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Paper 9
Entered: July 7, 2016

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 IPR2016-00408
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 Ground of Unpatentability

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

References	Basis	Claims Challenged
Van de Putte 2000[1] and Rau 2000[2]	§ 103	1–5

Petitioner relies also on the Declarations of Michael H. Weisman, M.D., a rheumatologist, and William J. Jusko, Ph.D., who studies pharmacokinetics. Pet. 7; *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

[1] L.B.A. van de Putte et al., *Six Month Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 ANNALS OF THE RHEUM. DISEASES OP.056 (July 2000) ("van de Putte 2000") (Ex. 1009).

[2] R. Rau et al., *Experience with D2E7*, 25 RHEUM. TODAY 83 (June 2000) (English Translation) ("Rau 2000") (Ex. 1012).

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. 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." Prelim. Resp. 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. (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." *Id*. at 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, *cited in*, Prelim. Resp. 18.

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 ground "discusses the same clinical trials and presents the same issues" as those raised by Coherus in the petition in IPR2016-00172. Prelim. Resp. 53. Patent Owner also asserts that 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.[3] *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).

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

D. Obviousness over van de Putte 2000 and Rau 2000

Petitioner contends that claims 1–5 are unpatentable under 35 U.S.C. § 103 as obvious over van de Putte 2000 and Rau 2000. Pet. 20–51. Petitioner asserts that van de Putte 2000 expressly teaches each limitation of claims 1–5 except for every-other-week administration. *Id*. at 2, 20. Petitioner asserts that Rau 2000 provides that missing teaching. *Id*. Even without the teachings of Rau 2000, Petitioner offers that "a person of ordinary skill in the art would have tried administering the van de Putte 2000 doses on an every-other-week basis." *Id*. at 2 (quoting *Hoffman-La Roche*

[3] 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. 18 (citing Ex. 1003 ¶ 12). Petitioner also includes a Declaration of Dr. Jusko, a pharmacokineticist. *Id*. 18–19; *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, which is consistent with Petitioner's definition. Prelim. Resp. 17.

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 presents a "textbook example of hindsight." *Id*.

1. *van de Putte 2000*

van de Putte 2000 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. 1009, 2. 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 2000 reports the percentage of patients receiving an ACR 20[4] response, as well as the median percent improvement in TJC, SWJC, and CRP for each of the dosing regimens and placebo after three and six months of treatment. *Id*.

The results are reproduced below.

[4] ACR 20 is short hand for the American College of Rheumatology improvement criteria. Ex. 1011, 4.

	% Response or Improvement				
Treatment	Plac/40 mg	20 mg	40 mg	80 mg	
Treatment period [months]	3/6		3/6	3/6	3/6
ACR 20	10/59	49/56	57/64	56/63	
TJC [Median]	5/55		57/69	61/63	55/63
SJC [Median]	16/56		42/54	59/68	61/62
CRP [Median]	1/67		54/59	67/58	64/66

The table above shows the results of the clinical study described in van de Putte 2000 after three and six months of treatment. *Id*. Based on the results, van de Putte 2000 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 statistically equally efficacious when given s.c. in patients with active RA." *Id*.

2. Rau 2000

Rau 2000 discusses the D2E7 clinical trials DE001, DE003, DE004, DE007, and DE010. *See* Exs. 1012; 1003 ¶ 31. Rau 2000 concludes as follows:

> In summary, it can be established that the completely human TNFα antibody D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment over, up to now, two and one-half years. D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously. D2E7 is well tolerated and must be called a therapeutic step forward.

Ex. 1012, 8.

3. Analysis

Petitioner presents an explanation demonstrating where the limitations of the challenged claims may be found in the cited references. Pet. 20–51. 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* Pet. 20–22.

Petitioner asserts that "van de Putte 2000 expressly teaches each of the claimed features except for the every-other-week dose. Such a dose would have been obvious in view of Rau 2000." *Id*. at 20. Petitioner states that one of skill in the art at the time of the invention would have combined the teachings of van de Putte 2000 and Rau 2000 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 2000 subcutaneous dosing regimens because each dosing regimen was determined to be effective for treating RA. *Second*, Rau 2000 would have provided motivation to optimize the van de Putte 2000 doses to a less frequent every-other-week dosing interval. Specifically, Rau 2000 explains that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." *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.

Id. at 21–22 (citations omitted); *see* Ex. 1003 ¶¶ 34–51; Ex. 1004 ¶¶ 15–24.

Petitioner asserts that the

> efficacy of the weekly 20 mg dose reported in van de Putte 2000 would have at least suggested that an analogous, every-other-week 40 mg dose would have been an option worth investigating in light of Rau 2000. And a person of ordinary skill would have been particularly attracted to pursuing an every-other-week equivalent (*i.e.*, 40 mg) of the lowest weekly dose (*i.e.*, 20 mg) that had been shown to be efficacious in the prior art.

Pet. 26–27 (citing Ex. 1003 ¶¶ 50–51). Petitioner points out that Rau 2000 concludes that D2E7 can be administered either intravenously or subcutaneously every other week. *Id*. at 27 (citing Ex. 1012, 8; Ex. 1003 ¶ 42).

> Rau 2000 explains that D2E7 can be administered every other week because D2E7 has a "half-life of 12 days", which would have suggested to a person of ordinary skill in the art that D2E7 concentrations would have remained high enough to achieve clinical results over two weeks. This is consistent with Rau 2000's conclusion: "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously."

Id. at 27–28 (citing Ex. 1012, 8; Ex. 1003 ¶¶ 43–47). Petitioner also asserts that this conclusion is supported by D2E7's linear pharmacokinetics. *Id*. at 30–31 (citing Ex. 1004 ¶¶ 23–25). Petitioner concludes that given the finite number of options, administering 40 mg every 13-15 days to treat RA would have been obvious to try with a reasonable expectation of success in view of the three fixed doses disclosed in van de Putte 2000. *Id*. at 31–33 (citing Ex. 1003 ¶¶ 41, 48–51).

Patent Owner counters that Petitioner's reliance on a combination 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.[5] *Id.* at 2–5, 19–50. 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 Dr. Michael E. Weinblatt); Ex. 2003 (Declaration of 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 weekly dose (which it asserts is facially inferior to the 40 and 80 mg dosing regimens in van de Putte 2000) into a 40 mg every-other-week dose. Prelim. Resp. 29–43. "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."[6] *Id*. at 29.

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[5] In view of van de Putte 2000's disclosure of three doses as a starting point for a dose-finding phase II study (*see* Ex. 1009, 2) 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 opinions.

[6] 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. *See* Prelim Resp. at 27–29. 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 ¶ 39. Dr. Weisman testifies that no reliable dose-to-dose comparisons can be drawn from van de Putte 2000's parallel placebo study. *Id*. Dr. Weisman supports his position with van de Putte 2000's conclusion that each dose was "statistically equally efficacious." *Id*. (citing Ex. 1009, 2); *see* Ex. 1008, 7. Dr. Jusko agrees with that conclusion. *See* Ex. 1004 ¶¶ 15–16.

On this record, we do not agree with Patent Owner's assertion of hindsight. Specifically, the combined teachings of van de Putte 2000 and Rau 2000 do not appear to disclose that intravenous, weight-based dosing is the best alternative. van de Putte 2000 teaches that administering fixed doses of D2E7 to RA patients by subcutaneous injection is effective (*see* Ex. 1009, 2; Ex. 1003 ¶¶ 35–41) and Rau 2000 expressly concludes that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously" (Ex. 1013, 8; Ex. 1003 ¶ 43).

Petitioner also provides testimony that subcutaneous injections would be preferable because a patient can self-administer the injection at home and avoid complications with intravenous administration such as thrombosis (*see* Ex. 1003 ¶ 41) 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*.).[7]

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

[7] 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 ¶¶ 32, 41, 49. 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, increased patient compliance because of less frequent injection, and less cost to patient, were first discovered and enumerated in the '135 patent.

would not be an adequate predictor of dosing interval. Dr. Weisman testifies that Rau 2000 would have suggested that every-other-week administration of D2E7 is effective for treating RA. Ex. 1003 ¶ 42. Dr. Weisman explains that Rau 2000 states

> that D2E7 can be administered every other week because D2E7 has a "half-life of 12 days" (Ex. 1012 at 8), which would have suggested to a person of ordinary skill in the art that D2E7 concentrations would have remained high enough to achieve clinical results over two weeks. Indeed, Rau 2000 expressly concludes that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously."

Id. ¶ 43. [8]

Dr. Jusko testifies that "[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 Rau 2000's discussion of the half-life of D2E7. *Id*. ¶¶ 19–20.

Dr. Weisman disagrees with Patent Owner's declarant, Dr. Weinblatt, who testified during the prosecution of the '135 patent, that every-other-

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[8] Dr. Weisman also takes issue with Patent Owner's characterization of Rau 2000 as teaching that only an *intravenous* injection of D2E7 may be administered every other week and that Rau 2000 discourages subcutaneous administration. Ex. 1003 ¶¶ 45–46. Dr. Weisman concludes that "Rau 2000 would have at least provided a person of ordinary skill in the art with motivation to investigate every-other-week subcutaneous dosing given the known advantages of subcutaneous administration over intravenous administration" (*Id*. ¶ 45), and notes that "Rau 2000 expressly states that D2E7 is 'effective subcutaneously'" (*Id*. ¶ 46). On this record, we credit Dr. Weisman's testimony.

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 ¶ 47 & 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 2000 and Rau 2000, respectively, that a 20 mg weekly dose is clinically effective and that an every-other-week dose achieved favorable clinical results. *Id*.; *see also* Ex. 1004 ¶¶ 21–25 (discussing why concerns about overdosing, underdosing and anti-drug antibody development were unfounded in light of the teachings of the prior art).

Dr. Weisman also testifies that van de Putte 2000 teaches that each dose, including the 20 mg dose, produced an effective response. Ex. 1003 ¶ 35 (citing Ex. 1009, 2), 37. In van de Putte 2000, over the first three months, 39 to 47% of patients receiving D2E7 achieved an ACR 20 response compared to placebo, including the 20 mg dose, an efficacy that was maintained during the last three months of the study for each dose. *Id.* ¶ 37 (citing Ex. 1009, 2). Dr. Weisman testifies that "[i]n general, a roughly 30-40% increase in patients achieving an ACR20 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.* ¶ 36. Therefore, Dr. Weisman disagrees with Patent Owner's declarants Drs. Mould and Pope, who asserted during prosecution that van de Putte 2000 and Rau 2000, respectively, taught that a 20 mg dose of D2E7 was not effective. *Id*. ¶¶ 39–40. On this record, we credit Dr. Weisman's testimony.

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 van de Putte 2000 and Rau 2000. 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. 50–52. 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. 50. 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*. at 51 (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.

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 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 ground that claims 1–5 are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of van de Putte 2000 and Rau 2000;

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.

PETITIONER:

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