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Paper 9
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00409
Patent 8,889,135 B2

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

MITCHELL, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

Petitioners Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Petitioner") filed a petition (Paper 3, "Pet.") to institute an *inter partes* review of claims 1–5 (the "challenged claims") of U.S. Patent No. 8,889,135 B2 (Exhibit 1001, "the '135 patent"). *See* 35 U.S.C. §§ 311–319. Patent Owner AbbVie Biotechnology ("Patent Owner"), filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the '135 patent. Therefore, we institute an *inter partes* review for claims 1–5 of the '135 patent.

B. Related Proceedings

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

C. The '135 Patent (Ex. 1001)

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

D. Illustrative Claims

Claims 1 and 5 are independent claims of the '135 patent. Claims 2–4 depend directly or indirectly on claim 1. Claim 1 is illustrative of the challenged claims and recites:

> 1. A method for treating rheumatoid arthritis in a human subject, comprising administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13-15 days for a time period sufficient to treat the rheumatoid arthritis, wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a

> CDRl having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("V_H") chain region comprising a CDRl having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of SEQ ID NO:6 and a CDR3 having the amino acid sequence of SEQ ID NO:4.

Ex. 1001, 45:11–25.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 5–7.

References	Basis	Claims Challenged
Kempeni 1999[1] and van de Putte 1999[2]	§ 103	1–5
Rau 1998,[3] Schattenkirchner 1998,[4] and van de Putte 1999	§ 103	1–5

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

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

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

[4] Manfred Schattenkirchner et al., *Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNF-Antibody D2E7 in Patien[t]s with Rheumatoid Arthritis – Results of a Phase I Study*, 41 (Supp.) ARTHRITIS & RHEUM. S57 (1998) ("Schattenkirchner 1998") (Ex. 1007).

Petitioner relies also on the Declarations of Michael H. Weisman, M.D., a rheumatologist, and William J. Jusko, Ph.D., who studies pharmacokinetics. *See* Exs. 1003, 1004.

II. ANALYSIS

A. Claim Interpretation

In an inter partes review, claim terms in an unexpired patent are given 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*, No. 15–446, 2016 WL 3369425, at *13 (U.S. June 20, 2016) (upholding the use of the broadest reasonable interpretation approach). Under the broadest reasonable interpretation approach, 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). An inventor may rebut that presumption by providing a definition of the term in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In the absence of such a definition, limitations are not to be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

Although Petitioner asserts that we need not construe expressly any term for purposes of our institution decision, Petitioner relies on the explanation provided in the petition in IPR2016-00172 for the ordinary meaning of "method for treating rheumatoid arthritis," "every 13-15 days," and "pharmaceutically acceptable composition." Pet. 19 (citing IPR2016-00172 Petition 14–17). That is an improper incorporation by reference of arguments asserted in another petition, which we will not consider here. *See*

37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document.").

Patent Owner seeks interpretation of the claim term "for a time period sufficient to treat the rheumatoid arthritis." Prelim. Resp. 18–19. For purposes of this decision and consistent with our Decision on Institution in IPR2016-00172, we will address the interpretation of this claim term that appears in both independent claims 1 and 5.

Patent Owner asserts that "for a time period sufficient to treat the rheumatoid arthritis" means "for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthritis." *Id*. at 18. Patent Owner supports this interpretation by reciting portions of the Specification that it concludes show that the claimed method requires significant reduction in the signs and symptoms of RA. *Id*. at 18–19 (citing Ex. 1001, 30:25–28, 6:23–27).

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

The support from the Specification upon which Patent Owner relies also does not convince us that "treat" in the claim phrase should be interpreted to mean "reduce significantly the signs and symptoms" of rheumatoid arthritis. Patent Owner points to a conclusion set forth for Example 3 in the Specification where it was determined that "subcutaneous,

biweekly D2E7 treatment combined with methotrexate was significantly better than placebo in reducing the signs and symptoms of RA at twenty-four weeks." Ex. 1001, 30:25–28, *cited in*, Prelim. Resp. 18. Patent Owner also points to definitions of terms involving "biweekly" as referring "to the time course of administering a substance (e.g., an anti-TNFα antibody) to a subject to achieve a therapeutic objective (e.g., the treatment of a TNFα-associated disorder)." *Id*. at 6:23–27, *quoted in*, Prelim. Resp. 19.

Patent Owner's first proffered Specification reference refers to a specific example and the second does not indicate a particular level of therapeutic efficacy in support of Patent Owner's interpretation. It is inappropriate to limit the scope of a claim by importing limitations from one example described in the Specification. *See JVW Enters., Inc. v. Interact Accessories, Inc*., 424 F.3d 1324, 1335 (Fed. Cir. 2005) ("We do not import limitations into claims from examples or embodiments appearing only in a patent's written description, even when a specification describes very specific embodiments of the invention or even describes only a single embodiment, unless the specification makes clear that 'the patentee . . . intends for the claims and the embodiments in the specification to be strictly coextensive.'").

For purposes of this decision, we do not need to interpret expressly the claim term "for a time period sufficient to treat the rheumatoid arthritis," except to note in light of our discussion above that the claim term does not require a particular level of efficacy.

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

Patent Owner urges us to decline to institute the asserted grounds under 35 U.S.C. § 325(d) because the first ground asserted in the Petition is

identical to the ground asserted by Coherus in the petition in IPR2016-00172, and the second ground "discusses the same clinical trials as the first ground and presents the same issues." Prelim. Resp. 56. Patent Owner also asserts that substantially the same prior art and arguments were considered by the Examiner during prosecution of the '135 patent. *Id*.

Under § 325(d), we have discretion to "reject the petition or request because[] the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). Considering all of the relevant facts and circumstances, Patent Owner's argument is insufficient to persuade us to exercise our discretion to deny the Petition. Petitioner relies on two declarations, from Drs. Weisman and Jusko, which Patent Owner does not allege are duplicative of evidence previously presented to the Office. *See Tandus Flooring, Inc. v. Interface, Inc*., Case IPR2013-00333, 2013 WL 8595289, at *2 (PTAB Dec. 9, 2013) (Paper 16) (declining to deny petition under § 325(d) where petitioner presented new declaration evidence); *Chimei Innolux Corp. v. Semiconductor Energy Lab. Co*., Case IPR2013-00066, 2013 WL 8595548, at *5 (PTAB Apr. 24, 2013) (Paper 10) (same). Also, we note that the Petitioner here is not a party or real-party-in-interest in the previously-filed *inter partes* review identified by Patent Owner. Finally, the Examiner relied upon testimonial evidence that was not subject to cross-examination in determining patentability of the claims. *See* Ex. 1002, 1584-87.

C. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1262. A prima facie case of obviousness is established when the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). We are mindful that the level of ordinary skill in the art also is reflected by the prior art of record.[5] *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc*., 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

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

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

D. Obviousness over van de Putte 1999 and Kempeni 1999

Petitioner contends that claims 1–5 are unpatentable under 35 U.S.C. § 103 as obvious over van de Putte 1999 and Kempeni 1999. Pet. 19–40. Petitioner asserts that van de Putte 1999 expressly teaches each limitation of claims 1–5 except for every-other-week administration. *Id*. at 2. Petitioner asserts that Kempeni 1999 provides that missing teaching. *Id*. Petitioner offers that "a person of ordinary skill in the art would have, at a minimum, tried administering the prior art doses, including the claimed 40 mg dose, subcutaneously on an every-other-week basis." *Id.* (quoting *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir.) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance."), *cert. denied*, 135 S. Ct. 878 (2014)).

Patent Owner counters that Petitioner's analysis "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." Prelim. Resp. 19. Patent Owner concludes that Petitioner's obviousness analysis for each ground presents a "textbook example of hindsight." *Id*.

1. *van de Putte 1999*

van de Putte 1999 describes the results of a dose-finding phase II study that compared three dose levels of D2E7 and placebo over three months in patients with long-standing active RA. Ex. 1008, 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 1999 reports the percentage of patients receiving an ACR 20[6] response, as well as the median percent improvement in TJC, SWJC, and CRP for each of the dosing regimens and placebo. *Id*.

The results are reproduced below.

	Placebo (n=70)	D2E7 20 mg (n=71)	D2E7 40 mg (n=70)	D2E7 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

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

2. Kempeni 1999

Kempeni 1999 teaches that D2E7 is a class of fully human, anti-TNFα antibody that "may have advantages in minimi[z]ing antigenicity in humans" compared to biologic TNF antagonists that are not fully human. Ex. 1011, 3. Kempeni 1999 further describes the results of several clinical studies investigating the use of D2E7 to treat RA patients. *Id*. at 3–5.

During the clinical trials, efficacy was assessed using the ACR 20 criteria. *Id*. at 3–4. 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. 1011, 4.

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 4.

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

Kempeni 1999 describes the results of the study as "encouraging," noting that the "therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1–2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." Ex. 1011, 4. Pharmacokinetic parameters were calculated for patients from all dose groups and the estimated mean terminal half-life of D2E7 was determined to be 11.6 to 13.7 days. *Id*.

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

intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." *Id*.

In a second study that evaluated the safety and efficacy of weekly subcutaneous 0.5 mg/kg weight-based administration of D2E7, patients were given either D2E7 or placebo weekly for a period of three months. *Id*. at 4–5. The dose was increased to 1 mg/kg subcutaneously weekly for non-responders or patients losing responder status. Ex. 1011, 5.

According to the preliminary data, "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." *Id*. Further, up to 78% of patients achieved an 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 1999 teaches that the data from these studies collectively suggest D2E7 "is safe and effective as monotherapy . . . when administered by single and multiple intravenous and subcutaneous injections. Additional studies are underway to further define optimal use of this novel treatment." *Id*.

3. Analysis

Petitioner presents an explanation demonstrating where the limitations of the challenged claims may be found in the cited references. Pet. 19–55.

Petitioner also relies on the Weisman and Jusko Declarations. *See* Exs. 1003 and 1004, respectively. Petitioner's argument focuses on the dosing requirement of the claims concerning "administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13-15 days for a time period sufficient to treat the rheumatoid arthritis." *See id*. at 19–21.

Petitioner asserts that "van de Putte 1999 expressly teaches each of the claimed features except for the claimed every-other-week dose and administration for 24 weeks (which is a limitation in dependent claims 3 and 4)." *Id*. at 19. Petitioner states that Kempeni 1999 provides these teachings, *id*., and one of skill in the art at the time of the invention would have combined the teachings of van de Putte 1999 and Kempeni 1999 to arrive at the claimed invention because

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

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

Petitioner asserts that the "efficacy of the weekly 20 mg dose reported in van de Putte 1999 would have at least suggested that an analogous, every-other-week 40 mg dose would have been an option worth investigating." Pet. 25 (citing Ex. 1003 ¶¶ 41–43); *see also id*. at 26–30 (stating Kempeni 1999 indicates that "D2E7 remains in the body for at least two weeks and is

therapeutically active during that time, suggesting that D2E7 would be compatible with every-other-week dosing") (citing Ex. 1003 ¶¶ 20, 37–38; Ex. 1004 ¶¶ 17–23). Petitioner concludes that given the finite number of options, "selection of the dose and dosing schedule would have been 'routine optimization' of the prior art therapy and yielded predictable results." *Id.* at 21–22, 30–31 (citing Ex. 1003 ¶¶ 41–44).

Patent Owner counters that Petitioner's reliance on combinations of references disclosing clinical studies of D2E7 having different routes of administration, dosing schedules, and dosing amounts is textbook hindsight. Prelim. Resp. 2, 19. Use of such impermissible hindsight, Patent Owner asserts, is borne out by Petitioner's ignoring that: (1) the intravenous, weight-based dosing that predominated the art was the best alternative; (2) concerns existed regarding under-dosing of monoclonal antibodies, as evidenced by "up-dosing" of patients in the studies; (3) half-life is not a reliable predictor of a dosing interval; and (4) an almost limitless number of dosing regimens could have been tried.[7] *Id.* at 2–5, 19–42. Patent Owner relies on several declarations submitted during prosecution to support its assertions. *See* Ex. 2001 (Declaration of Dr. Janet Pope); Ex. 2002 (Declaration of Michael E. Weinblatt); Ex. 2003 (Declaration of Dr. Diane R. Mould); Ex. 2004 (Declaration of Mr. Medgar Williams); Ex. 2005–2006 (Declarations of Dr. Hartmut Kupper). Patent Owner concludes that a person of skill in the art would not have been motivated to stretch the 20 mg

[7] In view of van de Putte 1999's disclosure of three doses as a starting point for a dose-finding phase II study (*see* Ex. 1008, 7) the argument that one of skill in the art faced a limitless number of dosing regimens appears not well-taken. We also do not agree with Patent Owner that Petitioner's declarants provide merely conclusory statements.

weekly dose (which it asserts is facially inferior to the 40 and 80 mg dosing regimens in van de Putte 1999) into a 40 mg every-other-week dose. Prelim. Resp. 27–28. "If one was motivated to modify the existing regimens at all, the solution would have been to modify the demonstrably more efficacious 40 or 80 mg weekly dosing regimens or the myriad of weight-based dosing regimens reported in the prior art." [8] *Id*.

On this record, we do not agree with Patent Owner's assertion of hindsight. Specifically, the combined teachings of van de Putte 1999 and Kempeni 1999 do not appear to disclose that intravenous, weight-based dosing is the best alternative. van de Putte 1999 teaches that administering fixed doses of D2E7 to RA patients by subcutaneous injection is effective (*see* Ex. 1008, 7; Ex. 1003 ¶ 32–35), and Kempeni 1999 discloses that D2E7 given subcutaneously is "safe and as effective as when administered intravenously" and that "subcutaneous self-administration is a promising approach for D2E7 delivery" (Ex. 1011, 5; Ex. 1003 ¶ 26).

Petitioner also provides testimony that subcutaneous injections would be preferable because a patient can self-administer the injection at home and

[8] Patent Owner's argument concerning the facial inferiority of a 20 mg weekly dose as compared to a 40 or 80 mg dose is based on an incorrect interpretation of the claims. We determined, based on the record before us, that the claims do not require a particular level of efficacy. *See supra* Sec. II.A. Also, Dr. Weisman disagrees with Dr. Mould, Patent Owner's declarant, that a 7–8% difference in ACR 20 response for 20 mg of D2E7 compared to 40 and 80 mg of D2E7 indicates a difference in efficacy between doses. Ex. 1003 ¶ 36. Dr. Weisman testifies that no reliable dose-to-dose comparisons can be drawn from van de Putte 1999's parallel placebo study. *Id*. Dr. Weisman supports his position with van de Putte 1999's conclusion that each dose was "nearly equally efficacious." *Id*. (citing Ex. 1008, 7). Dr. Jusko agrees with that conclusion. *See* Ex. 1004 ¶¶ 15–16.

avoid complications with intravenous administration such as thrombosis (Ex. 1003 ¶ 47), as well as testimony that a fixed dose is preferable to avoid the need to calculate dosage for each patient and to avoid dosing errors (*id*. at ¶ 48).[9] Dr. Weisman testifies that

> A person of ordinary skill in the art would have expected fixed D2E7 doses to be effective because D2E7 was known to be specific to TNFα, and D2E7 was determined to be safe in doses as high as 10 mg/kg, suggesting that a single D2E7 dosage amount could have been given to patients with variable weights without risking patient health. This conclusion would have been unquestionably confirmed by the DE007 study described in van de Putte 1999, which demonstrated that fixed subcutaneous doses were safe and effective for treating RA.

Id. (citations omitted).

We also do not agree on this record with Patent Owner's assertion that Petitioner ignored risks of dose-stretching for a two-week interval when under-dosing would be a concern, or Patent Owner's assertion that half-life would not be an adequate predictor of dosing interval. Dr. Weisman testifies that Kempeni 1999 suggests that "D2E7 remains in the body for at least two weeks and remains therapeutically active during that time, suggesting that D2E7 would be compatible with every-other-week dosing," and such dosing interval was, in fact, preferred. Ex. 1003 ¶¶ 37, 38. Dr. Jusko testifies that

[9] Patent Owner complains that Dr. Weisman improperly relies on statements in the Summary of the Invention in the '135 patent to support the motivation of one of skill in the art to choose a subcutaneous, every-other-week route of administration. Prelim. Resp. 21–22. Dr. Weisman, however, states that those advantages were well known to one of skill in the art. Ex. 1003 ¶ 29. It can hardly be said that the many advantages of that route of administration, such as a lower number of total injections and injection site reactions, increase patient compliance because of less frequent injection, and less cost to patient, were first discovered and enumerated in the '135 patent.

"[a]dministering a drug once every half-life is a well-known dosing interval. A person of ordinary skill in the art would have presumed that dosing every half-life is reasonably likely to be effective, absent data suggesting otherwise." Ex. 1004 ¶ 18. Dr. Jusko specifically explains how that would have been true in light of D2E7's linear pharmacokinetics. *Id*. ¶¶ 19–23.

Dr. Weisman disagrees with Patent Owner's declarant, Dr. Weinblatt, who testified during the prosecution of the '135 patent, that every-other-week dosing would have been concerning because of possible production of anti-drug antibodies and the statements of possible up-dosing for patients receiving the equivalent of a 40 mg dose of D2E7. Ex. 1003 ¶ 40 & n.7 (citing Ex. 1002, 1190 ¶ 43 (Dr. Weinblatt's Declaration)). Contrary to Dr. Weinblatt's testimony, Dr. Weisman points to statements in van de Putte 1999 and Kempeni 1999, respectively, that a 20 mg weekly dose is clinically effective and that an every-other-week dose achieved favorable clinical results. *Id*.; *see* Ex. 1004 ¶ 23.

Dr. Weisman also testifies that van de Putte 1999 teaches that each dose, including the 20 mg dose, produced an effective response. Ex. 1003 ¶ 32 (citing Ex. 1008, 7). In van de Putte 1999, 39 to 47% of patients receiving D2E7 achieved an ACR 20 response compared to placebo, including the 20 mg dose. *Id.* ¶ 34 (citing Ex. 1008, 7). Dr. Weisman testifies that "[i]n general, a roughly 30-40% increase in patients achieving an ACR 20 response with a TNFα agent over placebo would have been considered by a person of ordinary skill in the art to be sufficient to demonstrate clinical effectiveness." *Id.* ¶ 33. Therefore, Dr. Weisman disagrees with Patent Owner's declarant Dr. Weinblatt, who believed that a person of ordinary skill in the art would have had concerns that dose

stretching would compromise efficacy. *Id*. ¶ 40; *see* Ex. 1004 ¶ 24, 26–27 (discussing Dr. Mould's concerns with dose stretching).

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 biweekly would have been no more than a routine optimization of the dosing regimens disclosed and suggested by the combination of Kempeni 1999 and van de Putte 1999. Patent Owner's evidence and arguments present fruitful areas to pursue at trial, but do not overcome the evidence presented by Petitioner on the threshold question of a reasonable likelihood that it can show unpatentability of at least one of claims 1–5 of the '135 patent.

4. *Secondary Considerations of Nonobviousness*

Patent Owner asserts that objective evidence of nonobviousness, or secondary considerations, supports the patentability of claims 1–5 of the '135 patent. Prelim. Resp. 48–50. 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 asserts that the uncontroverted commercial success of HUMIRA®, a commercial formulation of the claimed subject matter, supports a determination of nonobviousness of the claims 1–5. Prelim. Resp. 48. Patent Owner states that it has shown a nexus between the commercial success and the claimed invention, pointing to the prosecution history of the '135 patent where the Examiner agreed with Patent Owner's declarant that the "combination of every other week dosing with subcutaneous flat unit

dosage forms" was a key design feature that contributed to HUMIRA®'s success. *Id*. (citing Ex. 2004 ¶ 28).

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-other-week administration to treat RA. *See* Ex. 2004 ¶¶ 28–30; Ex. 2031, 3 (lacking any discussion concerning whether sales of HUMIRA® were due to the 40 mg dose recited in the claims). Therefore, the showing of secondary considerations on this record does not persuade us to decline institution.

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

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

1. Rau 1998

Rau 1998 describes a study in which patients were treated with multiple intravenous doses of D2E7 every two weeks until the patient reached a good response according to European League Against Rheumatism ("EULAR") response criteria of an absolute Disease Activity Scale ("DAS") value of <2.4.[10] Ex. 1006, 5. After achieving a good EULAR response, a patient was retreated only when the DAS value increased to above 2.4 again. *Id*. Patients treated with 0.5 and 1 mg D2E7/kg body weight were offered the possibility of a dose escalation. *Id.*

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

The mean dosing interval for the study was 2.5 weeks. *Id*. Rau concluded that "D2E7 has been shown to be safe and efficacious in patients with active RA over 12 months." *Id.*

2. *Schattenkirchner 1998*

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

3. *Analysis*

Petitioner asserts that a "40 mg subcutaneous dose is the only element that is not expressly disclosed by Rau 1998. This element, however, would have been suggested by Schattenkirchner 1998 and van de Putte 1999." Pet. 40. Petitioner points out that Schattenkirchner 1998 demonstrates that "plasma concentrations of D2E7 after multiple s.c. [subcutaneous] injections are comparable with those after i.v. [intravenous] injections of D2E7," and that s.c. administration of D2E7 has been shown to be safe and efficacious. *Id*. at 43–44 (citing Ex. 1003 ¶ 46). Petitioner also relies on van de Putte 1999's disclosure of a 40 mg dose of D2E7. *Id*. at 41–42. Petitioner concludes that selecting the dose and route of administration would have

been a "routine optimization" of Rau 1998 yielding predictable results. *Id.* at 42 (citing Ex. 1003 ¶¶ 41–51).

In contesting Petitioner's showing, Patent Owner offers arguments similar to those presented in the first ground; namely, a person of ordinary skill would not have equated the intravenous, weight-based dosing schedules in Rau 1998 with a subcutaneous, fixed dosing regimen; would not have chosen a 40 mg every-other-week dosing scheme because such dosing is too low to serve as a one-size-fits-all; and would have faced innumerable possible combinations for a D2E7 dosing regimen. Prelim. Resp. 51–54. Patent Owner also relies on the same objective evidence of nonobviousness—the commercial success of HUMIRA®. *Id.* at 55.

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

III. CONCLUSION

After reviewing the information presented in the Petition and the Preliminary Response, as well as the evidence of record, we determine that the Petitioner establishes a reasonable likelihood that it will prevail in showing that at least one of claims 1–5 of the '135 patent are unpatentable. Our findings and conclusion 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 pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds:

1. Claims 1–5 are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Kempeni 1999 and van de Putte 1999;

2. Claims 1–5 are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Rau 1998, Schattenkirchner 1998, and van de Putte 1999;

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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