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Paper 8
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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 ERICA A. FRANKLIN, *Administrative Patent Judges*.

MOORE, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Coherus BioSciences Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") on December 7, 2015, requesting an *inter partes* review of claims 1 and 2 of U.S. Patent No. 9,073,987 B2 (Ex. 1001, "the '987 patent"). AbbVie Biotechnology, Ltd. ("Patent Owner") filed a Preliminary Response (Paper 7, "Prelim. Resp.") on March 15, 2016. We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the information presented in the Petition and the Preliminary Response, we are persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1 and 2 of the '987 patent. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

The parties identify the following U.S. patent applications and U.S. patents as "related in priority" 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[1]; and U.S. Patent No. 8,992,926. Pet. 2.

[1] Misdentified as U.S. Patent Number 8,984,790, an obvious typographical error.

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 seeking inter partes review of the '135 patent, IPR2016-00408 and IPR2016-00409[2]. Paper 6, 1. We are not aware of any pending civil litigation.

B. The Asserted Ground of Unpatentability

Petitioner asserts that claims 1 and 2 are unpatentable under 35 U.S.C. § 103(a) as obvious over van de Putte[3] and Kampeni.[4]

The Petition further refers to the following references as showing the background of the technology at issue and common knowledge in the art:

1. Rolf Rau et al., *Effective Combination of Fully Human Anti-TNF Antibody D2E7 & Methotrexate in Active Rheumatoid Arthritis*, Ann. Rheum. Dis., 217, No. 907 (1999) (Ex. 1005).

2. U.S. Patent No. 6,090,382, issued July 18, 2000 (Ex. 1008).

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[2] Filed by Boehringer Ingelheim, GmbH

[3] 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) ("van de Putte 1999"). (Ex. 1004)

[4] Joachim Kempeni, "Preliminary results of early clinical trials with the fully human TNFα monoclonal antibody D2E7," *Ann. Rheum. Dis.,* vol. 58, pp. 170-72 ("Kempeni"). (Ex. 1003).

3. Rolf Rau et al., *Long-term treatment with the fully human anti-TNF alpha-antibody D2E7 slows radio-graphic disease progression in rheumatoid arthritis*, Arthritis & Rheum., 42(S9):S400, No. 1978 (1999) (Ex. 1009).

4. Etanercept/ENBREL® label (1998) (Ex. 1011).

5. Infliximab/REMICADE® label (1999) (Ex. 1012).

6. Richard G. Hamilton, *The Human IgG Subclasses* (2001) (Ex. 1013).

7. *Updated consensus statement on tumour necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases*, 60 Am. Rheum. Dis. iii2–iii5 (2001) (Ex. 1015).

8. U.S. Department of Health & Human Services, Food & Drug Administration, *Guidance for Industry, Clinical Development Programs for Drugs, Devices and Biological Products for the Treatment of Rheumatoid Arthritis* (1999) (Ex. 1016).

9. Leo van de Putte et al., *A Single Dose Placebo Controlled Phase I Study of the Fully Human Anti-TNF Antibody D2E7 in Patients with Rheumatoid Arthritis*, Arthritis & Rheum., 41(S9):S57, No. 148 (1998) (Ex. 1017).

10. Rolf Rau et al., *Long-Term Efficacy and Tolerability of Multiple I.V. Doses of the Fully Human Anti-TNF-Antibody D2E7 in Patients with Rheumaoid [sic] Arthritis*, Arthritis & Rheum., 41(Suppl.):S55, No. 137 (1998) (Ex. 1018).

11. Manfred Schattenkirchner et al., *Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNFAntibody D2E7 in Patiens*

[sic] with Rheumatoid Arthritis-Results of a Phase I Study, Arthritis & Rheum., 41(S9):S57, No. 149 (1998) (Ex. 1019).

12. ENBREL® Summary Basis of Approval (1998) (Ex. 1020).

13. REMICADE® Summary Basis of Approval (1999) (Ex. 1021).

14. International Publication No. WO 98/04281, published February 5, 1998 (Ex. 1022).

15. Michael Weisman et al., *A dose escalation study designed to demonstrate the safety, tolerability and efficacy of the fully human anti-TNF antibody, D2E7, given in combination with methotrexate (MTX) in patients with active RA*, Arthritis & Rheum., vol. 43 (9 Suppl. 1):S391, No. 1948 (2000) (Ex. 1023).

16. Leo van de Putte et al., *One year Efficacy Results of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, Arthritis & Rheum., vol. 42(9 Suppl.):S269, No. 1218 (2000) (Ex. 1024).

The Petition also relies on the Declarations of Sharon Baughman, Ph.D. (Ex. 1006), James O'Dell, M.D. (Ex. 1007), and Brian Reisetter, RPh, MBA, Ph.D. (Ex. 1025).[5]

[5] Petitioner and Dr. Baughman describe the level of ordinary skill in the art as of June 8, 2001—the priority date of the '987 patent by virtue of the '135 patent. Pet. 27; Ex. 1006 ¶ 15. 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 ¶

C. The '987 Patent

The '987 patent, titled "Methods of Administering Anti-TNFα Antibodies," relates to methods for biweekly dosing regimens for the treatment of TNFα associated disorders, preferably 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.*, 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. Ex. 1001, Abstract.

D. Illustrative Claims

Petitioner challenges claims 1 and 2 of the '987 patent. Claim 1 is an independent claim. Claim 2 depends from claim 1. Claims 1 and 2 are reproduced below.

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15. 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. 26; 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. 26–27.

> 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.
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> 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. ANALYSIS

A. 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); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Under that standard, claim terms 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).

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

For purposes of this Decision, we determine that the following claim phrase requires discussion: "A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis," as recited in independent claim 1.

Petitioner proposes a construction for the preamble of claim 1 requiring reduction, of any degree. Pet. 15. Patent Owner, on the other hand, contends that the preamble is in need of no construction. Prelim. Resp. 18.

Generally speaking, "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) (*citing 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)).

The preamble of claim 1 does not appear to recite additional structure not included in the bodies of the claims. Nor does the preamble appear to be necessary to give life, meaning, and vitality to the claims. The dosage amount, timing, and active component is set in the claim. The preamble, therefore, recites an intended use, i.e., treating rheumatoid arthritis ("RA"). *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"). Accordingly, for purposes of this Decision, and based on the current record, we determine that the preamble is not limiting.

We determine that no express claim construction is necessary for any other claim term for purposes of this decision.

B. Section 325(d) – Discretion to Decline to Institute

Patent Owner urges us to decline to institute the asserted ground, under 35 U.S.C. § 325(d), because substantially the same prior art and arguments were advanced by the Examiner during prosecution of the '987 patent. Prelim. Resp. 1, 47–51. Specifically, Patent Owner contends that "Petitioner relies on the exact same references that were presented and thoroughly considered by the Examiner during prosecution" without presenting "persuasive new evidence to supplement the record that was before the Office during examination." *Id.* at 49.

Section 325(d) provides: "[i]n determining whether to institute . . . a proceeding . . . , the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments

previously were presented to the Office." In other words, as Patent Owner recognizes, the decision whether to deny a petition under § 325(d) is discretionary, not mandatory. Having considered the record before the Office during examination, as well as the parties' arguments and the presently enlarged record, we decline to exercise our discretion to deny the Petition. Rather, we are persuaded that sufficient reason exists, based on the different record before us, to address the arguments and information presented in the Petition, as discussed below.

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

Petitioner asserts that the subject matter of claims 1–2 would have been obvious over the combination of Kempeni and van de Putte. Pet. 30–41. For the reasons set forth below, we are persuaded that there is a reasonable likelihood that Petitioner would prevail on its asserted ground.

1. Overview of Kempeni

Kempeni teaches that D2E7 is a class of fully human anti-TNFα antibody that "may have advantages in minimising antigenicity in humans" compared to biologic TNF antagonists that are not fully human. 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 was assessed using, *inter alia*, the ACR 20[6] criteria. *Id.* at 1–2. To be classified as a responder according to ACR 20

[6] ACR 20 is short hand for the American College of Rheumatology improvement criteria. Ex. 1003, 2. The ACR criteria as used herein is indicated as ACR 20. As

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) or placebo by intravenous injection. *Id.* Patients were evaluated for four weeks to determine the pharmacokinetics of D2E7 and to evaluate the safety and efficacy of the compound in terms of onset, duration, and magnitude of response. *Id.*

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

Patients who continued in the study were given a second blinded dose that was identical to the first and, subsequently, given active drug every two weeks until a "good" response was achieved. *Id.* Patients who did not respond well after

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we understand it, the ACR is reported as % improvement, comparing disease activity at two discrete time points (usually baseline and post-baseline comparison).

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 ACR 20 response after three months of treatment, leading to the conclusion that "D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery." *Id.*

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

Kempeni 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. Overview of van de Putte

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 ACR 20 response, as well as the median percent improvement in TJC, SWJC, and CRP for each of the dosing regimens and placebo.

The results are reproduced below.

	Placebo	D2E7	D2E7	D2E7
	(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 s.c. in patients with active RA." *Id.*

3. Analysis

Petitioner asserts that a person of ordinary skill would have been motivated from the above 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. 1–2, 30–39 (citing Exs. 1003, 1004, 1006 ¶ 73; Ex. 1007 ¶ 33). Petitioner contends that the subject matter of the challenged claims would have been obvious as "at best, routine optimization of RA treatments using D2E7 already disclosed in the prior art." Pet. 36.

Patent Owner argues that Petitioner's position "gives insufficient weight to the uncertainty in the art, the significant safety and efficacy concerns associated with dosing anti-TNFα biologics, and the lack of critical pharmacokinetic information regarding D2E7 in the art" and is "a textbook example of hindsight." Prelim. Resp. 20.

Patent Owner contends that there was a clear preference in the antibody therapeutics art and early D2E7 clinical trials for weight-based dosing administered intravenously, not subcutaneously. *Id.* at 21–23.

Patent Owner further contends that a skilled artisan would have considered intravenous, weight-based dosing "a better alternative" for addressing safety and efficacy concerns. *Id.* at 23.

We find that the Petitioner has provided evidence sufficient to show a skilled artisan would have had a reason to administer a fixed dose subcutaneously. Specifically, van de Putte describes that administering fixed doses of D2E7 in the specified amounts to RA patients by subcutaneous injection is effective and Kempeni describes that D2E7 given subcutaneously is "safe and as effective as when administered intravenously." Ex. 1003, 3; Ex. 1004, 1.

Further, Petitioner provides evidence that shows that ordinarily skilled artisans would have recognized subcutaneous injection as preferable to intravenous infusion, because patients can self-administer the treatment. Pet. 31 (citing Ex. 1006 ¶ 51); *see* Ex. 1008, 21:25–27. Likewise, Petitioner identifies known advantages of fixed dosing over weight-based dosing, including that fixed dosing requires no patient action beyond injection or disposal of unused medicament. Pet. 31 (citing 1006 ¶ 52; Ex. 1008, 22:65–23:1).

Patent Owner also argues that a person of ordinary skill in the art would have dismissed the 20 mg dose as too low because of the superiority of the available data for the 40 mg and 80 mg weekly doses. Prelim. Resp. 24 (citing Ex. 2001 ¶ 20). Similarly, Patent Owner argues that the goal of a skilled artisan engaged in the design of a D2E7 dosing regimen was not to obtain mere superiority over a placebo, to achieve marginal efficacy, or to reduce a sign or symptom of RA "to some extent[;]" rather, the goal "was to provide the highest level of efficacy possible while maintaining patient safety." *Id.* at 27 (citing Ex. 2001 ¶ 44; Ex. 2003 ¶¶ 44–45).

Patent Owner's arguments are premised on a claim element which is not present – namely, some specified level of efficacy in the treatment. Because we are convinced, based on the current record, that the broadest reasonable interpretation of the claims requires no specified level of efficacy, we are unpersuaded by Patent Owner's arguments regarding superiority of the 40 and 80 mg doses to the 20 mg dose disclosed in van de Putte.

In any event, we note that all that is required to show obviousness is a reasonable expectation of success, not conclusive proof of superior efficacy. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363–64 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). As Petitioner explains, van de Putte discloses that 20, 40, and 80 mg D2E7 administered weekly were "nearly equally efficacious" and all "statistically significantly superior to placebo" for all efficacy parameters studied. Pet. 21, citing Ex. 1004, 1.

Further, van de Putte's tabulated clinical responses show similar percentages of patients achieving ACR 20 response and median percent improvement in TJC, SWJC, and CRP for each of the 20, 40, and 80 mg doses. Ex. 1004, 1. Van de Putte's clinical data for the 20, 40, and 80 mg doses also are all higher than the 20 percent improvement thresholds for SWJC, TJC, and CRP that Kempeni discloses as demonstrating efficacy pursuant to the ACR 20 criteria. Ex. 1003, 2.

Patent Owner next urges that one would not have been motivated to stretch the 20 mg weekly van de Putte dose into a 40 mg every other week dose. Prelim. Resp. 28. According to Patent Owner, patients in the Kempeni study received

intravenous, weight-based doses according to a variety of different dosing schedules, including weekly, every-other-week, and every four weeks, depending on their responses, and no conclusion can be drawn from Kempeni to any specific schedule of subcutaneous administration. *Id*. at 29. Patent Owner also urges that a 0.5 mg/kg weight-based intravenous dose disclosed in Kempeni cannot be equated to a 40 mg subcutaneous dose due to absorption differences. *Id.*, citing Ex. 2003 ¶ 40; Ex. 2006 ¶ 18; and Ex. 2018, 8–9.

In particular, Patent Owner argues that transforming weight-based doses into fixed doses simply by multiplying by average patient weight (as Petitioner does when multiplying the 0.5 mg/kg intravenous biweekly dose into a 40 mg fixed dose based on an 80 kg patient) is a "well-known pharmacokinetic fallacy." *Id.* at 30 (citing Ex. 2003 ¶¶ 33–41).

Patent Owner further asserts that the art as a whole at the relevant time taught away from using 0.5 mg/kg as a fixed dose across all patients, instead favoring higher doses due to inadequate clinical response, and that Petitioner fails to explain sufficiently why dose-stretching would have focused on a 40 mg dose every other week. *Id.* at 30–31. According to Patent Owner, if a clinician were to experiment with different doses, routes of administration, and dosing frequencies, as Petitioner contends, there would be innumerable possible combinations. *Id.* at 32.

Petitioner's analysis, however, is not based primarily on transforming a 0.5 mg/kg intravenous biweekly dose into a 40 mg subcutaneous biweekly dose. Rather, Petitioner asserts, with supporting testimony from Dr. Baughman, that a

skilled artisan would have been led to biweekly dosing based on the known 11.6 to 13.7 day half-life of D2E7. Pet. 33; Ex. 1006 ¶¶ 48, 56–57, 63–68. Pointing to the clinical results reported in van de Putte, Petitioner explains that a skilled artisan would have recognized that at least 30 mg of D2E7 would have remained circulating in a patient's blood one week after administration of a 40 mg dose, and that this amount is greater than the 20 mg dose van de Putte disclosed as efficacious when administered weekly. *Id.* at 35; Ex. 1006 ¶ 68. Petitioner further points to Kempeni's teaching that D2E7 could be administered safely over a broad range of doses to show that a skilled artisan would have reasonably expected biweekly dosing of 40 mg to be safe. *Id.* at 36 (citing Ex. 1003, 2 and Ex. 1006 ¶ 57).

Patent Owner contends that one of ordinary skill in the art would not have had a reasonable expectation of success. Prelim. Resp. 35. According to Patent Owner, half-life alone would not have been a predictor for establishing a D2E7 dosing regimen. Half-life is one of many factors that contribute to the ability to predict dosing frequency. Prelim. Resp. 35–38 (citing Ex. 2003 ¶¶ 64, 68, 76–78; Ex. 2002 ¶ 57; Ex. 2006 ¶ 5). Dr. Baughman's own patent applications are cited as evidence of this complexity. Prelim. Resp. 38, citing Ex. 2029.

Patent Owner also contends that Petitioner's calculations regarding the amount of D2E7 that would have been circulating in the blood one and two weeks after injection are "indisputably incorrect," because they disregard the fact that delivery of a drug subcutaneously was known to cause a variable, and often significant, reduction in the amount of drug absorbed into the bloodstream. *Id.* at

40–41 (citing Ex. 2003 ¶ 40; Ex. 2006 ¶ 18; Ex. 2018, 8–9). Thus, argues Patent Owner, even assuming a 14-day half-life for each D2E7 dose was administered, the amount of D2E7 circulating in the blood one and two weeks after injection would have been "substantially lower" than the amounts Petitioner identifies in its analysis. *Id.* at 41.

Patent Owner further asserts that Petitioner's arguments also ignore significant risks that a skilled artisan would have understood to be associated with dose-stretching. *Id.* at 33–34. According to Patent Owner, among those known risks were the potential adverse consequences of under-dosing, including the formation of anti-drug antibodies that could compromise safety and efficacy. *Id.* (citing Ex. 2001 ¶¶ 46–48; Ex. 2002 ¶¶ 37–40; Ex. 2003 ¶¶ 57–60).

Patent Owner's arguments in this regard create issues of material fact as to whether a skilled artisan would have relied upon half-life or dose-stretching based on known half-life to establish a dosing regimen for D2E7. We find these factual disputes best resolved during trial when we are able to assess Petitioner's and Patent Owner's evidence and arguments upon review of the entire record. We invite the parties to brief these issues more fully in the Patent Owner Response and Petitioner Reply.

Finally, Patent Owner asserts that the Petitioner has failed to address the limitation of a 40 mg dosage unit form. Prelim. Resp. 42. We are unpersuaded by this argument. Van de Putte describes doses of 40 mg.

At this stage of the proceeding, and based on the current record, we are persuaded that there is a reasonable likelihood that Petitioner would prevail in

showing that the selection of a 40 mg total body dose administered subcutaneously every 13-15 days would have been no more than a routine optimization of the dosing regimens disclosed and suggested by the combination of Kempeni and van de Putte, in view of the state of the art.

That a skilled artisan would have been led to optimize the dosing regimens disclosed in these references in order to treat the patient with as little drug as possible to reduce potential side effects, while at the same time attaining a therapeutic response and improving patient compliance "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)). Accordingly, we conclude that Petitioner is reasonably likely to prevail in its assertion that the subject matter of claims 1 and 2 would have been obvious over Kempeni and van de Putte.

4. Secondary Considerations of Nonobviousness

Patent Owner asserts that objective evidence of nonobviousness ("secondary considerations") supports patentability of claims 1–5. Prelim. Resp. 44–47. Secondary considerations, when present, must "be considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citation omitted). Secondary considerations may include any or all of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir.

2007). To be relevant, evidence of nonobviousness must be commensurate in scope with the claimed invention. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner argues that HUMIRA® is a commercial formulation of the claimed subject matter, that it "indisputably is a commercial success," and it has achieved that commercial success despite being the third anti-TNFα antibody product introduced to the market. Prelim. Resp. 44. Patent Owner further argues that the nexus between HUMIRA®'s commercial success and dosing regimen has been "widely[] recognized, with the dosing regimen identified as a 'key design feature[.]'" *Id.* at 44-45 (citing Ex. 2004 ¶¶ 28–31; Ex. 2031, 3).

We recognize that the Federal Circuit has indicated that if evidence shows that a referenced commercial embodiment is "the invention disclosed and claimed in the patent" (a fact not disputed in relation to HUMIRA® here), we are to presume that any commercial success of that product is due to the patented invention. *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 734, 747 (Fed. Cir. 2016) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)).

The record before us at this time, however, indicates that the commercial success of HUMIRA® is not commensurate in scope with the claimed invention—40 mg subcutaneous every 13-15 days, administration to treat RA. For example, although the evidence Patent Owner presents attributes the overall sales of HUMIRA® in part to subcutaneous, flat dosing every two weeks, there appears to

be little indication that sales are due to the 40 mg dose amount recited in the claims. *See, e.g.*, Ex. 2004 ¶¶ 28–30; Ex. 2031, 3.

Moreover, evidence cited by Patent Owner also attributes overall sales of HUMIRA® to the fully human D2E7 anti-TNFα antibody, which was known in the prior art. *See* Ex. 2031, 3. Patent Owner's evidence further indicates that HUMIRA® has been FDA-approved and "has enjoyed success" in treating autoimmune diseases other than the recited RA, such as psoriatic arthritis, and intestinal disorders, such as Crohn's disease, since October 2005 and February 2007, respectively. Ex. 2004 ¶¶ 5, 38. Accordingly, at this stage of the proceeding, the arguments and information of record do not persuade us to decline to go forward with a trial.

III. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner establishes a reasonable likelihood that it will prevail in showing that claims 1–2 of the '987 patent are unpatentable. Our findings and conclusions are not final and may change upon consideration of the full record developed during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that an *inter partes* review is instituted as to:

Claims 1 and 2, on the ground of unpatentability over Kempeni and van de Putte under 35 U.S.C. § 103;

FURTHER ORDERED that no other ground of unpatentability is authorized; and

FURTHER ORDERED that notice is hereby given of the institution of a trial commencing on the entry date of this decision, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4.

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