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Paper 11
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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.

GENENTECH, INC.,
Patent Owner.

Case IPR2015-00417
Patent 7,976,838 B2

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

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 1–14 of US 7,976,838 B2 (Ex. 1001; "the '838 patent"). Genentech, Inc. ("Patent Owner") filed a Patent Owner Preliminary Response. Paper 9 ("Prelim. Resp.").

Upon consideration of the above-mentioned Petition and Preliminary Response we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. 35 U.S.C. § 314(a). We authorize institution of an *inter partes* review as to claims 1–14.

A. Related Proceedings

The parties inform us of no related litigations. Pet. 4; Paper 6, 2. Concurrent with the present *inter partes* review, Petitioner also requested review of claims in U.S. Patent No. 7,820,161 (Case IPR2015-00415) and U.S. Patent No. 8,329,172 (Case IPR2015-00418). *Id.* Patent Owner notes that while these three proceedings involve the same counsel, the subject patents are not formally related and the patents do not have the same ownership. Paper 6, 2.

B. The '838 patent (Ex. 1001)

The '838 patent discloses methods of treating rheumatoid arthritis ("RA") in a human patient who experiences an inadequate response to a TNFα-inhibitor. Ex. 1001, Abstract, 4:3–24. The methods of the claimed invention involve administration of an antagonist that binds to a B cell

surface marker, such as CD20. *Id.* at 4:60–65. CD 20 is a B cell surface marker. *Id.* at Abstract. The '838 patent expressly defines the term "antagonist" as follows:

> [A] molecule which, upon binding to a B cell surface marker, destroys or depletes B cells in a mammal and/or interferes with one or more B cell functions, e.g. by reducing or preventing a humoral response elicited by the B cell. The antagonist preferably is able to deplete B cells (i.e. reduce circulating B cell levels) in a mammal treated therewith. Such depletion may be achieved via various mechanisms such antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC), inhibition of B cell proliferation and/or induction of B cell death (e.g. via apoptosis). Antagonists included within the scope of the present invention include antibodies, synthetic or native sequence peptides and small molecule antagonists which bind to the B cell marker, optionally conjugated with or fused to a cytotoxic agent. The preferred antagonist comprises an antibody.

Id. at 6:64–7:12.

In particular, the '838 patent discloses treating patients who have experienced an inadequate response to a TNFα-inhibitor. *Id.* The '838 patent expressly defines the term "inadequate response to a TNFα-inhibitor" as follows:

> [A]n inadequate response to previous or current treatment with a TNFα-inhibitor because of toxicity and/or inadequate efficacy. The inadequate response can be assessed by a clinician skilled in treating the disease in question.

Id. at 5:19–24. The '838 patent specifically discloses Etanercept (ENBREL®), Infliximab (REMICADE®) and Adalimumab (HUMIRA™) as examples of TNF inhibitors. *Id.*

C. Challenged Claims

Claims 1, 2, 8, 10 and 11 are the independent claims among the challenged claims, and are reproduced below:

> 1. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody that binds to CD20, wherein the antibody is administered as two intravenous doses of 1000 mg.
>
> 2. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody which binds to CD20 in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond, wherein the antibody is administered as two intravenous doses of 1000 mg.
>
> 8. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient rituximab, wherein rituximab is administered as two intravenous doses of 1000 mg.
>
> 10. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient rituximab, and methotrexate, wherein the patient has no erosive progression at weeks 24 and beyond, and wherein rituximab is administered as two intravenous doses of 1000 mg.
>
> 11. A method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient rituximab, and

> methotrexate, wherein rituximab is administered as two intravenous doses of 1000 mg.

Claims 3–7 depend from claim 2, either directly or indirectly. Claim 9 depends directly from claim 8. Claims 12–14 depend directly from claim 11.

D. Prior Art and Supporting Evidence

Petitioner relies on the following prior art:

Edwards JCW et al., *Efficacy and Safety of Rituximab, a B-Cell Targeted Chimeric Monoclonal Antibody: A Randomized, Placebo-Controlled Trial in Patients with Rheumatoid Arthritis*, Abstracts of the American College of Rheumatology 66th Annual Meeting, Oct. 24-29, 2002 (New Orleans, LA). Ex. 1003 ("Edwards").

Genentech Press Release: *Preliminary Positive Data from Investigational Randomized Phase II Trial Demonstrates Rituxan as a Potential Treatment for Rheumatoid Arthritis*, (Oct. 28, 2002). Ex. 1004 ("Genentech Press Release").

Curd et al., WO 00/67796 . Ex. 1005 ("Curd").

De Vita S. et al., *Ruolo Patogentico Dei Linfociti B Nella Sinovite Reumatoide: Il Blocco Selettivo B Cellulare Puo Indurre Risposta Clinica In Pazienti con Artrite Reumatoid Refrattaria*, Official Journal of the Italian Society of Rheumatology, Vol. 53, No. 3 (Suppl. No. 4) (2001) [ENGLISH TRANSLATION]. Ex. 1006 ("De Vita").

Tuscano JM, *Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis with Rituximab*, Arthritis Rheum 46:3420, LB 11 (2002). Ex. 1008 ("Tuscano").

Edwards JCW et al., *Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes*, Rheumatology 40:205-211 (2001). Ex. 1022 ("Edwards IV").

Petitioner further relies on the Declaration of Joachim R. Kalden, M.D. ("Kalden Decl.") (Ex. 1002).

E. Asserted Grounds

Based on our understanding of the Petition, Petitioner challenges claims 1–14 of the '838 patent on the following grounds. Pet. 12–57.[1]

Reference[s]	Basis	Claims challenged
Edwards	§ 102	1–5, 7–9, 11–13
Genentech Press Release	§ 102	1–5, 7–9, 11–13
Edwards	§ 103(a)	1–5, 7–14
Edwards and De Vita	§ 103(a)	1–5, 7–14
Edwards and Tuscano	§ 103(a)	1–5, 7–14
Genentech Press Release	§ 103(a)	1–5, 7–14
Genentech Press Release and De Vita	§ 103(a)	1–5, 7–14
Genentech Press Release and Tuscano	§ 103(a)	1–5, 7–14
Curd	§ 103(a)	1–5, 7–14
Curd and De Vita	§ 103(a)	1–5, 7–14

[1] At pages 55–57 of its Petition, Petitioner provides a table of various possible combinations of Curd, Genentech Press Release, Edwards, De Vita, and Tuscano that could be made to assert an obviousness ground. *See* Pet. 55 ("The challenged claims are also obvious … as set forth below:"). This table can at best be described as confusing and uninformative. The headings of this analysis portion of the Petition inform us as to the relevant claims and claim elements being considered, and the discussion that follows in the Petition provides a detailed analysis informing us as to the Petitioner's position regarding the unpatentability of claims 1–14. Pet. 35–55.

Reference[s]	Basis	Claims challenged
Curd and Edwards IV	§ 103(a)	1–5, 7–14
Curd and Tuscano	§ 103(a)	1–5, 7–14
Curd, De Vita, and Edwards IV	§ 103(a)	1–5, 7–14
Curd, De Vita, and Tuscano	§ 103(a)	1–5, 7–14
Edwards and Curd	§ 103(a)	6
Genentech Press Release and Curd	§ 103(a)	6
Curd	§ 103(a)	6
Curd and De Vita	§ 103(a)	6
Curd and Edwards IV	§ 103(a)	6
Curd and Tuscano	§ 103(a)	6
Curd, De Vita, and Edwards IV	§ 103(a)	6

II. ANALYSIS

A. Claim Interpretation

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also* Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012); *In re Cuozzo Speed Techs., LLC*, No. 2014-1301, slip op. at 10–19 (Fed. Cir. 2015). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257

(Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We interpret the following terms of the challenged claims as part of our analysis. The Petition does not require explicit construction of any other claim term at this time. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)).

1. *The Preamble Phrase "a human patient who experiences an inadequate response to a TNFα-inhibitor"*

    a. *Whether the preamble of the independent claims is limiting*

"[A] preamble is a claim limitation if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *Poly-Am., L.P. v. GSE Lining Tech., Inc*., 383 F.3d 1303, 1309 (Fed. Cir. 2004) (internal quotation marks omitted). "The effect preamble language should be given can be resolved only on review of the entirety of the patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim." *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc*., 868 F.2d 1251, 1257 (Fed. Cir. 1989).

We recognize that, in general, "[a]n intended use or purpose usually will not limit the scope of the claim because such statements usually do no

more than define a context in which the invention operates." *Boehringer Ingelheim Vetmedica, Inc. v. Schering–Plough Corp*., 320 F.3d 1339, 1345 (Fed. Cir. 2003)("*Boehringer*"). "But, . . . preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise." *Id*. (*citing Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002).

In *Boehringer*, for example, the Federal Circuit found the "growing and isolating . . . virus" language of a preamble was limiting because "'growing' and 'isolating' are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself." *Boehringer*, 320 F.3d at 1344–45. Without the preamble, the court found that "the claimed method [was] reduce[d] to nothing more than a process for producing cytopathic effects in sheets of cultured MA–104 cells—a process whose absence of fathomable utility rather suggests the academic exercise." *Id*. at 1345. The court thus recognized that one of ordinary skill in the art would not understand the utility of the process without the "growing" and "isolating" language of the preamble.

We conclude that, as in *Boehringer*, one of ordinary skill in the art would not understand the utility of the process of the challenged claims, viewed in light of the specification, without the preamble language of the claim. The body of each of the independent claims 1, 2, 8, 10, and 11 is absent any clear language indicating that the utility of the invention is a treatment for rheumatoid arthritis. Further, the preamble of the claims inform as to the identity of "the patient" recited in the body of the claim, which is a human patient who experiences an inadequate response to a

TNFα-inhibitor. Hence, the preamble of the claim recites the essence of the invention and is limiting.

Our views on claim construction shall not be deemed final until the record is complete, we have finished our review of the complete record, and rendered our Final Decision.

B. Principles of Law

An *inter partes* review may be instituted only if "the information presented in the [Petition and Preliminary Response] shows that there is 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). To prevail in its challenges to the patentability of the claims, a petitioner must establish facts supporting its challenges by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A claim is unpatentable under 35 U.S.C. § 102 if a prior art reference discloses every limitation of the claimed invention, either explicitly or inherently. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir.1995); *see MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (holding that "[t]o anticipate, a single reference must teach every limitation of the claimed invention," and any limitation not taught explicitly must be taught inherently and would be so understood by a person experienced in the field); *In re Baxter Travenol Labs*., 952 F.2d 388, 390 (Fed. Cir. 1991) (the dispositive question is "whether one skilled in the art would reasonably understand or infer" that a reference teaches or discloses all of the elements of the claimed invention).

The principle of inherency, in the law of anticipation, requires that

any information missing from the reference would nonetheless be known to be present in the subject matter of the reference, when viewed by persons experienced in the field of the invention. We note, however, that "anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation, [or the reference] cannot inherently anticipate the claims." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (internal citation omitted); *see Hitzeman v. Rutter*, 243 F.3d 1345, 1355 (Fed. Cir. 2001) ("consistent with the law of inherent anticipation, an inherent property must necessarily be present in the invention described by the count, and it must be so recognized by persons of ordinary skill in the art") (citations omitted); *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (that a feature in the prior art reference "could" operate as claimed does not establish inherency).

Thus, when a claim limitation is not set forth explicitly in a reference, evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991) (citations omitted). It is not sufficient if a material element or limitation is "merely probably or possibly present" in the prior art. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (citations omitted); s*ee W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983) (anticipation "cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references") (citation omitted); *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (to anticipate, the

asserted inherent function must be present in the prior art).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious 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 skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

C. Asserted Grounds of Unpatentability

1. Anticipation of Claims 1–5, 7–9, and 11–13 by Edwards or Genentech Press Release

a. Summary of Edwards (Ex. 1003)

Edwards discloses the results of a study involving 161 patients with RA, all of whom were rheumatoid factor positive and receiving methotrexate. Ex. 1003. The patients were separated into four patient groups: Group A (continuing methotrexate alone); Group B (rituximab alone); Group C (rituximab and cyclophosphamide); and Group D (rituximab plus continuing methotrexate). *Id.* Patients receiving rituximab were given two IV doses of 1000mg. *Id.* In addition, all groups received a

17-day course of corticosteroids. *Id.* All three rituximab regimens were "well tolerated" and produced "substantial clinical benefit in RA," with the combination therapies producing "the highest levels of ACR20, 50, and 70 responses." *Id.*

b. Summary of Genentech Press Release (Ex. 1004)

Genentech Press Release reports the preliminary result from "a randomized, doubleblind, placebo-controlled Phase II study examining the use of Rituxan® (Rituximab) in the treatment of rheumatoid arthritis (RA)." Ex. 1004. "Rituxan was administered as two intravenous infusions, with doses (1g) given two weeks apart." Patients participating in the study received intravenous and oral corticosteroids. *Id.* The Genentech Press Release summarized the results of the study as follows:

> • Patients receiving Rituxan alone (n=31): 18 patients (58%) experienced ACR20 responses, 10 patients (32%) experienced ACR50 responses and 4 patients (13%) experienced ACR70 responses.
>
> . . .
>
> • Patients receiving Rituxan plus methotrexate (n=30): 24 patients (80%) experienced ACR20 responses, 15 patients (50%) experienced ACR50 responses, and 7 patients (23%) experienced ACR70 responses.

Id. at 2.

According to the Genentech Press Release, the resulting data "suggest that targeting B-cells with Rituxan may represent a completely new approach to treating patients with rheumatoid arthritis." *Id.* at 1.

c. Discussion

Petitioner sets forth the above teachings of Edwards and Genentech

Press Release and contends that claims 1–5, 7–9, and 11–13 of the '838 patent are anticipated by Edwards or Genentech Press Release. Pet. 20–25, 54–55.

Petitioner first argues that "[t]he broadest reasonable construction of the preamble phrase 'in a human patient who experiences an inadequate response to a TNFα-inhibitor,' is that it is not a limitation of claims 1, 2, 8, [and 11]," and thus Edwards and Genentech Press Release expressly disclose each element of independent claims 1, 2, 8, 10, and 11. Pet. 35–36, 49–50. As set forth above, however, we do not agree with Petitioner that the preamble of independent claims 1, 2, 8, and 11 is not a claim limitation.

Rather, we agree with Patent Owner that neither Edwards nor Genentech Press Release describes any study participant as a TNFα-inadequate responder, and thus the claim element of "in a human patient who experiences an inadequate response to a TNFα-inhibitor" recited in the preamble of each of the independent claims is not expressly disclosed by either Edwards or Genentech Press Release. Prelim. Resp. 23. Accordingly, we are not persuaded by Petitioner's arguments that Edwards and Genentech Press Release expressly disclose each element of the challenged claims.

Petitioner further contends, however, that the claim element "in a human patient who experiences an inadequate response to a TNFα-inhibitor" is inherently disclosed by Edwards and Genentech Press Release. Pet. 3, 36. Specifically, Petitioner contends that treatment of non-responders to TNFα-inhibitors is inherent to the treatment of RA "due to the high percentage of non-responders to TNFα-inhibitors, which constitutes at least 40% of all RA patients." Pet. 3. Thus, "in a study involving 160 patients, such as the prior art study designed by Dr. Edwards, for example, about 60 non-responders to

TNFα-inhibitors would be necessarily present and the 'limiting' preamble phrase would be met." *Id.*; *see also, id.* at 36 (citing, *inter alia*, Ex. 1002 at ¶ 50 (stating the patient response rate to TNFα-inhibitors is about 60%)).

Patent Owner disagrees with Petitioner's conclusions with regard to inherency, and argues that Petitioner's inherency position is based on probabilities. Prelim. Resp. 23–26. We agree. Even with the high percentage of non-responders to TNFα-inhibitors, for each individual attempt to practice the claim, there is only a possibility that treatment according to method disclosed in the prior art would result in the claimed method. It is well established, however, that "inherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention." *In re Montgomery*, 677 F.3d 1375, 1384 (Fed. Cir. 2012), citing *Glaxo Inc. v. Novopharm Ltd*., 52 F.3d 1043, 1047 (Fed.Cir.1995) (holding that even though the defendant's experts reproduced a prior art method "thirteen times and each time they made [the claimed] crystals," the patentee's chemists twice produced different crystals from the same method, thus precluding inherency).

Upon review of Petitioner's analysis and supporting evidence, we determine that Petitioner has not established a reasonable likelihood that it would prevail in demonstrating unpatentability of claims 1–5, 7–9, and 11–13 based on anticipation by Edwards or Genentech Press Release.

2. Obviousness of 1–5 and 7–14 Over the Combination of Edwards and Tuscano

a. Summary of Tuscano (Ex. 1008)

Tuscano discloses the results of "a clinical trial using rituximab alone

for the treatment of erosive RA in patients that have previously failed multiple DMARD's *including infliximab*." Ex. 1008 (emphasis added). Rituximab was administered in an escalating dose starting at 100 mg/m^2 in week one, rising to 375 mg/m^2 in week 2, and then reaching 500 mg/m^2 in weeks 3 and 4. *Id.* After 5 months of treatment, all 7 patients had improved joint scores, and 3 achieved an ACR20 response. *Id.* Tuscano concludes as follows:

> While the current patient numbers are small, and enrollment is ongoing, this data supports the hypothesis that B lymphocytes mediate pathology in RA, and that rituximab is a promising agent for patients with DMARD and infliximab-refractory RA.

Id.

b. Discussion

Petitioner contends that claims 1–5 and 7–14 of the '838 patent would have been obvious over the combination of Edwards and Tuscano. Pet. 54–55. In support of its assertion that the combination of Edwards and Tuscano renders claims 1–5 and 7–14 obvious, Petitioner sets forth the foregoing teachings of Edwards (summarized in Sec. II.C.1.a above) and Tuscano and provides a detailed analysis explaining how each claim limitation is disclosed in the combination of references. Pet. 21–22, 27–28 and 42–57.

Petitioner contends that Edwards discloses "(i) treating RA by administering two 1000 mg doses of anti-CD20 antibody rituximab alone and in conjunction with methotrexate and corticosteroids; and (ii) ACR50 and ACR70 clinical responses." *Id.* at 54. Petitioner further contends that treating RA patients who do not respond to TNFα-inhibitors was expressly

disclosed in the prior art. Pet. 37, 41, 54. Specifically, Petitioner directs our attention to Tuscano and contends that Tuscano discloses the treatment of infliximab-refractory RA patients with rituximab. *Id.* at 37 (citing Ex. 2008). Petitioner further contends that "[t]he results of the Tuscano study showed that 'rituximab is a promising agent for patients with DMARD and infliximab-refractory RA.'" *Id.* (quoting Ex. 2008).

Petitioner further relies on the Declaration of Dr. Kalden to support a position that "[a] person of ordinary skill treating RA patients would have tried alternative methods of treatment for patients who did not adequately respond to TNFα-inhibitors like infliximab and etanercept." Kalden Decl. ¶ 70; Pet. 37–38. Dr. Kalden also notes that it was known that the patient response rate to TNFα-inhibitors is about 60%, indicating that the size of the patient population was significant. Ex. 1002,¶¶ 50, 65; Pet. 1.

Patent Owner argues that Tuscano discloses the use of a dose that is different from the recited two intravenous doses of 1000 mg. Prelim. Resp. 41. Specifically, Patent Owner points out that "the dose reported in Tuscano was '100 mg on wk #1, followed by 375 mg/m^2 on wk #2, and 500 mg/m^2 on wks 3 and 4.'" *Id.* (citing Ex. 1008). Patent Owner further contends that "Tuscano would not encourage administering rituximab to infliximab-refractory patients because those 7 patients showed little or no improvement after treatment with rituximab." *Id.* at 42.

We are not persuaded by Patent Owner's arguments in this regard. Edwards discloses a method of treating rheumatoid arthritis with the administration of two intravenous doses of 1000 mg rituximab, an antibody that binds CD20. Ex. 1003. Tuscano discloses the treatment of rheumatoid arthritis using rituximab in patients where treatment with infliximab, a

TNFα-inhibitor, had failed. Ex. 1008. Based on the current record, Tuscano appears to cure the deficiency of Edwards identified by Patent Owner. *See In re Merck & Co. Inc*., 800 F.2d 1091, 1097 (Fed. Cir. 1986) (Each reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.").

Upon review of the information presented in the Petition and Preliminary Response, we have determined that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing that claims 1–5 and 7–14 of the '838 patent would have been obvious over the combination of Edwards and Tuscano.

3. Obviousness of Claim 6 Over the Combination of Curd, De Vita, and Edwards IV

a. Summary of Curd (Ex. 1005)

Curd discloses the intravenous administration of rituximab to patients with a clinical diagnosis of rheumatoid arthritis. Ex. 1005, 25:9–28. Curd also discloses combination therapies involving methotrexate and corticosteroids. *Id.* at 25:10–16 ("[T]he patient is optionally further treated with any one or more agents employed for treating RA such as . . . immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages."); *id.* at 8:28–29 (referring to "steroids such as glucocorticosteroids, e.g., prednisone, methylprednisolone, and dexamethasone"); *id.* at 26:1–3 ("Further adjunct therapies (such as glucocorticoids, prednisone, azathioprine, cyclophosphamide, vinca-laden platelets or Danazol) may be combined with the RITUXAN® therapy. . . .").

b. Summary of De Vita (Ex. 1006)

De Vita discloses the administration of rituximab to rheumatoid arthritis patients who were non-responsive to TNFα-inhibitors. Ex. 1006. The rituximab treatment involved "4 intravenous infusions per week of 375 mg/m^2 each." *Id.* A patient who had not responded to TNFα therapy achieved an ACR 20 response in month +5. *Id.*

c. Summary of Edwards IV (Ex. 1022)

Edwards IV discloses "[a]n open study of B-lymphocyte depletion was undertaken in rheumatoid arthritis (RA) patients to test the hypothesis that B lymphocytes may be essential to disease perpetuation." Ex. 1022, Abstract. "Five patients with refractory RA were treated with a monoclonal anti-CD20 antibody, cyclophosphamide and prednisolone and followed for 12-17 months." *Id.* Edwards IV disclosed the following dosing schedule: "four i.v. infusions (over 3 h) on days 2, 8, 15, 22, of 300, 600, 600 and 600 mg respectively." *Id.* at 206. At 26 weeks of the study, "all patients satisfied the American College of Rheumatology ACR50 and patients 1-3 the ACR70 criteria of improvement without further therapy." *Id.* at Abstract. The authors conclude that "[t]hese finding are consistent with the concept that RA is critically dependent on B lymphocytes and suggest that B-lympocyte depletion may be a safe and effective therapy." *Id.*

d. Discussion

Claim 6 depends from claims 2 and 3 and thus requires the administration of rituximab as two intravenous doses of 1000 mg. Claim 6 further requires the treatment with methotrexate and a corticosteroid regimen, and specifically, a regimen of methylprednisolone and prednisone.

Petitioner contends that claim 6 of the '838 patent would have been obvious over the combination of Curd, De Vita, and Edwards IV. Pet. 57.

In support of its assertion that the combination of Curd, De Vita, and Edwards IV renders claim 6 obvious, Petitioner sets forth the foregoing teachings of Curd, De Vita, and Edwards IV and provides a detailed discussion explaining how each claim limitation is disclosed in the combination of references. Pet. 22, 25–27, 37–38, 41–44, 46, and 52–54. We determine that Petitioner has established a reasonable likelihood it would prevail on this basis. Our reasoning follows.

The Petitioner does not contend that the recited element of "two intravenous doses of 1000 mg" is disclosed in any of Curd, De Vita, or Edwards IV. Indeed, none of Curd, De Vita, or Edwards IV discloses "two intravenous doses of 1000 mg." Curd, however, discloses the administration of "one or more initial dose(s) of the [rituximab] antibody" and that subsequent intravenous doses of rituximab can be "in the range from about 20mg/m^2 to about 1000mg/m^2." Ex. 1005, 23:23–27. Example 1 of Curd discloses a dosing schedule for treating RA patients with rituximab of "375 mg/m^2 IV days 1, 8, 15, 22." *Id.* at 25:17–23. De Vita discloses that rituximab was administered to RA patients in "4 intravenous infusions per week of 375 mg/m^2 each." Ex. 1006. Edwards IV discloses treatment of RA with "four i.v. infusions (over 3 h) on days 2, 8, 15, 22, of 300, 600, 600 and 600 mg respectively." Ex. 1022, 206.

Petitioner contends that the dosing regimen recited in the challenged claims would have been a routine step in the development of any treatment regimen to move from a dosing regimen requiring four infusions totally 1500 mg/m^2 (Ex. 1005) or 2100 mg/m^2 (Ex. 1022) to two infusions of 1000

mg. *Id.* at 43–44 (citing Ex. 1002, ¶¶ 87–88). Specifically, Petitioner contends as follows:

> In light of the known dosing schedules for rituximab, a person of ordinary skill would have had a reasonable expectation of success for two IV doses of 1000 mg based on the fact that less frequent doses (e.g., biweekly) would increase patient compliance. (Ex. 1002 at ¶ 88.) Moreover, a person of ordinary skill would optimize dosing of rituximab when treating RA in clinical practice. (*Id*.) Such dosage optimization is a routine step in the development of any treatment regimen. (*Id*.) This is precisely what Dr. Edwards did when he went from using four weekly doses in Edwards IV (totaling 2100 mg) to two bi-weekly doses of 1000 mg in the subsequent Roche study (Edwards VI).

Pet. 43. Dr. Kalden supports Petitioner's conclusion with the following:

> It is my opinion that the requirement of administering rituximab in two intravenous doses of 1000 mg would be obvious to a person of ordinary skill. A skilled practitioner would try to optimize the dose for treating RA patients by investigating different doses of treatment principles for monoclonal antibodies like rituximab to find the optimal dose for the application in clinical practice. Such dosage optimization would be routine in the development of any treatment regimen. The recommended dose for treating non-Hodgkin's lymphoma (375 mg/m^2 weekly x 4) would have been a natural starting point for a person of ordinary skill in the art ordinary skill to determine an appropriate dosing regimen for rituximab when treating RA. A person of ordinary skill would also understand that less frequent doses (e.g., biweekly) would increase patient compliance. Thus a person of ordinary skill in the art ordinary skill would have a reasonable expectation of success using two IV doses of 1000 mg.

Ex. 1002, ¶ 88.

Patent Owner argues that Petitioner does not establish a reasonable

expectation of success and that "even if there had existed 'only a finite number' of treatments, it would not have followed that there was a reasonable expectation of success that one of them would work." Prelim. Resp. 35–36. We are not persuaded based on the current record. In this case, the prior art shows that a patient who had not responded to TNFα therapy achieved an ACR 20 response in month +5 after receiving 4 intravenous infusions per week of 375 mg/m^2 rituximab each. Ex. 1006. The fact that a suggested dose of two intravenous doses of 1000 mg had not been established yet does not demand a conclusion of nonobviousness. All that is required to show obviousness is a reasonable expectation of success, not conclusive proof of 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).

Further, Petitioner contends that there was a need to solve the problem of patient compliance. Pet. 43 (citing *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014)). We are persuaded, based on the current record, that Petitioner is likely to establish that the selection of two intravenous doses of 1000 mg would have been a routine optimization of the therapy suggested by the combination of Curd, De Vita, and Edwards IV. The motivation to optimize the therapy disclosed in the combined references in order to improve patient compliance "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer,* 480 F.3d at 1348 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)). Regarding the claim limitations recited in claim 6, Patent Owner contends that "[Curd] does not identify either methylprednisolone or prednisone in particular." Prelim. Resp. 52. We are not persuaded. Curd

expressly names methylprednisolone and prednisone for use in combination therapies. Ex. 1005, 8:28–29, 25:10–16, 26:1–3.

Patent Owner further contends that "[Curd] expressly teaches away from administering anything else with rituximab when it states that '[p]referably however, the patient is *only* treated with RITUXAN®.'" *Id.* (quoting Ex. 1005 at 25)(emphasis in original). We are not persuaded. For a reference to teach away, it must state more than a general preference for an alternative invention. It must '"criticize, discredit, or otherwise discourage"' investigation into the invention claimed. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009), quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed.Cir. 2004).

Upon review of the information presented in the Petition and Preliminary Response, we have determined that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing that claim 6 of the '838 patent would have been obvious over the combination of Curd, De Vita, and Edwards IV.

4. Secondary Considerations of Nonobviousness

As to secondary considerations, we note that factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17 (1966). Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary

skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–1472 (Fed. Cir. 1984).

Such a conclusion, however, requires the finding of a nexus to establish that the evidence relied upon traces its basis to a novel element in the claim and not to something in the prior art. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). All types of objective evidence of nonobviousness must be shown to have nexus. *In re GPAC Inc*., 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Kao*, 639 F.3d at 1069 (unexpected results); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need).

Objective evidence of nonobviousness must also be reasonably commensurate in scope with the claim. *In re Kao*, 639 F.3d at 1068. This does not mean that the proffered evidence must reach every embodiment within the scope of the claim, so long as an "adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner." *Id.*

Patent Owner argues objective indicia of non-obviousness in the form of unexpected results, long-felt need, and commercial success. Prelim. Resp. 53–59. We are not persuaded, based on the current record, for the reasons that follow.

a. Unexpected Results and Long-Felt Need

A showing of nexus involves establishing that novel elements in the claim, not prior-art elements, account for the objective evidence put forward to show nonobviousness. *In re Kao*, 639 F.3d at 1068. Patent Owner argues that treatment of rheumatoid arthritis in patients who did not respond to anti-

TNFα therapy is supported by evidence of unexpected results and long-felt need. Prelim. Resp. 54–57. As discussed above in Sections II.C.2 and II.C.3, however, the treatment of rheumatoid arthritis in patients who did not respond to anti-TNFα therapy was known. *See e.g.*, Ex. 1008 (disclosing "a clinical trial using rituximab alone for the treatment of erosive RA in patients that have previously failed [treatment with an anti-TNFα antibody."). Patent Owner does not otherwise identified what novel elements in the claims anchor its objective evidence.

Based on the information presented at this stage of the proceeding, we are not persuaded that Patent Owner has shown sufficiently the existence of secondary considerations.

b. Commercial Success

Patent Owner asserts that the claimed methods have led to significant commercial success, based on worldwide sales of rituximab. Prelim. Resp. 58–59. (citing, e.g., Ex. 2013,[2] 47). The overall sales, however, are described as being attributable to the use of rituximab in oncology, e.g., to treat non-Hodgkin's lymphoma, as well as to its use in immunology. *See, e.g.*, Ex. 2013, 47 ("It remains difficult to precisely determine the sales split between Rituxan use in oncology and immunology settings."). As such, Patent Owner has failed, on the current record, to establish sufficient nexus between the commercial success of the product and any element recited in the claims.

[2] US Securities and Exchange Commission Form 10-K (2008).

5. Obviousness of Claim 6 Over the Combination of Edwards and Curd or Genentech Press Release and Curd

Claim 6 depends from claim 1 and further requires the treatment with methotrexate and a corticosteroid regimen, and specifically, a regimen of methylprednisolone and prednisone. Petitioner contends that claim 6 of the '838 patent would have been obvious over the combination of Edwards and Curd or Genentech Press Release and Curd. Pet. 56.

As discussed above, both Edward and Genentech Press Release fail to either expressly or inherently disclose the claim element "in a human patient who experiences an inadequate response to a TNFα-inhibitor." In its Petition, Petitioner fails to adequately explain how Curd cures this deficiency of Edwards and Genentech Press Release. Rather, Curd is relied on for (i) its disclosure of the intravenous administration of more than one doses of rituximab in the treatment of rheumatoid arthritis (*id.* at 25–26, 41–42), or (ii) its disclosure of combination therapies for rheumatoid arthritis (*id.* at 26, 31, 51–53). Accordingly, we are not persuaded that the combination of Edwards and Curd or the combination of Genentech Press Release and Curd disclose each element of claim 6.

Upon review of the information presented in the Petition and Preliminary Response, we have determined that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claim 6 of the '838 patent would have been obvious over the combination of Edwards and Curd or Genentech Press Release and Curd.

6. Obviousness of Claim 6 Over Curd

Petitioner contends that claim 6 of the '838 patent would have been obvious over Curd alone. In its Petition, however, Petitioner fails to adequately explain how Curd discloses each element of claim 6. In particular, Petitioner fails to identify where Curd discloses treating a human patient who experiences an inadequate response to a TNFα-inhibitor as required by claim 6. Accordingly, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing that claim 6 of the '838 patent would have been obvious over Curd.

7. Petitioner's Remaining Proposed Obviousness Grounds for Claims 1–14

Petitioner provides a table listing additional proposed obviousness grounds for claims 1–14. Pet. 55–57. Having reviewed the other grounds of unpatentability involving claims 1–14 asserted by Petitioner under 35 U.S.C. § 103 in the Petition, we exercise our discretion and decline to institute on the other grounds in the Petition in light of the determination that there is a reasonable likelihood that the challenged claims 1–14 are unpatentable based on the grounds of unpatentability for which we already institute an *inter partes* review. *See* 37 C.F.R. § 42.108(a); 35 U.S.C. § 325(d).

III. ORDER

For the reasons given, it is

ORDERED that the Petition is granted with regard to the following asserted grounds:

(i) Claims 1–5 and 7–14 of the '838 patent under 35 U.S.C. § 103(a) as obvious over the combination of Edwards and Tuscano; and

(ii) Claim 6 of the '838 patent under 35 U.S.C. § 103(a) as obvious over the combination of Curd, De Vita, and Edwards IV.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '838 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial is limited to the grounds listed in the Order. No other grounds are authorized.

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