Paper No. 55
Filed: July 14 , 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00188
Patent 9,017,680 B2

PATENT OWNER'S NOTICE OF APPEAL

via E2E
Patent Trial and Appeal Board

via Hand Delivery
Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, Room 10B20
600 Dulany Street
Alexandria, VA 22314

via CM/ECF
United States Court of Appeals for the Federal Circuit

Pursuant to 35 U.S.C. §§ 141 and 142 and 37 C.F.R. §§ 90.2 and 90.3, Patent Owner AbbVie Biotechnology Ltd. hereby provides notice that it appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision entered June 9, 2017 (Paper 54) and from all underlying orders, decisions, rulings, and opinions regarding U.S. Patent No. 9,017,680 B2 in *Inter Partes* Review No. IPR2016-00188. This notice is timely under 37 C.F.R. § 90.3, having been filed within 63 days after the date of the Final Written Decision.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Patent Owner anticipates that the issues on appeal include but are not limited to: the Board's determination that claims 1-4 are unpatentable under 35 U.S.C. § 103 as obvious; the Board's claim constructions; the Board's violation of the Administrative Procedure Act through its failure to address arguments and/or reliance on evidence, arguments, and theories not articulated by Petitioner until after Patent Owner filed its Patent Owner's Response (Paper 31); the unconstitutionality of *inter partes* review under Article III and the Seventh Amendment of the U.S. Constitution; and any finding or determination supporting or relating to these issues, as well as all other issues decided adversely to Patent Owner in any order, decision, ruling, or opinion.

Pursuant to 35 U.S.C. § 142 and 37 C.F.R. § 90.2(a), this notice is being filed with the Director of the United States Patent and Trademark Office, and a copy of this notice is being concurrently filed with the Patent Trial and Appeal Board. In addition, a copy of this notice, along with the required docketing fees,

are being filed with the Clerk's Office of the United States Court of Appeals for the Federal Circuit via CM/ECF.

Respectfully submitted,

Dated: July 14, 2017

By: /Steven P. O'Connor/

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CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of July, 2017, a true and correct copy of the foregoing "**PATENT OWNER'S NOTICE OF APPEAL**" was filed with the Patent Trial and Appeal Board through the Board's electronic system and filed by hand with the Director of the United States Patent and Trademark Office, at the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, Room 10B20
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I also hereby certify that on this 14th day of July, 2017, a true and correct copy of the foregoing "**PATENT OWNER'S NOTICE OF APPEAL**," and the filing fee, were filed with the Clerk's Office of the United States Court of Appeals for the Fed eral Circuit via CM/ECF.

I also hereby certify that a true and correct copy of the foregoing "**PATENT OWNER'S NOTICE OF APPEAL**" was served by electronic mail on this 14th day of July, 2017 on counsel of record for the Petitioner as follows:

Petitioner has consented to electronic service by email to IPR40299-0013IP1@fr.com.

Dated: July 14, 2017 By: /Steven P. O'Connor/
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EXHIBIT A

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Paper No. 54
Entered: June 9, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,
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ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00188
Patent 9,017,680 B2

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

SCHEINER, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
Determining Claims 1–4 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 1–4 (collectively, "the challenged claims") of U.S. Patent No. 9,017,680 B2 (Ex. 1001, "the '680 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 1–4 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. On June 13, 2016, we instituted trial to determine whether claims 1–4 of the '680 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of and van de Putte[1] and Kempeni.[2] Paper 9 ("Institution Decision or "Inst. Dec.").

AbbVie Biotechnology Ltd. ("Patent Owner") filed a Response (Paper 31, "PO Resp."), and Petitioner filed a Reply (Paper 41, "Reply"). Petitioner supports its Petition with the Declarations of Dr. Sharon Baughman (Ex. 1006), Dr. James O'Dell (Ex. 1007), and Dr. Brian Reisetter (Ex. 1025). Patent Owner relies on the Declarations of Dr. Allan Gibofsky (Ex. 2065), Dr. Brian Harvey (Ex. 2066), Dr. Jerry A. Hausman (Ex. 2067), Dr. Jeffrey M. Sailstad (Ex. 2068), and Dr. Alexander A. Vinks (Ex. 2069).

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

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

Oral argument was heard on February 16, 2017, and a transcript of the argument has been entered into the record (Paper 53, "Tr.").

B. Related Proceedings

The parties do not inform us of any related litigation, but indicate that the '680 patent is a continuation of U.S. Patent Application No. 10/163,657, which issued as U.S. Patent No. 8,889,135 ("the '135 patent"), and that U.S. Patent No. 9,073,987 ("the '987 patent") is also a continuation of Application No. 10/163,657. In addition to the present Petition, Petitioner filed petitions seeking *inter partes* review of the '135 and '987 patents: IPR2016-00172 and IPR2016-00189, respectively. Pet. 3, Paper 6, 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.

C. The '680 Patent (Ex. 1001)

Tumor necrosis factor α ("TNFα"), a cytokine produced by numerous cell types, has been implicated in activating tissue inflammation and causing joint destruction in the auto immune disease, rheumatoid arthritis ("RA"). Ex. 1001, 1:15–16, 25:36–40. The '680 patent, titled "Methods of Administering Anti-TNFα Antibodies," issued on April 28, 2015, and discloses administering a total body dose of 20, 40, or 80 mg of an anti-TNFα antibody having the six complementarity determining regions ("CDRs") and heavy chain regions of D2E7—a known recombinant human anti-TNFα antibody— together with the anti-rheumatic drug methotrexate ("MTX"), to rheumatoid arthritis patients according to a "biweekly dosing regimen[] . . . preferably via a subcutaneous route . . . [p]referably . . . every 9–19 days, more preferably, every 11–17 days, even more preferably, every

13–15 days, and most preferably, every 14 days." *Id.* at 3:7–42, 6:26–39, 9:53–67, 29:15–30:29.

D. Illustrative Claim

Petitioner challenges claims 1–4 of the '680 patent. Claim 1, the sole independent claim, is illustrative.

> A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising:
>
> administering to said patient, in combination with methotrexate, a human anti-TNFα antibody,
>
> wherein the human anti-TNFα antibody is administered subcutaneously in a total body dose of 40 mg 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.

Ex. 1001, 51:23–52:25.

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 52:26–29. Claim 3 specifies that the anti-TNFα antibody in the method of claim 1 "is administered from a 40 mg dosage unit form," and claim 4 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 52:30–35.

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 1–4.

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 priority date of the '135 patent, of which the '680 patent is a continuation. 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. 28; Ex. 1006 ¶ 15; Ex. 1007 ¶ 12, 13. Dr. Baughman describes the ordinarily skilled 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. 28; Ex. 1007 ¶ 12 (Dr. O'Dell agreeing with Dr. Baughman's definition of the skilled physician). Dr. Baughman describes the ordinarily skilled 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. 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 and it is 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). Only terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999).

We determine that only the following two claim terms require discussion for resolution of the controversy in this case.

1. "method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis"

This claim term appears in the preamble of claim 1, the only independent claim. Petitioner argues that "the broadest reasonable interpretation of the phrase 'method of reducing signs and symptoms' does not require a particular level of efficacy . . . [but] merely require[s] that the 'signs and symptoms' the patient exhibits are reduced relative to their level prior to administration of the antibody plus methotrexate." Pet. 16.

In its Preliminary Response, Patent Owner argued, on the one hand, that "[t]he plain and ordinary meaning of a 'method of reducing signs and

symptoms' is clear . . . [and] no construction is needed." Prelim. Resp. 19. On the other hand, however, Patent Owner argued that we "should reject Petitioner's proposed interpretation of the preamble because it is inconsistent with the specification, which discloses that administration of [anti-TNFα antibody] and [methotrexate] produces a meaningful improvement in a variety of clinical outcome measures such as ACR20, ACR50,[3] and SWJ (swollen joint count)." *Id.* (citing Ex. 1001, Figs. 1b, 2, 3, 30:23–26).

In the Institution Decision, based on the then existing record, we determined that the preamble phrase "method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis" is not limiting, except to the extent that it specifies the patient to whom the anti-TNFα is administered. Inst. Dec. 6. Petitioner does not dispute our preliminary determination regarding that phrase, but Patent Owner argues that "[a]s of June 2001, a treating physician who satisfied the definition of a [person of ordinary skill in the art] would have understood the claims to require meaningful therapeutic efficacy." PO Resp. 62 (citing Ex. 2065 ¶¶ 20, 92, 93). Patent Owner again argues that we should "adopt a construction consistent with the specification, which discloses that administration of D2E7 and [methotrexate] produces a meaningful improvement in a variety of clinical outcome measures such as ACR20 and ACR50." PO Resp. 63 (citing Ex. 1001, Figs. 1B, 2, 3, 30:23–26).

We have reassessed our initial determination in light of the arguments and evidence developed at trial, and maintain that initial determination, for the reasons discussed below.

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[3] ACR20 and ACR50 refer to the American College of Rheumatology improvement criteria. Ex. 1003, 2.

As we explained in the Institution Decision, "a preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)). On the other hand, "a preamble is not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.'" *Id.* (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)).

Here, the steps of the method, dosage amount, timing, route of administration, and active component are all specified in the body of the claim. The phrase "reducing the signs and symptoms of rheumatoid arthritis," therefore, merely recites an intended use. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003) (statements of intended use typically do not limit the scope of a claim because they "usually do no more than define a context in which the invention operates"). Stated another way, the claims do not expressly recite any particular level of efficacy, meaningful or otherwise. Rather, the claims require administering the antibody in a particular dosage amount, by a particular route, at a particular interval—to a patient with moderately to severely active rheumatoid arthritis.

The portions of the specification relied on by Patent Owner do not persuade us otherwise. The specification of the '680 patent explains that the data in Figures 1B and 2–4 "indicate that subcutaneous, biweekly D2E7 treatment combined with methotrexate was significantly better than placebo in reducing the signs and symptoms of RA," and that all of the doses "were

statistically significantly more effective than placebo." Ex. 1001, 30:23–27. A statement that the treatment is significantly better than placebo, however, does not necessarily mean that the treatment produces a "meaningful" improvement in a variety of clinical outcome measures—nor does it explain what a meaningful outcome would be. In that regard, we note that the "outcome measures" Patent Owner directs us to in Figures 1B and 2–4 are not all the same. Figure 1B depicts ACR20 and ACR50 responses, Figure 2 depicts ACR20, ACR50, and ACR70 responses, Figures 3A and 3B depict tender joint count and swollen joint count, respectively, and Figure 4 depicts results from a health survey form (SF-36) indicative of overall health status as reported by patients. Ex. 1001, 5:44–67. Patent Owner's proposed construction, which requires reducing "meaningfully" the signs and symptoms of RA is not tied to any particular "outcome measure" provided in Figures 1B and 2–4, and would have the effect of introducing ambiguity into the claims.

Accordingly, we maintain our determination that the preamble phrase "method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis" is not limiting, except to the extent that it specifies the patient to whom the anti-TNFα is administered.

2. "40 mg dosage unit form"

According to the '680 patent, "dosage unit form" "refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound[.]" Ex. 1001, 23:9–12. Petitioner contends, "[b]ased upon this definition, a '40 mg dosage unit' form would encompass a syringe filled with 40 mg of D2E7." Pet. 17.

"For the limited purpose of [its] preliminary response, Patent Owner [did] not contest this" (Prelim. Resp. 20), and does not address the term in its Patent Owner Response.

We have reassessed our initial determination in light of the evidence developed at trial (Inst. Dec. 7), and maintain our determination that the broadest reasonable interpretation of "40 mg dosage unit form" encompasses a syringe filled with 40 mg of D2E7.

C. Obviousness of Claims 1–4 over van de Putte and Kempeni

Petitioner argues that the combination of van de Putte and Kempeni would have rendered obvious the subject matter of claims 1–4. Pet. 32–44. The thrust of Patent Owner's 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. PO Resp. 20–64. 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 1–4 would have been obvious over the combination of van de Putte and Kempeni, 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.

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)[4] 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 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

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

weeks until a "good" DAS (Disease Activity Score)[5] 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 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.*

In a third clinical study that evaluated the safety of 1 mg/kg single subcutaneous or intravenous injections of D2E7—in some cases in combination with the anti-rheumatic drug methotrexate—it was determined that the safety profile of single dose D2E7 administration was "comparable to that of placebo." *Id.*

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[5] 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.

According to Kempeni, the data from these studies collectively suggest that D2E7 "is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections" and "[a]dditional 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 of the study described in van de Putte 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

Ex. 1004, 1. 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. The prior art discloses or suggests each and every element of the challenged claims

Petitioner asserts that the combined teachings of van de Putte and Kempeni disclose or suggest each element of the challenged claims. Pet. 40–42 (claim chart mapping the language of the claims to the disclosures of van de Putte and Kempeni). In particular, Petitioner argues that the only difference between the disclosure of van de Putte and the challenged claims is that van de Putte describes: "dosing 40 mg of D2E7 weekly, rather than every 13-15 days (*i.e.* biweekly), as recited in the claims," and also fails to describe "administering D2E7 in combination with methotrexate." *Id.* at 27. Petitioner asserts that Kempeni accounts for those differences. *Id.* Specifically, Petitioner points to Kempeni's teachings that: (1) D2E7 has an estimated mean terminal half-life of 11.6–13.7 days; (2) D2E7 was administered in biweekly intravenous infusions; (3) "plasma

concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration"; and (4) D2E7 was administered with methotrexate." *Id.* Petitioner also directs us to Kempeni's disclosure of biweekly intravenous dosing of 0.5 mg/kg of D2E7, which neither party disputes is roughly equivalent to the 40 mg fixed subcutaneous dose (in an 80 kg patient). *Id.* at 28; Tr. 46:6–21 (counsel for Patent Owner explaining that Patent Owner does not dispute, as a best case, Petitioner's contention that the 0.5 mg/kg intravenous dose is roughly equivalent to the 40 mg subcutaneous dose); Ex. 1055, 159:4–160:1.

Patent Owner does not challenge Petitioner's showing that the prior art discloses each element of claims 1–4. *See generally* PO Resp. Based on the full trial record, we determine that van de Putte and Kempeni collectively disclose each limitation of the challenged claims. That is, we agree with Petitioner that van de Putte discloses all of the elements of claims 1–4, with the exceptions of biweekly dosing, and administering the antibody in combination with methotrexate. 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. D2E7, therefore, was administered in a pharmaceutically acceptable composition, in unit dosage form. *Id.* Further, D2E7 is a known recombinant human anti-TNFα antibody having the six CDRs and heavy chain constant region required by claims 1–4, and the amino acid sequences for the variable light and variable heavy chain regions required by claims 2 and 4. Ex. 1001, 3:40–42 (explaining that D2E7 is "described in U.S. Pat. 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, as well as administering the antibody with methotrexate. 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), and also teaches that "D2E7 is safe and effective . . . in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections." Ex. 1003, 2, 3.

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 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, in combination with methotrexate, as recited in claims 1–4 of the '680 patent, and would have expected such a dose to be safe and effective in treating RA. Pet. 2, 32–39 (citing Ex. 1006 ¶¶ 48, 51–53, 56–58, 63–73; Ex. 1007 ¶¶ 25–33, 43). Patent Owner contests 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; PO Resp. 22 (alleging no reasonable expectation of success). We address the parties' arguments and evidence on those issues below.

(1) Fixed, subcutaneous dosing

With respect to type of dose and administration, 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. 33–34 (citing Ex. 1022, 1546; Ex. 1006 ¶¶ 51–53; Ex. 1008, 22:65–23:1).

Patent Owner does not challenge Petitioner's showings in this regard, *see generally* PO 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 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. 33; Ex. 1006 ¶ 51; Ex. 1022, 9 (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)). And 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. 35–38. 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. 35. In particular, 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 10. Petitioner relies primarily on Dr. Baughman's testimony that pharmacokineticists frequently 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." Ex. 1006 ¶ 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. 37. According to Petitioner, "a central principle of drug development is the desirability of administering the lowest effective drug dose." *Id.* (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 dosage." Pet. 37; Ex. 1006 ¶ 69. As noted above, Dr. Baughman 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}[6] 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 knowledge of the half-life alone does not provide sufficient information to develop a dosing regimen. PO Resp. 45–48. In particular, Patent Owner contends that terminal half-life (what Kempeni discloses) does not impart information about: (1) drug

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

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 47. Patent Owner further asserts that the ordinary artisan would have taken factors such as C_{min}, C_{max}, and AUC (area under the curve)[7] into account when designing a dosing regimen, which Dr. Baughman did not do. *Id.* at 45–49 (citing Ex. 2069 ¶¶ 107–113, 116–118). Additionally, Patent Owner notes that several FDA-approved monoclonal antibodies in the prior art were dosed more or less frequently than their terminal half-lives. *Id.* at 48; Ex. 2069 ¶¶ 112–113.

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's 20 mg weekly dose to a 40 mg biweekly dose based on the known half-life of D2E7. As with other 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, Petitioner asserts in the Petition that the ordinary artisan would have doubled van de Putte's 20 mg dose to 40 mg and weekly dosing interval to biweekly based

[7] C_{max} is the highest blood level observed between doses and AUC is the total area under the concentration time curve that reflects the total amount of drug observed in the blood. Ex. 1006 ¶ 62; Ex. 2069 ¶ 35.

on the single PK parameter of the antibody's 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 evidence from which we can make that determination. That is, neither Petitioner nor Dr. Baughman direct us to a drug with a dosing interval that corresponds to its half-life (i.e., a single 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 at 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. PO Resp. 48 (citing Ex. 1012, 2, 12; Ex. 2007, 1–2; Ex. 2010, 1–2; Ex. 2013 3, 17; Ex. 2072, 96:22–9:73, 140:24–141:5); Ex. 2069 ¶ 112. 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 evidence from which we can conclude that dosing frequency would have been selected based on half-life alone, as asserted in the Petition.

Petitioner's arguments in the Reply appear to be a shift from the position taken in the Petition. For example, in the Petition, Petitioner argued

that that the skilled artisan would have been motivated to develop the appropriate dosing regimen for D2E7 based on half-life alone. Pet. 35 (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), *id.* (basing dose selection on the half-life data disclosed in Kempeni). In the Reply, Petitioner 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 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).

Moreover, Patent Owner argues persuasively that half-life is not the only factor the skilled artisan would have considered in modeling a dosing regimen. *See* PO Resp. 45–49; Ex. 2069 ¶¶ 114–117. Petitioner appears to admit as much, explaining 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 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 '680 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 an overly simplistic approach to modeling a dosing regimen without explaining adequately, and with supporting evidence, why the ordinary artisan would have used such an approach.[8] Accordingly, we are not persuaded Petitioner demonstrates, by a preponderance of the evidence, that the person of ordinary skill in the art would have been motivated to choose the claimed dosing regimen based on half-life.

(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. 28, 36 (citing Ex. 1003, 2). 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. 28 (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. 36 (citing Ex. 1006 ¶ 72).

[8] 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. PO Resp. 2–3; *see id.* at 21–27 (setting forth further arguments why Dr. Baughman's half-life analysis is flawed). We need not address those additional criticisms, however, because we already determine that Dr. Baughman's half-life analysis is entitled to little or no weight.

Patent Owner responds that Petitioner's argument is based on a misreading of Kempeni and the DE003 study. Specifically, Patent Owner asserts that Kempeni's "bare bones description of the 'biweekly' phase . . . fails to disclose" subcutaneous dosing, a 40 mg dose, fixed-weight dosing, or a biweekly dosing regimen sustained over a defined period of time. PO Resp. 50. We do not agree. Dr. Vinks testifies 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 clarifies that there is no dispute that the 0.5 mg/kg intravenous dose is equivalent to the 40 mg subcutaneous dose.[9] Tr. 46:6–21. Thus, contrary to Patent Owner's argument, Kempeni 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.

[9] 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 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).

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.'" PO Resp. 50 (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.*

We do not agree. 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).

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.[10] We agree with Patent Owner that, for some portion of the treatment period, patients were treated "only upon disease flare up." *Id.*; *see* PO Resp. 50. That disclosure, however, does not negate Kempeni's teaching of biweekly dosing. Nor does it teach away from biweekly dosing. Rather, we find that such disclosure represents, at most, an alternative dosing schedule to the biweekly dosing Kempeni discloses. In any event, we note 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 dosing D2E7 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).

Second, Patent Owner 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." PO Resp. 50–51 (citing Ex. 2069 ¶ 34). On that point, Dr. Vinks testifies that the bioavailability

[10] Additional prior art references support our 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.

(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 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 those teachings, 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.

Third, Patent Owner 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. PO Resp. 51. 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 12, 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 37, 51 (citing Ex. 2114, 4). 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 39, 51.

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.[11] 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. After having considered the arguments and evidence before us, we agree with 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.

[11] In a conference call with the Board, Patent Owner objected to the section of Petitioner's Reply that addresses up-dosing, and several exhibits cited in that section, as outside of the proper scope of a reply. *See* Paper 44, 2. In denying Patent Owner's request to strike or supplement the record, we explained that we would determine whether the material, or any portion of the material, exceeds the proper scope of a reply when preparing the final written decision. *Id.* at 4. We have reviewed the material in light of Patent Owner's objections and determine that Petitioner's arguments are within the proper scope of a reply because they directly respond to Patent Owner's assertions that reports of up-dosing would have taught away from the claimed invention. We do not consider Petitioner's citations to statements from the declaration of Dr. Kupper from the patent prosecution history (i.e., Ex. 2003 ¶ 13) in determining whether reports of up-dosing would have taught away from the claimed invention, however, because Petitioner does not establish that those statements describe information that was publicly available as of the June 2001 priority date of the '680 patent. We further note that Patent Owner spent time at the oral argument discussing up-dosing and the conclusion that one of ordinary skill would have drawn from the reported up-dosing and Rau 2000. *See, e.g.*, Tr. 49:6–50:2, 50:20–51:12.

Like Kempeni, Rau 2000 describes the DE001/DE003 clinical study and results of that study. Ex. 2114, 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. 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 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." *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. PO Resp. 37, 51.

We do not find that Rau 2000 indicates that the 0.5 mg/kg dose was "inadequate," 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 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. 2114, 6. But that is 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.1.

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 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 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 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 anti-drug antibodies" ("ADAs"). PO Resp. 28, 40. 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 26, 32–37. 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 40–44. 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 4–6. 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 6–7. 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.* at 7. 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.

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. And 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 much weight because, as both parties note, the minimum effective dose of D2E7 "was undefined in June 2001." Ex. 2003 ¶ 53 n.2; PO 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 ("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* PO 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)). 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 13–14; *see* Ex. 1003, 2 (reporting that D2E7 has a half-life of

[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. 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. 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, 218:15–220:3; Ex. 1056, 33:5–16).

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. PO Resp. 37–38. 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." PO Resp. 38 (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 39 (citing 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. 15. And 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 "[r]heumatologists routinely rely on numerical trends, even if not statistically validated," PO Resp. 38 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.

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. PO Resp. 56–62. "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 anti-TNFα antibody used in the claimed method, to support the nonobviousness of the challenged claims. PO Resp. 59–62.

"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 1829.

There is no dispute in this case that HUMIRA® is commercially successful. PO 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)." PO Resp. 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. 29–31. 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. 31; 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 '680 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. 21; 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, 3:40–42; *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 '680 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 in the claims of the '680 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. PO Resp. 56–57. 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 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.* at 56–57.

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. 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, 5 ("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.

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. PO Resp. 57–59. 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* PO Resp. 57–59. 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 1–4 of the '680 patent would have been obvious over the combination of van de Putte and Kempeni.

III. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–4 of the '680 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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