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Paper 14
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01923
Patent 7,976,838 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Pfizer, Inc. ("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."). Pursuant to our authorization (Paper 11), Petitioner filed a Reply to Patent Owner's Preliminary Response addressing Patent Owner's arguments regarding discretionary denial under 35 U.S.C. § 314(a). Paper 12 ("Reply").

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

Previously, the'838 patent was challenged in IPR2015-00417 by petitioners Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Boehringer"). *Inter partes* review was instituted for claims 1–14. IPR2015-00417, Paper 11. Thereafter, the case was terminated upon a request by Boehringer. IPR2015-00417, Paper 18.

Prior to termination in IPR2015-00417, Celltrion, Inc. ("Celltrion") filed a petition challenging the '838 patent in IPR2015-01733 and a motion for joinder with IPR2015-00417. IPR2015-01733, Papers 2, 3. Subsequently, the Celltrion petition was dismissed without prejudice upon a request by Celltrion. IPR2015-01733, Paper 12.

Celltrion later filed a petition challenging the ’838 patent in IPR2016-01667. That petition was subsequently denied. IPR2016-01667, Paper 15.

Patent Owner informs us of the following litigation involving the ’838 patent: *Genentech, Inc. v. Sandoz, Inc*., 2:17-cv-13507 (D.N.J. 2017). Paper 7, 2. Patent Owner further directs our attention to two additional petitions recently filed by another Petitioner, Sandoz, Inc. (“Sandoz”). Prelim. Resp. 25 (citing *Sandoz, Inc. v. Genentech, Inc*., IPR2017-02036, Paper 1, 5 (Aug. 31, 2017); *Sandoz, Inc. v. Genentech, Inc*., IPR2017-02042, Paper 1, 6 (Aug. 31, 2017)).

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 tumor necrosis factor α (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.

The Specification describes treating patients who have experienced an inadequate response to a TNFα-inhibitor. *Id*. at 6:64−7:12. The Specification 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 5:25–29.

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

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. Asserted Grounds

Petitioner challenges claims 1–14 of the '838 patent on the following grounds. Pet. 6–7.

Ground	Reference[s]	Basis	Challenged Claims
1	Edwards 2002,[1] Takemura,[2] Klimiuk,[3] and Ulfgren[4]	§ 103	1–5, 7–14

[1] Ex. 1003, JCW Edwards 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) ("Edwards 2002").

[2] Ex. 1005, Takemura et al., *T Cell Activation in Rheumatoid Synovium is B Cell Dependent*, 167 J. IMMUNOLOGY 4710–4718 (2001) ("Takemura").

[3] Ex. 1006, Klimiuk et al., "Tissue Cytokine Patterns Distinguish Variants of Rheumatoid Synovitis," 151(5) AM. J. PATHOLOGY 1311–1319 (1997) ("Klimiuk").

[4] Ex. 1007, Ulfgren et al., *Systemic Anti-Tumor Necrosis Factor α Therapy in Rheumatoid Arthritis Down-Regulates Synovial Tumor Necrosis Factor α Synthesis*, 43(11) ARTHRITIS & RHEUMATISM 2391–2396 (2000) ("Ulfgren").

Ground	Reference[s]	Basis	Challenged Claims
2	Edwards 2002, Takemura, Klimiuk, Ulfgren, and Curd[5]	§ 103	6
3	Edwards 2001,[6] Rituxan Label,[7] Takemura, Klimiuk, and Ulfgren	§ 103	1–3, 7–8
4	Edwards 2001, Rituxan Label, Takemura, Klimiuk, Ulfgren, and Curd	§ 103	4–6, 9–14

Petitioner supports its challenge with the Declaration of Elena M. Massarotti, M.D. (Ex. 1002).

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms 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.

[5] Ex. 1008, Patent Application Publication No. WO 00/67796 A1 by John G. Curd et al., published Nov. 16, 2000 ("Curd").

[6] Ex. 1004, J.C.W. Edwards & G. Cambridge, *Sustained Improvement in Rheumatoid Arthritis Following a Protocol Designed to deplete B Lymphocytes*, 40 RHEUMATOLOGY 205–11 (2001) ("Edwards 2001").

[7] Ex. 1008, Physicians' Desk Reference® (53rd ed. 1999) (excerpted), "Rituxan™ (Rituximab)" ("Rituxan Label").

2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner and Patent Owner propose constructions for certain claim terms. Pet. 26–30; Prelim. Resp. 30–38. We interpret the following terms of the challenged claims as part of our analysis. For the purposes of this Decision, 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. "an inadequate response to a TNFα-inhibitor"

The Specification expressly defines the term "inadequate response to a TNFα-inhibitor" as "an inadequate response to previous or current treatment with a TNFα-inhibitor because of toxicity and/or inadequate efficacy." Ex. 1001, 5:25−28. We determine that definition is "set forth with reasonable clarity, deliberateness, and precision," *see In re Paulsen*, 30 F.3d at 1480, so as not to require further construction. The parties do not dispute this construction. *See* Pet. 26; Prelim. Resp. 30.

B. Prior Art

Petitioner relies upon the following prior art in support of its challenges.[8]

[8] Although Tuscano and De Vita 2002 are not relied upon to form the basis for the specific patentability challenges upon which we institute trial, the parties rely upon the teachings of these references to support their respective

1. Edwards 2002 (Ex. 1003)

Edwards discloses the results of a study involving 161 patients with RA. 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 i.v. infusions of 1000mg. *Id.* In addition, all groups received a 17-day course of corticosteroids. *Id.* Edwards discloses that 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.*

2. Takemura (Ex. 1005)

Takemura discloses the results of a study where synovial tissues from RA patients were implanted in mice, which were then treated with rituximab. Ex. 1005, 2. Takemura studied patients with follicular and diffuse synovitis. Takemura discloses that "in both experimental systems, the adoptive transfer experiments in follicular and diffuse synovitis and in the B cell depletion experiments, B cells proved to be critical for the

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positions. Ex. 1002 ¶ 170; *see also*, Pet. 62–63. We, therefore, consider Tuscano and De Vita 2002 as relevant background art in our evaluation of Petitioner's patentability challenges. *See Genzyme Therapeutic Prod. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1369 (Fed. Cir. 2016) (stating that "the Board may consider a prior art reference to show the state of the art at the time of the invention); *see also, Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015) ("Art can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.").

functional activity of proinflammatory CD4 T cells." *Id.*

Takemura discloses that "[t]his study links T cell activation in rheumatoid synovitis to the presence of B cells, thus assigning a novel function to B cells in the disease process." *Id.* at 6. In particular, Takemura discloses that "elimination of B cells from the synovial tissue disrupted T cell activation and the production of proinflammatory monokines." *Id.* Takemura discloses that "the frequency of tissue-infiltrating T cells and macrophages decreased markedly, to the extent of abrogating synovial inflammation." *Id*. at 9. Takemura concludes that because "T cell activation and its downstream effects, such as production of the proinflammatory monokines, . . . [is] suppressed by depleting $CD20^+$ B cells," the "elimination of B cells [by using rituximab] could be developed into a potent immunosuppressive therapy" for RA. *Id*. at 9.

3. Klimiuk (Ex. 1006)

Klimiuk discloses that RA "synovitis is a heterogeneous entity with three distinct histologically defined phenotypes," defined as granulomatous synovitis, follicular synovitis, and diffuse synovitis. Ex. 1006, 1–2. Klimiuk discloses that the "phenotypic heterogeneity is correlated to a specific combination of T-cell- and macrophage-derived cytokines," such as IFN-γ, IL-4, IL-1β, and TNFα. *Id.* at 2. Relevant to the cytokine TNFα, Klimiuk discloses that each RA phenotype correlates to different levels of TNFα, where (1) granulomatous synovitis has high levels of TNFα; (2) follicular synovitis has intermediate levels of TNFα; and (3) diffuse synovitis has low levels of TNFα. *Id.* at 5 (Figure 3), 8. Klimiuk suggests that the correlation between phenotypic heterogeneity and cytokine levels

raises "the possibility that several pathomechanisms may cause an RA-like syndrome." *Id.* at 2.

4. Ulfgren (Ex. 1007)

Ulfgren discloses the results of a study investigating the effects of infliximab, a TNFα-inhibitor, on cytokine levels in the synovial tissue of 8 RA patients. Ex. 1007, 1. Ulfgren reports that "[s]ynovial TNFα synthesis was reduced 2 weeks after infliximab treatment." *Id.* More particularly, Ulfgren discloses that "it is noteworthy that the 4 individuals meeting the ACR50 were those with the highest levels of TNFα the image analysis methods." *Id.* at 5. Ulfgren further discloses "a highly significant correlation between baseline TNFα expression and the change in expression in response to anti-TNFα." EX1007, 5.

Ulfgren concludes that "[h]igh levels of synovial TNFα production prior to treatment may predict responsiveness to therapy." *Id.* at 1. Ulfgren further concludes that "patients with low levels of synovial TNFα production prior to treatment may be least likely to benefit from anti-TNFα therapy." *Id.* at 6.

5. Curd (Ex. 1008)

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. . . .").

6. De Vita 2002[9] (Ex. 1016)

De Vita 2002 discloses the administration of rituximab to five RA patients who had been nonresponders to other therapies. Ex. 1016, 1. Two of the five RA patients had been non-responsive to TNFα-inhibitors. *Id.* The rituximab treatment involved "4 intravenous infusions per week of 375 mg/m^2 each." *Id.* One of the patients who had not responded to TNFα therapy achieved an ACR 20 response in month +5. *Id.* 2–4. The other patient saw no response. *Id.* De Vita 2002 concludes as follows:

> Anti-CD20 therapy (a safe therapeutic option in patients with B cell lymphoma) proved clinically beneficial in 4 of 5 patients with aggressive, refractory RA, indicating that B cells were critical in sustaining chronic inflammation and disease activity in such patients. . . . Furthermore, *previous treatments targeted to T cell/synoviocyte cell-mediated immune response had proved ineffective in the patients studied herein*. Biologic evidence of anti–B cell activity was observed, i.e., B cell depletion in the peripheral blood and decrease in serum RF titer. This was accompanied by clinical and laboratory improvement in the absence of concomitant treatments that might substantially impair B cell number and function (Figure 1). Such a link between decreased RF levels and clinical response is well

[9] Ex. 1016, De Vita et al., "*Efficacy of Selective B Cell Blockade in the Treatment of Rheumatoid Arthritis: Evidence for a Pathogenic Role of B Cells*," 46(8) ARTHRITIS & RHEUMATISM 2029-2033 (2002) ("De Vita 2002").

> recognized with other drugs that are effective in RA, and may reflect the biologic relevance of B cell blockade also in the course of other treatments that do not directly target the B cells.

Id. at 4 (emphasis added).

7. Tuscano[10] (Ex. 1017)

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.

C. Asserted Grounds of Unpatentability

1. Obviousness of Claims 1–5 and 7–14 Over the Combination of Edwards 2002, Takemura, Klimiuk, and Ulfgren

Petitioner contends that claims 1–5 and 7–14 of the '838 patent are obvious over the combination of Edwards 2002, Takemura, Klimiuk, and

[10] Ex. 1017, Joseph M Tuscano, "*Successful of Infliximab-Refractory Rheumatoid Arthritis with Rituximab*," 46(12) ARTHRITIS & RHEUMATISM 3420 (2002) ("Tuscano").

Ulfgren. Pet. 36–45. In support of this assertion, Petitioner sets forth the foregoing teachings of Edwards 2002, Takemura, Klimiuk, and Ulfgren and provides a detailed analysis explaining how each claim limitation is disclosed in the combination of references. *Id.*

To begin, Petitioner contends that Edwards 2002 expressly discloses every limitation of claims 1–5 and 7–14 with the exception of treating a TNFα-inhibitor inadequate-responders ("TNFIR"). *Id.* at 36–37; Prelim. Resp. 43–47. In particular, Petitioner relies on Edwards 2002 for its disclosure that treating RA patients with two intravenous doses of 1000 mg of rituximab achieves "substantial clinical benefit in RA," with combination therapies (e.g. rituximab plus methotrexate) producing "the highest levels of ACR20, 50, and 70 responses." *Id*. (citing Ex. 1002 ¶ 87).

For the claim element requiring treating TNFIRs, Petitioner contends that a person of ordinary skill in the art would have understood, in view of Takemura, Klimiuk, and Ulfgren, that RA patients with diffuse synovitis express low levels of TNFα, and as such, would not respond adequately to a TNFα-inhibitors ("TNFi"). *Id.* at 37–40 (citing Ex. 1002 ¶¶ 88–96; Ex. 1005; Ex. 1006; Ex. 1007). Specifically, Petitioner contends the following:

> Klimiuk taught that RA patients with diffuse synovitis have low levels of TNFα; Ulfgren taught that RA patients with low levels of TNFα respond inadequately to TNFis; and Takemura taught that rituximab is nevertheless an effective treatment for RA patients with diffuse synovitis. EX1002 ¶95.

Id. at 40. Petitioner asserts further that "TNFis work by inhibiting a specific proinflammatory cytokine—TNFα—that is produced downstream from a sequence of cellular reactions starting with the 'activation' of T-cells." *Id.* at 41. Rituximab, however, "acts upstream in the sequence of cellular

reactions that causes RA by depleting the B-cells that support the presence of T-cells, thus reducing the production of all three pro-inflammatory cytokines—not just TNFα." *Id.* (citing Ex. 1005, 6; Ex. 1002 ¶¶ 96–98).

Moreover, Petitioner argues that

> there was no known relationship between a patient's TNFα levels and rituximab's effectiveness in depleting B-cells, which instead results from targeting the CD20 antigen expressed on the surface of B-cells. EX1002 ¶98. Thus, there was no reason for a POSA to expect that a patient's inadequate response to a TNFi (which was caused by low levels of TNFα) would have any impact on the effectiveness of rituximab in treating RA. *Id*. Accordingly, by virtue of the fact that the method of Edwards 2002 was known to be effective in treating RA, a POSA would have expected the method to remain equally effective in patients who experienced an inadequate response to a TNFi. *Id.*

Id. at 41–42.

Additionally, Petitioner argues that the claimed methods do not produce unexpected results or satisfy a long-felt need. *Id.* at 62–64. Here, Petitioner asserts that the treatment of rheumatoid arthritis in patients who did not respond to anti-TNFα therapy was known in the art. *Id.* at 62 (citing Ex. 1037, 25; Ex. 1017, 3); *see also,* Ex. 1002 ¶ 170 (citing Ex. 1017, 3) (noting a lack of unexpected results because "Tuscano disclosed a treatment protocol using rituximab that was clinically beneficial for a TNFi-inadequate responder in 2002").

Patent Owner responds arguing that none of Takemura, Klimiuk, or Ulfgren discuss TNFIRs or their treatment with the claimed antibodies. Prelim. Resp. 44. Patent Owner further argues that

> while Petitioner attempts to equate "diffuse synovitis" in Klimiuk and Takemura with being a TNFIR (Pet. at 39–40), Petitioner cannot reconcile Klimiuk's own description of diffuse

> synovitis (Ex. 1006 at 7) with its position that these patients represent the same hard-to-treat TNFIRs, or that a POSITA would be motivated to look to a non-conventional treatment like rituximab for these patients. Indeed, neither Klimiuk or Takemura report any clinical data showing efficacy of any drug in patients, and Petitioner's attempt to bridge this gap based on *in vitro* models of the disease cannot meet its burden as this is not how the impact of an RA drug is measured. Instead, as even Petitioner acknowledges, it is based on actual improvement seen in the patient. *See* Pet. at 9.

Prelim. Resp. 44.

Patent Owner argues also that "De Vita[2002]'s results show the assumptions underlying Petitioner's arguments are unsupported." *Id.* at 46. In particular, Patent Owner argues that, "[i]n De Vita 2002, TNFIRs saw (1) no response or (2) only a transient ACR20 response with subsequent relapse, together with worsened joint erosion. . . while other RA patients saw ACR50 and ACR70 responses." *Id.* Patent Owner argues that "contrary to Petitioner's assumption, the two populations of patients did not react in the same way to rituximab treatment." *Id.* at 46–47.

At this stage of the proceeding, we find Patent Owner's arguments unpersuasive. With regard to Klimiuk, Petitioner's reference to "hard-to-treat TNFIRs" is made in the context of patients who were hard-to-treat with TNFis. Pet. 3. This description does not conflict with Petitioner's position that a person of ordinary skill in the art would have known that TNFIRs respond poorly to TNFis due to the low level of TNFα expression in the synovial fluid. Pet. 37–42. Nor does this description conflict with Petitioner's position that a person of ordinary skill in the art would have been motivated to use rituximab for TNFIRs because rituximab works upstream of TNFα in the known disease pathology and, as such, a person of

ordinary skill in the art would have expected rituximab to be effective to treat RA patients regardless of their TNFα levels. *Id.*; Ex. 1002 ¶¶ 88–98.

With regard to De Vita 2002, this reference discloses the administration of rituximab to five RA patients who had been nonresponders to other therapies. Ex. 1016, 1. Two of the five RA patients had been non-responsive to TNFα-inhibitors. *Id.* De Vita 2002 discloses that the "anti-CD20 therapy proved clinically beneficial in 4 of 5 patients with aggressive, refractory RA." *Id.* at 4. De Vita 2002 also noted that "[a] particular sensitivity to anti-CD20 therapy among selected RA patients may be hypothesized" based on the presence of an antibody called "rheumatoid factor" ("RF"), because "responder patients were all RF positive, while the nonresponder patient was RF negative." *Id.* at 5; Pet. 62; Ex. 1002 ¶¶ 166–167. Accordingly, we are not persuaded that De Vita 2002 sufficiently discredits Petitioner's position that a person of ordinary skill in the art would have expected rituximab to be effective to treat RA patients regardless of their TNFα levels.

Based on the current record, we find Petitioner's arguments persuasive. Because we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least claim 1 of the '838 patent, we institute *inter partes* review to determine whether claims 1–5 and 7–14 of the '838 patent would have been obvious over the combination of Edwards 2002, Takemura, Klimiuk, and Ulfgren.

2. Obviousness of Claim 6 over the Combination of Edwards 2002, Takemura, Klimiuk, Ulfgren, and Curd

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 Edwards 2002, Takemura, Klimiuk, Ulfgren, and Curd. Pet. 46–47. In particular, Petitioner argues that "[a]lthough Edwards 2002 did not specifically disclose which corticosteroids were administered to patients, both methylprednisolone and prednisone were commonly used corticosteroids, and the prior art taught that they could be combined with rituximab." *Id.* (citing Ex. 1002 ¶¶ 112–115). Petitioner further relies on Curd's disclosure of treating RA patients with rituximab and the use of "steroids such as glucocorticosteroids, e.g., prednisone, methylprednisolone, and dexamethasone." *Id.* (citing Ex. 1008, 8:28–29).

In its Preliminary Response, Patent Owner does not specifically address the merits of Petitioner's Ground 2.

Based on the current record, we conclude that Petitioner has presented sufficient information to show 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 2002, Takemura, Klimiuk, Ulfgren, and Curd.

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

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).

D. Patent Owner's Discretionary Denial Arguments

1. Discretionary Denial Under § 325(d)

Institution of an *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding"). Accordingly, our rules provide that "the Board may authorize the review to proceed" or "deny some or all grounds for unpatentability for some or all of the challenged claims." 37 C.F.R. § 42.108(a), (b). Our discretionary determination of whether to institute review is guided, in part, by 35 U.S.C. § 325(d), which states, in relevant part:

> (d) MULTIPLE PROCEEDINGS -- . . . In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

35 U.S.C. § 325(d).

Our discretion under § 325(d) involves a balance amongstseveral competing interests. *See Neil Ziegman, N.P.Z., Inc. v. Stephens*, Case IPR2015-01860, slip op. at 12–13 (PTAB Feb. 24, 2016) (Paper 11) ("While petitioners may have sound reasons for raising art or arguments similar to those previously considered by the Office, the Board weighs petitioners' desires to be heard against the interests of patent owners, who seek to avoid harassment and enjoy quiet title to their rights.") (citing H. Rep. No. 112-98, pt. 1, at 48 (2011)). "On the one hand, there are the interests in conserving the resources of the Office and granting patent owners repose on issues and

prior art that have been considered previously." *Fox Factory, Inc. v. SRAM, LLC*, Case IPR2016-01876, slip op. 7 (PTAB Apr. 3, 2017) (Paper 8). "On the other hand, there are the interests of giving petitioners the opportunity to be heard and correcting any errors by the Office in allowing a patent—in the case of an *inter partes* review—over prior art patents and printed publications." *Id*.; *see also Cultec, Inc. v. Stormtech LLC*, Case IPR2017-00777 (PTAB Aug. 22, 2017) (Paper 7) (denying institution under § 325(d) where reference was applied throughout prosecution).

a. Petitioner's Grounds 1 and 2

Patent Owner requests that we deny institution of trial under 35 U.S.C. §325(d) because "the Petition relies on substantially the same art and arguments previously presented in *both* prosecution and prior IPRs (IPR2015-00417 by Boehringer; IPR2015-01733 and IPR2016-01667 by Celltrion)." Prelim. Resp. 10.

For the reasons set forth below, we decline to exercise our discretion to deny institution with respect to Petitioner's Grounds 1 and 2 under § 325(d).

(1) Art and Arguments Presented in Prosecution

Relevant to Petitioner's Grounds 1 and 2, Patent Owner argues that Edwards 2002 is identified in the '838 patent in a paragraph identifying "[p]ublications concerning therapy with Rituximab" (Ex. 1001 3:33–57), was cited by the Examiner in an Information Disclosure Statement during prosecution (Ex. 2007, 394), and "[a]t no point did the Examiner reject any Challenged Claim in light of Edwards 2002, alone or in combination with other cited art." Prelim. Resp. 14.

Patent Owner acknowledges that none of Takemura, Klimiuk, and Ulfgren were considered by the Examiner during prosecution, but argues that Petitioner's reliance on these references "offers nothing new or better than arguments already considered and rejected during prosecution." *Id.* at 15. In particular, Patent Owner contends that

> During prosecution, the pending claims were . . . initially rejected under 35 U.S.C. § 102 as anticipated by De Vita 2002 (Ex. 2007 at 383–384)—a more pertinent reference than Petitioner's references, as detailed below. The Examiner found De Vita 2002 taught methods of treating RA using rituximab in patients who did not respond to TNFα-inhibitor therapy. *Id*. at 384. But in overcoming the rejection, the patentee noted that De Vita *failed to disclose* both the *claimed dosing regimen* of two doses of 1000 mg (instead using four doses of 375 mg/m^2) as well as the claimed clinical responses of ACR50, ACR70, and no erosive progression. *Id*. at 406–407. . . .
>
> Given that art disclosing the actual *in vivo* treatment of TNFIRs was before the Examiner, Petitioner's substitution of other references merely alleged to imply that such treatment would be *possible* certainly offers nothing new or better than arguments already considered and rejected during prosecution

Id. Patent Owner also notes that the pending claims were initially found obvious in light of Edwards 2001, Jenkins (Ex. 2003), and Goldenberg (Ex. 2001), but that the Examiner withdrew the rejection after the patentee "distinguished Edwards 2001 based on its use of four rituximab doses of 300 mg, 600 mg, 600 mg and 600 mg, not the two claimed doses of 1000 mg, explaining that the claimed dosing regimen was not merely optimization." *Id.* at 14–15.

In contrast to the Examiner's rejections discussed above, Petitioner's arguments supporting Grounds 1 and 2 rely-in-part on Edwards 2002. *See*

Pet. 36–47. Unlike the art relied upon by the Examiner, Edwards 2002 discloses the claimed two intravenous doses of 1000 mg antibody. Ex. 1003. While Edwards 2002 is listed on an Information Disclosure Statement and referenced by the '838 patent, the Examiner made no reference at all to the content of Edwards 2002, and specifically its disclosure of the recited dose, during examination of the '828 Patent.

More significantly, Takemura, Klimiuk, and Ulfgren are relied upon by Petitioner as evidence of rituximab's distinct mechanism of action to support its argument that a person of ordinary skill in the art would have understood that Edwards 2002's method would have been effective in RA patients with different types of synovitis in a manner that was independent of their response to TNF-inhibitors. *See* Pet. 40–42. We do not understand this argument to have been before the Examiner.

Petitioner's arguments with respect to Edwards 2002, Takemura, Klimiuk, and Ulfgren, therefore, differ substantially from arguments considered or positions taken by the Examiner during prosecution. Petitioner also relies on the testimony and analysis of Dr. Massarotti as evidence of unpatentability not available during prosecution. Ex. 1002. Given the limited discussion of Edwards 2002 in the intrinsic record, and in light of Petitioner's new arguments and evidence, we are not persuaded by Patent Owner's arguments that the Petition relies on substantially the same art and arguments previously presented in prosecution.

(2) Art and Arguments Presented in Prior IPRs

Patent Owner asserts that, in IPR2016-01667, Petitioner Celltrion unsuccessfully asserted obviousness in view of (1) the combination of

Edwards 2002 and Tuscano, and (2) the combination of De Vita 2001[11], Curd, and Goldenberg[12]. Prelim. Resp. 18 (citing IPR2016-01667, Paper 15, 10–18). Patent Owner contends that "Petitioner's Ground[s 1 and 2] relies on the same teachings in Edwards 2002 and Curd that the Board acknowledged and rejected in [IPR2016-01667]." Prelim. Resp. 19. Patent Owner further contends that "Petitioner makes substantially the same arguments here, removing art allegedly disclosing the actual treatment of RA patients with rituximab (*i.e.*, Tuscano, De Vita 2001, and Goldenberg) and replacing it with art that does not (Takemura[,] Klimiuk, and Ulfgren).

We have considered Patent Owner's contentions, but do not discern that the Petition presents substantially the same prior art or arguments previously considered by the Office. For example, as discussed above, Takemura, Klimiuk, and Ulfgren are relied upon by Petitioner to support new arguments—that is, a person of ordinary skill in the art would have understood that the effectiveness of rituximab, which acts upstream and independently of TNFα expression levels, would not be affected by TNFα expression levels. *See* Pet. 40–42. Furthermore, Petitioner does not rely on Tuscano to support its obviousness rationale, as was the case in IPR2016-01667. Rather, Petitioner and its expert rely on Tuscano to support an argument for lack of unexpected results, because treatment of rheumatoid arthritis in patients who did not respond to anti-TNFα therapy was previously shown to be successful. Pet. 62; Ex. 1002 ¶ 170. Given that

[11] Not of record.

[12] Ex. 2001, Patent Application Publication No. WO 00/74718 A1 by David M. Goldenberg et al., published Dec. 14, 2000 ("Goldenberg").

Petitioner's Ground 1 and 2 presents both new arguments and evidence, we are not persuaded by Patent Owner's arguments that the Petition relies on substantially the same art and arguments previously presented in prior IPRs.

b. Petitioner's Grounds 3 and 4

Because we have already exercised our discretion and declined to institute on Petitioner's Grounds 3 and 4 (Section II.C.3, above), we need not reach Patent Owner's arguments seeking discretionary denial under 35 U.S.C. § 325(d) regarding these Grounds.

2. Discretionary Denial Under § 314(a)

Alternatively, Patent Owner requests that we deny institution of trial under 35 U.S.C. § 314(a), pursuant to the doctrine of *General Plastic Industries Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential), in view of other previously and concurrently filed petitions involving the'838 patent, identified in Section I.A hereinabove. Prelim. Resp. 22–30. Petitioner asks that we decline to expand *General Plastic* to challenges filed by a different petitioner. *See* Reply 1–5.

In *General Plastic*, the Board identified seven nonexclusive factors that bear on the issue of whether the Board should invoke its discretion to deny institution of an *inter partes* review, based on a follow-on petition on the same patent, under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a):

1. Whether the same petitioner previously filed a petition directed to the same claims of the same patent;
2. Whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;

3. Whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;
4. The length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
5. Whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;
6. The finite resources of the Board; and
7. The requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic, slip. op. at 15–16 (citing *NVIDIA Corp. v. Samsung Elec.* Co., IPR2016-00134, slip op. 6–7 (PTAB May 4, 2016) (Paper 9)). In applying these factors, we consider not only the congressional intent that *inter partes* review proceedings provide an effective and efficient alternative to district court litigation, but also the potential for abuse of the review process through repeated attacks by the *same petitioner with respect to the same patent*. *See Gen. Plastic*, slip. op. at 18n.1 (citing H.R. Rep. No. 112-98, pt. 1, at 40 (2011) ("Allowing similar, serial challenges to the same patent, by the same petitioner, risks harassment of patent owners and frustration of Congress's intent in enacting the Leahy-Smith America Invents Act").

In this case, Patent Owner acknowledges that Petitioner is not a petitioner on any previously or concurrently filed petitions involving the'838 patent. *Id.* at 25. Patent Owner further acknowledges that *General Plastic* involved follow-on petitions by the same petitioner. *Id.* at 24–25.

Nonetheless, Patent Owner asks that we expand *General Plastic* to a new petitioner because, according to Patent Owner, the Petition here is similar to previously-filed petitions involving the'838 patent. *Id.* at 26.

Petitioner argues that its

> Petition, unlike the prior petitions, focuses on the pathology of RA and rituximab's distinct mechanism of action, rebutting Patent Owner's assertions during prosecution that these RA patients were "hard to treat." E.g., EX2007, 413. The Petition cites prior art that the Board and Examiner have not considered and relies on experts who have not testified about the '838 patent.

Reply 3.

Upon considering the respective positions of the parties, we decline to expand *General Plastic* to the facts of this case and determine that it is more appropriate to limit our analysis for discretionary denial of *inter partes* review for a new petitioner to § 325(d). *See* Section II.D.1.

III. CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of at least one challenged claim.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim.

IV. ORDER

For the reasons given, it is

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

Claims 1–5 and 7–14 of the ’838 patent under 35 U.S.C. § 103(a) as obvious over the combination of Edwards 2002, Takemura, Klimiuk, and Ulfgren; and

Claim 6 of the ’838 patent under 35 U.S.C. § 103(a) as obvious over the combination of Edwards 2002, Takemura, Klimiuk, Ulfgren, and Curd.

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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