relying in part upon the testimony of Dr. Baughman and Dr. O'Dell, that a person of ordinary skill would have been led from the disclosures of van de Putte and Kempeni to administer 40 mg of D2E7 subcutaneously every 13–15 days, as recited in claims 1 and 2 of the '987 patent, and would have expected such a dose to be safe and effective in treating RA. Pet. 30–41 (citing Ex. 1006 and Ex. 1007 extensively).

Patent Owner "hotly contest[s]" whether the ordinarily skilled artisan would have had a reason to select the claimed dosing regimen, and also contests whether one of ordinary skill would have expected success in treating RA using that regimen. *See, e.g.*, Tr. 42:5–6; Resp. 1, 21 (alleging no reasonable expectation of success and serious safety and efficacy concerns). We address the parties' arguments and evidence on those issues below.

(1) Fixed, subcutaneous dosing

With respect to type of dose and administration of the dose, Petitioner asserts that van de Putte'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. 30–33 (citing Ex. 1002, 9; Ex. 1006 ¶¶ 51–53; Ex. 1008, 22:65–23:1).

Patent Owner does not specifically challenge Petitioner's showings in this regard, *see generally* Resp., 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 had 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. 30-31; Ex. 1006 ¶ 51; Ex. 1022, 7 (stating that "[i]n general, subcutaneous administration is more desirable for doctors and patients than intravenous 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. Baughman testifies that fixed dosing would have been easier and less costly for patients: fixed dosing "requires no patient action beyond injection," whereas body weight dosing requires the patient to prepare each injection before administration. Ex. 1006 ¶ 52; *see also* Ex. 1008, 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."). Dr. Baughman also points to the fixed dose, subcutaneous administration that had been approved for the anti-TNFα antibody ENBREL in 1998. Ex. 1006 ¶ 53.

Finally, we note that patients in the clinical study described in van de Putte were receiving subcutaneous fixed doses, and Kempeni explained that "subcutaneous self administration is a promising approach for D2E7 delivery." Ex. 1003, 3; Ex. 1004, 1; *see* Ex. 1006 ¶¶ 54–55.

(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 dosing regimen to administer 40 mg doses on a biweekly schedule and expect success in treating RA with that regimen. Those arguments fit into two categories based on Kempeni's disclosures: the first based upon the 11.6 to 13.7 day half-life of D2E7, and the second based upon administration of 0.5 mg/kg of D2E7 biweekly. *See* Pet. 32–36. As explained below, we are not persuaded by Petitioner's first argument, but are persuaded by the second argument.

(i) Dose selection and interval based on half-life

Petitioner asserts that a skilled artisan "would have been motivated to modify [the] van de Putte . . . dosing protocol to administer subcutaneous doses biweekly, rather than weekly" based upon the 11.6 to 13.7 day half-life of D2E7 that Kempeni reports. Pet. 33. Dr. Baughman also observes that Kempeni describes biweekly dosing of D2E7 as a viable treatment protocol. Ex. 1006 ¶ 72; Pet. 34.

Petitioner contends that, based on the half-life of D2E7, the person of ordinary skill would have stretched van de Putte's 20 mg weekly dosing to 40 mg biweekly dosing and would have expected success in treating RA. Reply 6–9. Petitioner relies primarily on Dr. Baughman's testimony that pharmacokineticists "routinely" use half-life "to develop the appropriate dosing frequency." Ex. 1006 ¶ 66; Pet. 35.

According to Dr. Baughman, the half-life reported in Kempeni would have suggested dosing less frequently than once a week because "administration of one subcutaneous dose of 40 mg D2E7 [biweekly] would

still be enough to treat RA, as [the amount circulating in the blood] would be equal to or greater than that reached with the 20 mg weekly dose, which was shown to be efficacious by the ACR 20 data in van de Putte." *Id.* ¶ 68.

Dr. Baughman illustrates that concept in a table that approximates the amount of D2E7 circulating in the blood over a two-week period based on the half-life of D2E7 and the doses studied in van de Putte. *Id.* ¶ 67. Dr. Baughman's half-life table is reproduced below.

D2E7 Dose Administered	D2E7 Circulating One Week After Injection	D2E7 Circulating Two Weeks After Injection
20 mg	15 mg	10 mg
40 mg	30 mg	20 mg
80 mg	60 mg	40 mg

Note: The above results assume linear PK; that is, the half-life does not change with dose. (Kempeni, EX. 1003.)

Dr. Baughman's table shows calculations of the approximate amount of 20 mg, 40 mg, and 80 mg from the van de Putte study that she asserts would be circulating in the body one week and two weeks after subcutaneous injection. Ex. 1006 ¶ 67.

Likewise, Petitioner relies on Dr. Baughman's half-life analysis in arguing that that the "logical dosage choice for treating RA with subcutaneous biweekly injections of D2E7 would have been 40 mg." Pet. 34. According to Petitioner, "a central principle of drug development is the desirability of administering the lowest effective drug dose." *Id.* at 34–35 (citing Ex. 1006 ¶ 69 ("The goal is to treat the patient with as little drug as possible in order to reduce potential side effects, while at the same time attaining a therapeutic response.")). In that regard, Petitioner contends, and Dr. Baughman testifies, that, based on van de Putte's clinical data and the

roughly reported half-life of D2E7, a person of ordinary skill in the art "would have recognized that 40 mg biweekly represented the lowest effective dose." *Id.* at 35; Ex. 1006 ¶ 69.

Dr. Baughman further testifies that the amount of D2E7 circulating in the second week after administration of one subcutaneous dose of 40 mg D2E7 would still be enough to treat RA because it would be equivalent to or greater than the amount reached with the 20 mg weekly dose, which van de Putte found to be efficacious. Ex. 1006 ¶ 68. Similarly, Dr. Baughman testifies that the ordinary artisan would have expected success in treating RA with the 40 mg biweekly dose because, "at the end of the second week after dosing 40 mg, the C_{min}[8] would be greater than or similar to the C_{min} at the end of the first week after dosing 20 mg." Ex. 1006 ¶ 71.

Patent Owner responds that Petitioner's and Dr. Baughman's analysis based on half-life is flawed because half-life alone does not provide sufficient information to develop a dosing regimen. Resp. 44–48. In particular, Patent Owner contends that terminal half-life (what Kempeni discloses) does not impart information about: (1) drug concentrations in the blood or at the site of action, or how those concentrations correlate to safety and efficacy; (2) how long the drug remains in the body; or (3) how long the drug lasts at the site of action, all of which would have been important in developing a safe and efficacious dosing regimen. *Id.* at 44–48.

A question before us then, is whether a person of ordinary skill in the art would have had a reason to modify van de Putte's 20 mg weekly dose to a 40 mg biweekly dose based on the known half-life of D2E7. As with other

[8] C_{min} is lowest blood level observed between doses. Ex. 1006 ¶ 62.

factual questions, Petitioner bears the burden of proving that the skilled artisan would have been motivated to make such a modification. *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").

After reviewing the entire record developed during trial, we find that Petitioner does not carry its burden to show that a person of ordinary skill in the art would have been so motivated. As explained above, in the Petition Petitioner asserts that the ordinary artisan would have doubled van de Putte's 20 mg dose to 40 mg and weekly dosing interval to biweekly based on the single PK parameter of half-life.

In support of that assertion, Dr. Baughman testifies that "half-lives are routinely used to develop the appropriate dosing frequency." Ex. 1006 ¶ 66. Dr. Baughman's testimony in that regard may be valid, but the record in this case does not include sufficient persuasive evidence from which we can make that determination. That is, neither Petitioner nor Dr. Baughman directs us to a monoclonal antibody drug with a dosing interval that corresponds to its particular half-life, or to other evidence supporting the assertion that skilled artisans routinely use half-lives to develop a dosing schedule. Accordingly, Dr. Baughman's testimony on those issues is entitled to little or no weight. 37 C.F.R. § 42.65(a).

Moreover, we note that Patent Owner identifies several prior art therapeutic antibodies that were not dosed according to a frequency equal to a single half-life, including: (1) REMICADE, which is dosed only once every 3–6 half-lives; (2) RITUXAN, which is dosed once every 2.8 half-lives; (3) MYLOTARG, which is dosed once every 5 half-lives; and (4) ZENAPAX, which is dosed once every 0.6 half-lives. Resp. 47 (citing

Ex. 1012, 2, 12; Ex. 2007, 1–2; Ex. 2010, 1–2; Ex. 2013 3, 17; Ex. 2072, 96:22–97:3); Ex. 2069 ¶ 112. This evidence tends to suggest half-life has limited applicability in determining dosing regimens.

Petitioner does not dispute that evidence, but replies that it does not suggest that "half-life has no bearing on dosing regimen." Reply 10. We agree. Petitioner, however, does not point to sufficient persuasive evidence from which we can conclude that dosing frequency would have been selected based on its particular half-life alone, as asserted in the Petition.

Petitioner argued in the Petition that the skilled artisan would have been motivated to develop the appropriate dosing regimen for D2E7 based on half-life *alone*. Pet. 33 (contending that, "[b]ased upon the . . . half-life of D2E7 reported in Kempeni," a skilled artisan would have been motivated to modify van de Putte's dosing protocol to administer subcutaneous doses biweekly, rather than weekly), 35 (basing dose selection on the half-life data disclosed in Kempeni).

In the Reply, Petitioner now contends that before June 2001, skilled artisans "routinely relied on half-life *as a factor* when designing a dosing regimen." Reply 8 (emphasis added). Such a substantive shift in position, however, "is foreclosed by the statute, [Federal Circuit] precedent, and Board guidelines." *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286–87 (Fed. Cir. 2017).

Patent Owner argues that half-life is not the only factor the skilled artisan would have considered in modeling a dosing regimen. *See* Resp. 44–48; Ex. 2069 ¶¶ 114–117. Petitioner similarly states in the Reply that Dr. Vinks "agreed that for some drugs C_{max} and AUC can be important parameters," Reply 11. And Dr. Baughman notes that those parameters, as

well as C_{min}—which Dr. Baughman posits "might be the best parameter to indicate the threshold of efficacy"—would have been important to a skilled artisan in modeling a dosing regimen. Ex. 1006 ¶ 62.

Dr. Baughman discounts those factors because they "were not reported as being indicative of safety or efficacy as of the June 2001 filing date of the '987 patent." Ex. 1006 ¶ 62. Dr. Baughman, however, does not explain adequately why the skilled artisan would have disregarded those parameters that she, and others, considered important, or why the absence of those factors from the disclosures of Kempeni and van de Putte suggests that half-life would have provided enough information to model a dosing regimen.

In our view, Dr. Baughman takes a simplistic approach to modeling a dosing regimen without explaining adequately, and without sufficient supporting evidence, why the ordinary artisan would have used such an approach.[9] Accordingly, we are not persuaded Petitioner demonstrates, by a preponderance of the evidence, that a person of ordinary skill in the art would have been motivated to choose the claimed dosing regimen based on half-life.

[9] Patent Owner provides additional criticisms of Dr. Baughman's half-life analysis. For example, Patent Owner asserts that Dr. Baughman analyzed the wrong time interval by focusing on drug levels after a single administration instead of looking at the drug levels after multiple doses. Resp. 22–23; *see id.* at 24–25 (setting forth further arguments why Dr. Baughman's half-life analysis is flawed including bioavailability). We need not address those additional criticisms, however, because we already determine that Dr. Baughman's half-life analysis is entitled to minimal weight.

(ii) Dose selection and interval based on Kempeni's biweekly dosing protocol

Petitioner also argues that the skilled artisan would have been motivated to dose 40 mg of D2E7 biweekly and would have expected such a dose to be safe and effective based on the clinical study Kempeni describes (i.e., the DE003 study) in which patients received intravenous biweekly doses of D2E7. Pet. 30, 35-36. In that regard, Petitioner argues that the 0.5 mg/kg intravenous dose administered in that study is equivalent to a 40 mg subcutaneous dose. Pet. 26 (Table). Petitioner further asserts Kempeni discloses that persons of ordinary skill not only tried biweekly dosing of D2E7, but also "demonstrated that it was a viable treatment protocol." Pet. 34 (citing Ex. 1006 ¶ 72).

Patent Owner responds that Petitioner's argument is based on a misreading of Kempeni and the DE003 study. Resp. 49. Specifically, Patent Owner asserts that Kempeni's "bare bones description of the 'biweekly' phase of Kempeni fails to disclose" subcutaneous dosing, a 40 mg dose, fixed-weight dosing, or a biweekly dosing regimen sustained over a defined period of time. *Id*.

Dr. Vinks testifies for Petitioner that a 0.5 mg/kg dose is equivalent to a 40 mg fixed dose for an 80 kg (i.e., average) patient. Ex. 1055, 159:4–160:1. And counsel for Patent Owner does not deny that there is no dispute that the 0.5 mg/kg intravenous dose is equivalent to the 40 mg subcutaneous dose.[10] Tr. 46:6–21. Thus, contrary to Patent Owner's argument, Kempeni

[10] Counsel for Patent Owner states that such equivalency "would have been a best case." Tr. 46:11–12. That is, Patent Owner agrees that the two doses are equivalent, but contends that if the 0.5 mg/kg dose is insufficient to treat

expressly discloses a dose that is equivalent to the recited subcutaneous 40 mg dose.

Kempeni also teaches biweekly administration. Ex. 1003, 2 ("D2E7 was administered every two weeks" in the dose range from 0.5 to 10 mg/kg). Accordingly, Kempeni explicitly provides a motivation for converting van de Putte's weekly dosing regimen into a biweekly dosing regimen. Kempeni also suggests that the person of ordinary skill would have expected success in treating RA with such a dosing regimen. That is, Kempeni concludes that long term treatment with D2E7 in the dose range from 0.5 to 10 mg/kg "was well tolerated." *Id.* Additional record evidence confirms that reasonable expectation of success. Ex. 2114, 8 (D2E7 "can be administered every two weeks as an intravenous injection . . . or subcutaneously. D2E7 is well tolerated and must be called a therapeutic step forward.").

Patent Owner points to Kempeni's disclosure that treatment was discontinued during the biweekly phase of the DE003 study "once a response was rated as 'good' and patients were retreated 'only upon disease flare up.'" Resp. 49. (citing Ex. 1003, 2). Thus, Patent Owner contends that the focus on personalized doses and schedules in the DE003 study would have taught away from the fixed dosing regimen of the claims. *Id* (citing Ex. 2065, ¶¶ 83–85).

We see the evidence somewhat differently. A reference teaches away from the claimed invention if it criticizes, discredits, or would have

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RA, the 40 mg subcutaneous dose also is insufficient, given the lower bioavailability of a drug after subcutaneous administration. Tr. 46:16–21. We address that contention below in discussing Patent Owner's argument that Kempeni, and the prior art as a whole, teach away from the 0.5 mg/kg dose. *See infra* §§ II.C.3.b.(2)(ii)–(2)(iii).

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).

Kempeni 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. 1003, 2 (emphasis added). Thus, far from criticizing, discrediting, or discouraging the person of ordinary skill from pursuing a biweekly regimen, as explained above, Kempeni expressly discloses such dosing frequency.[11]

We agree with Patent Owner that, for some portion of the treatment period, patients were treated only on flare up. Resp. 49; Ex. 1003, 2. That disclosure, however, does not negate Kempeni's teaching of biweekly dosing. Nor does it fairly teach away from biweekly dosing. We also agree that some patients were "updosed" for "inadequate clinical response." Resp. 50; Ex. 1003, 2–3.

[11] Additional prior art references support the finding regarding Kempeni's disclosure. For example, one reference 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." Ex. 2114, 4.

We find that such disclosure represents, at most, an alternative dosing schedule to the biweekly dosing Kempeni discloses, with patient variability accommodated. In any event, we find that persons of ordinary skill were not led in a direction divergent from that taken by Patent Owner. To the contrary, evidence in the record demonstrates that skilled artisans conducted studies dosing D2E7 subcutaneously in fixed doses, and on a biweekly schedule. Ex. 1004, 1 (disclosing that D2E7 was administered subcutaneously in fixed doses of 20, 40, and 80 mg); Ex. 1005, 3 (describing the DE010 study, in which patients initially were treated with 1 mg/kg D2E7 intravenously, 1 mg/kg D2E7 subcutaneously, or placebo, but thereafter received subcutaneous injections of 1 mg/kg D2E7 biweekly in the open label portion of the study).

Patent Owner next argues that even if the 0.5 mg/kg intravenous dose disclosed in Kempeni is equivalent to a 40 mg subcutaneous dose, the 0.5 mg/kg dose "would have delivered substantially more drug" to the patient than a 40 mg subcutaneous dose because "only a fraction of the subcutaneous dose is absorbed in the blood stream." Resp. 49–50 (citing Ex. 2069 ¶ 34). On that point, Dr. Vinks testifies that the bioavailability (i.e., amount of drug that reaches the systemic circulation relative to an intravenous administration) of a drug administered subcutaneously "is almost always lower than for the same drug administered intravenously." Ex. 2069 ¶ 34.

We agree with Patent Owner that there is evidence supporting the position that a drug administered subcutaneously can be less bioavailable than a drug administered intravenously. *See* Ex. 2018, 8–9 (explaining that the absolute bioavailability of proteins after subcutaneous administration "is

generally variable and incomplete relative to an [intravenous] dose with values ranging from about 20% up to 100%"). Nevertheless, Kempeni discloses that plasma concentrations of D2E7 after multiple subcutaneous doses are "comparable to those achieved with intravenous administration," and that D2E7 administered subcutaneously is "as effective as when administered intravenously." Ex. 1003, 3. Given the evidence of those teachings in the record, we are not persuaded that the difference in bioavailability between an intravenous and subcutaneous dose would have counseled against administering a subcutaneous 40 mg dose of D2E7 biweekly.

Patent Owner additionally argues that the skilled artisan would not have understood the 0.5 mg/kg dose in the biweekly study that Kempeni discloses to suggest that a 40 mg biweekly regimen would have been effective to treat RA. Resp. 50. Specifically, Patent Owner contends that patients were up-dosed due to inadequate response in all trials that evaluated the 0.5 mg/kg dose. *Id.* (citing Ex. 1003, 2–3; Ex. 1023); *see also id.* at 11–12, 36–37 ("up-dosing occurred even in trials involving intravenous administration"). Patent Owner further asserts that at least one prior art reference (i.e., Rau 2000) emphasized that D2E7 doses ***greater*** than 1 mg/kg resulted in "long-lasting reduction of disease activity." *Id.* at 36, 50 (citing Ex. 2114, 4)(emphasis in original). According to Patent Owner, Kempeni, and the prior art as a whole, taught away from administering low doses (i.e., 0.5 mg/kg or 1 mg/kg) across all patients. *Id.* at 37–38, 50.

Petitioner replies that up-dosing of the 0.5 mg/kg dose did not show that the dose was insufficient to treat RA. *See* Reply 15–16. On that point, Petitioner asserts that Kempeni and Rau 2000 "both teach that the 0.5 mg/kg

bi-weekly dose was 'sufficient' and reduced the signs and symptoms of RA in patients," even if it resulted in only a moderate response. *Id.* at 19–20. After having considered the arguments and evidence before us, on balance, it supports the position of Petitioner that the up dosing reported in Kempeni and Rau 2000 would not have dissuaded a person of ordinary skill from pursuing 40 mg biweekly dosing as a viable option.

Like Kempeni, Rau 2000 describes the DE001/DE003 clinical study and results of that study. Ex. 2114, 5–6, 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. 2114, 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. 1003, 2 (Kempeni describing the transition from DE001 to DE003). Patients were subsequently administered injections when disease activity increased, at a minimum interval of two weeks. Ex. 2114, 5.

As Patent Owner noted during argument, 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." *Id.* at 6, Fig. 2; *see* Tr. 48:21–49:5. Rau 2000 also reports that there was a worsening in ESR (erythrocyte sedimentation rate) after one week in the 0.5 mg/kg group. *Id.* at 6. Patent Owner relies on these statements in Rau 2000 as support for its argument that the 0.5 mg/kg dose was ineffective. Resp. 36, 50.

Patent Owner's argument has some evidentiary support in Rau 2000, but 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. 2114, 6, Fig. 2; Ex. 2218, 6, Fig. 2 (high resolution version of Rau 2000 that depicts the figures with better clarity).

We do acknowledge that Rau 2000 discloses an increase in the number of swollen joints when the dosing interval was extended beyond two weeks, but find, based upon the totality of the evidence of record, 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. 2114, 6. However, swollen joints are only one of the ACR20 criteria. *See* Ex. 1003, 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. Ex. 2114, 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* § II.B, above.

Further, Kempeni concludes that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." Ex. 1003, 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 and 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 or the DE001/DE003 study results that Rau 2000 describes.

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

Patent Owner also 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 known threat of ADAs (anti-drug antibodies). Resp. 27–28. With respect to the PK data, Patent Owner argues the data suggest that, at steady-state, the trough concentrations (i.e., C_{min}) would have been expected to be too low and the fluctuations between C_{min} and C_{max} greater than those of the 20 mg weekly van de Putte dose, thereby teaching away from the claimed dosing regimen. *Id.* at 28, 31–36.

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 39–43. 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 32–36; *see* Ex. 2069 ¶¶ 131–150.

Petitioner replies that the ordinary artisan would have relied on the published clinical data to design a D2E7 dosing regimen, not theoretical PK modeling, and that those data would have led to 40 mg biweekly dosing with the reasonable expectation that it would treat the signs and symptoms of RA. Reply 4–7. Petitioner further asserts that Patent Owner's modeling theory is flawed in that it assumes that a skilled artisan would have been motivated solely to pursue the most efficacious dosing regimen possible. *Id.* at 7. Petitioner argues that a skilled artisan would have balanced efficacy with a number of other factors when designing a dosage regimen, including safety and patient preference. *Id.* Petitioner also contends that the conclusions Patent Owner and Dr. Vinks draw from the PK modeling are irrelevant because there is no evidence that the C_{min} value for a 20 mg weekly dose was the appropriate C_{min} to use as the therapeutic floor. *Id.* at 11–12.

We are persuaded by Petitioner's arguments. Here, record evidence supports Petitioner's argument that a skilled artisan would have pursued one of two approaches to designing a dosing regimen: a clinical approach testing different doses and dosing intervals, as Patent Owner did for D2E7, or a theoretical model approach. Indeed, Patent Owner's PK expert during prosecution outlined the two alternative approaches to drug dosage development and explained that Patent Owner developed the D2E7 dosing regimen through clinical trials. Ex. 2003 ¶ 62. Dr. Vinks testifies that the publicly available PK information in June 2001 would not have permitted a PK/PD correlation for modeling purposes, because it did not report patient specific data. Ex. 2069 ¶¶ 130–131; *see* Ex. 2003 ¶¶ 64, 68 (patient specific data is necessary for theoretical modeling). Nevertheless, Dr. Vinks performed such a modeling exercise.

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 Dr. Vinks draws from the modeling are not entitled to significant weight because, as both parties note, the minimum effective dose of D2E7 "was undefined in June 2001." Ex. 2003 ¶ 53 n.2; Resp. 21; Reply 12. Thus, comparing the C_{min} of a 40 mg biweekly dose to the C_{min} of van de Putte'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 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. 1003, 1; *see* Ex. 1056, 56:8–57:22. That is, Kempeni 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. 1003, 1. Kempeni further states that the fully human D2E7, "may have greater therapeutic potential" and "advantages in minimising antigenicity in humans." *Id.*; *see also* Ex. 2114, 8 ("Since D2E7 consists only of human sequences, allergic reactions are less probable than with non-human monoclonal antibodies.").

Although counsel for Patent Owner acknowledges there could be differences in the risk of developing ADAs when dosing a chimeric antibody such as REMICADE, Tr. 43:21–44:18, 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.[12] *See* Resp. 39–43; Ex. 2069 ¶¶ 64, 69–71, 163.

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. 2069 ¶ 41 (citing Ex. 2049, 11); *see also id.* ¶ 148 ("It was reported in the prior art that 'the magnitude of fluctuations between the maximum and minimum steady-state plasma concentrations are an important consideration for any drug that has a *narrow therapeutic range*'" (emphasis added)).

[12] We also note that Kempeni reports D2E7 was safe and efficacious over a wide range of doses (i.e., from 0.5 mg/kg to 10 mg/kg). Ex. 1003, 3. 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 that were described as allergic . . . did not recur in the same patients with continuation of treatment" and "did not require any therapeutic intervention." Ex. 2114, 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 20–21 (citing Ex. 1011, 4; Ex. 1012, 7; Ex. 1055, 219:4–220:3).

Nothing in the record, however, suggests that D2E7 has such a narrow therapeutic range. Rather, as Petitioner explains, D2E7 has a wide therapeutic window and a relatively long half-life. Reply 13–14; *see* Ex. 1003, 2 (reporting that D2E7 has a half-life of 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, regarding the clinical data, Patent Owner points to the prior art trials that report patient up dosing. Resp. 36–38. As explained above, however, we are not persuaded that reports of up dosing would have taught away from the claimed dosing regimen. Patent Owner further contends that van de Putte also observes "[t]he trend of better efficacy with higher or more frequent doses." Resp. 37 (citing Ex. 2065 ¶¶ 17, 64–66; Ex. 2069 ¶ 93). In that regard, Patent Owner notes that the 20 mg weekly dose "appeared to be less effective than the 40 mg and 80 mg weekly doses" because the data show that the 20 mg dose was "numerically inferior" to the other doses. *Id.* (citing Ex. 1004, 1; Ex. 1024 (van de Putte 6 month data); Ex. 2129 (van de Putte 1-year data)).

Patent Owner continues that a skilled artisan "would have been unlikely to pursue the 20 mg weekly dose of van de Putte and would have been discouraged from making changes to that dosing regimen that would be expected to decrease its efficacy." *Id.* This is so, argues Patent Owner, because the goal of a person of ordinary skill engaged in the design of a D2E7 dosing regimen "would not have been to obtain mere superiority over placebo or to achieve marginal efficacy[;] . . . [t]he goal would have been to eliminate disease activity or reduce it to the fullest extent possible." *Id.* at

37–38 (citing Ex. Ex. 2025, 3; 2065 ¶¶ 71, 92–93; Ex. 2074, 48:24–49:1, 64:18–65:12).

We disagree that the evidence supports an assertion that the 20 mg dose was insufficiently efficacious. First, as we explained in the Institution Decision, van de Putte discloses that 20, 40, and 80 mg of D2E7 administered weekly were "all statistically significantly superior to placebo" for all efficacy parameters studied (i.e., van de Putte discloses that all three doses treated RA). Ex. 1004, 1; Inst. Dec. 16–17. Van de Putte's tabulated clinical responses show similar percentages of patients achieving ACR20 response and median percent improvement in TJC, SWJC, and CRP for each of the 20, 40, and 80 mg doses. Ex. 1004, 1.

Although Patent Owner argues that rheumatologists "routinely rely on numerical trends, even if not statistically validated," Resp. 37 n.7, as both parties' experts note, the van de Putte study was not designed for dose to dose comparisons. Ex. 1006 ¶ 61; Ex. 2069 ¶ 93. To the extent that such dose to dose comparisons are permissible to make from the van de Putte data, the authors of the study (i.e., persons of at least ordinary skill as of June 2001) concluded that the "20, 40 and 80 mg/week were nearly equally efficacious when given [subcutaneously] in patients with active RA." Ex. 1004, 1.

We also are not persuaded that the only goal of a skilled artisan in June 2001 would have been to eliminate disease activity or reduce it to the fullest extent possible, as Patent Owner argues. Patent Owner's argument in this regard looks to what a rheumatologist would have considered the ideal goals of treatment, not what would have been considered practically achievable for every patient. *See* Ex. 2074, 66:12–25 (Dr. O'Dell's

testimony that "if the disease activity continues, it's not completely controlled, [but] that does not mean your treatment has been a complete failure. Oftentimes you're only able to improve things and not get rid of them entirely."), 73:12–18 (complete remissions of RA are "disappointingly rare," even today).

In other words, we agree with Petitioner that the skilled artisan designing a dosing regimen through clinical trials would have balanced efficacy with other factors including safety and patient preference. Ex. 1006 ¶ 69; Ex. 2006 ¶ 23; Ex. 2049, 11 (a multiple-dosage regimen should balance "patient convenience with the achievement and maintenance of maximal clinical effectiveness"); Ex. 2074, 68:6–9 (the expectations for clinical trials were "to improve by ACR20," which is "the FDA standard"); Ex. 2119, 67 (dosing intervals may need to be adjusted "to make the frequency of administration convenient for patient compliance").

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.

b. 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. 55–61. "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 commercial success of HUMIRA, a commercial formulation of the anti-TNFα antibody used in the claimed method, to support the nonobviousness of the challenged method claims. Resp. 58–61.

"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 1329. 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 significant dispute in this case that HUMIRA is commercially successful. Resp. 58; Reply 26 ("HUMIRA® has been commercially successful . . ."); *see* Ex. 1025 ¶ 9 (Dr. Reisetter testifying that HUMIRA "has been commercially successful since its introduction in 2003"); Ex. 2067 ¶¶ 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. 58–59.

Petitioner, on the other hand, contends that any presumption of nexus has been rebutted because the reasons for HUMIRA's commercial success are "unrelated to the claimed dosing regimen." Reply 26; Pet. 29–30. To support its position, Petitioner directs us to some of Patent Owner's additional patents covering HUMIRA, including the patent directed to the antibody itself and several patents directed to formulations of HUMIRA. Pet. 30; Reply 26; Ex. 1047.

Petitioner also points to Patent Owner's argument in a different *inter partes* review proceeding involving a formulation patent covering HUMIRA. Reply 26. There, Patent Owner argued that the formulation covered by the patent and sold as HUMIRA "was a marked advance over the low-concentration and lyophilized formulations of its day." Ex. 1046, 61. Patent Owner continued that the commercial success of HUMIRA

> was driven in large part by (i) the ability of patients to self-administer a liquid antibody formulation via single dose subcutaneous administration . . . without lyophilization and the accompanying need for reconstitution, and (ii) the fact that it is

> stable enough to be commercially viable (*e.g.*, to withstand shipping and storage for periods of time typical for biologic therapies.)

Id. Thus, Patent Owner has relied on features other than the dosing regimen recited in the '987 patent claims as driving the commercial success of HUMIRA.

Petitioner correctly notes that Patent Owner does not account for the other patents covering HUMIRA in its efforts to establish commercial success. *See* Tr. 65:21–66:15; Ex. 1057, 112:4–21 (Dr. Hausman testifying that he did not investigate whether other patents drove the commercial success of HUMIRA). Further, as we noted in the Institution Decision, some of the record evidence attributes HUMIRA's commercial success to the fully human D2E7 anti-TNFα antibody, rather than the recited dosing regimen. Inst. Dec. 22; 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.").

Also, as explained above, the D2E7 antibody was known and patented. Ex. 1001, 3:28–38; *see generally* Ex. 1008. "Where market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the 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 '987 patent, or the formulation that Patent Owner argued was the driver of commercial success in another *inter partes*

review, 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 the '987 patent claims. 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. 55–56. 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.* at 55–56 (citing Ex. 2065 ¶¶ 21–32, 90, 91). In particular, Patent Owner asserts that although two anti-TNFα agents were approved as of 2001 (i.e., REMICADE and ENBREL), "a need existed for additional biologics with more advantageous dosing regimens," and HUMIRA satisfied that need where biologics from other companies failed. *Id.*

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, the prior art already disclosed biweekly D2E7 dosing regimens. *See* Ex. 1011 (ENBREL required twice weekly administration); Ex. 1003, 2 (Kempeni describing biweekly dosing of D2E7).

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. 1011, 6 ("The recommended dose of ENBREL for adult patients with [RA] is 25 mg given twice weekly as a subcutaneous injection"); Ex. 1004, 1 (van de Putte 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 sufficiently.

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. 1003, 1 (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. 2065 ¶ 88 (Dr. Gibofsky's testimony that prior art anti-TNFα inhibitor TNFbp dimer failed because a "'significant antibody response' was reported 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. 56–58. Patent Owner does not direct us to sufficient persuasive 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. 56–58.

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 and 2 of the '987 patent would have been obvious over the combination of Kempeni and van de Putte.

III. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1 and 2 of the ’987 patent are unpatentable; 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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