

BOARD AND PARTIES ONLY

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*.

FINAL WRITTEN DECISION
Claims 1–14 Not Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

ORDERS

Dismissing Petitioner's Motion to Exclude (Paper 81)
37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Exclude (Paper 82)
37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Seal (Papers 63, 84, 97)
without Prejudice
37 C.F.R. § 42.55

Granting Patent Owner's Motion to Seal (Paper 64)
37 C.F.R. § 42.55

Denying Petitioner's Motion to Seal (Paper 71)
without Prejudice to Patent Owner
37 C.F.R. § 42.55

Modifying Previous Order Granting Patent Owner's
Motion to Seal (Paper 61)
37 C.F.R. § 42.55

I. INTRODUCTION

This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has failed to establish by a preponderance of the evidence that claims 1–14 of U.S. Patent No. 7,976,838 B2 (Ex. 1001; “the ’838 patent”) are unpatentable.

A. Procedural History

Pfizer, Inc. (“Petitioner”) filed a Petition (Paper 2; “Pet.”) to institute an *inter partes* review of claims 1–14 of the ’838 patent. Genentech, Inc.

(“Patent Owner” or “Genentech”) filed a Patent Owner Preliminary Response. Paper 8 (“Prelim. Resp.”).

On April 4, 2018, we instituted an *inter partes* review of claims 1–14 of the ’838 patent on two of four grounds of unpatentability set forth in the Petition. Paper 14 (“Decision on Institution” or “Dec.”). On May 4, 2018, pursuant to *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348 (2018), we modified our Decision on Institution to include review of all challenged claims and all grounds presented in the Petition. Paper 21.

Subsequently, Patent Owner filed a Patent Owner Response (Paper 44; “PO Resp.”), Petitioner filed a Reply (Paper 69; “Reply”), and Patent Owner filed a Sur-Reply (Paper 85; “Sur-Reply”).

Petitioner supports its challenge with the Declarations of Elena M. Massarotti, M.D. (Ex. 1002; Ex. 1067), Scott Bennett, Ph.D. (Ex. 1034), Michael L. Grossbard, M.D. (Ex. 1041), and Jonathan Charles Wright Edwards (Ex. 1059).

Patent Owner relies on the Declarations of Robert Ferraro (Ex. 2078), Katherine Nolan-Stevaux (Ex. 2079), Mark C. Benyunes, M.D.¹ (Ex. 2080), Eva Hessey (Ex. 2081), Stacie Knight (Ex. 2082), Stephanie Mendelsohn (Ex. 2083), Joanne Quan, M.D. (Ex. 2084), Urs Schleuniger (Ex. 2085), Tim Shaw (Ex. 2086), Randall Stevens, M.D.² (Ex. 2087), and Gregg J. Silverman, M.D. (Ex. 2094).

¹ The ’838 patent identifies Dr. Benyunes as an inventor. Ex. 1001.

² Dr. Stevens is named as a co-inventor for the ’838 patent via a certificate of correction. Ex. 2007, 533–37.

Oral argument was conducted on January 17, 2019. A transcript is entered as Paper 105 (“Tr.”).

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 (“TNF α ”) 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 ’838 patent identifies the antibody rituximab³ as “a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen.” *Id.* at 2:32–34.

The ’838 patent describes treating patients who have experienced an inadequate response to a TNF α -inhibitor. *Id.* at 6:64–7:12. The ’838 patent expressly defines the term “inadequate response to a TNF α -inhibitor” as follows:

[A]n inadequate response to previous or current treatment with a TNF α -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.

³ Rituximab was commercialized as Rituxan in the United States and as MabThera outside the United States. Ex. 2085 ¶ 5.

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 TNF α -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 TNF α -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 TNF α -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 TNF α -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 TNF α -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 Prior Art

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”).

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”).

Ex. 1009, Physicians’ Desk Reference® (53d ed. 1999) (excerpted), “Rituxan™ (Rituximab)” (“Rituxan Label”).

Ex. 1005, Seisuke Takemura et al., *T Cell Activation in Rheumatoid Synovium is B Cell Dependent*, 167 J. IMMUNOLOGY 4710–4718 (2001) (“Takemura”).

Ex. 1006, Piotr A. Klimiuk et al., *Tissue Cytokine Patterns Distinguish Variants of Rheumatoid Synovitis*, 151(5) AM. J. PATHOLOGY 1311–1319 (1997) (“Klimiuk”).

Ex. 1007, Ann-Kristin 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”).

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

E. Asserted Grounds

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

Ground	References	Basis	Challenged Claim(s)
1	Edwards 2002, Takemura, Klimiuk, and Ulfgren	§ 103	1–5, 7–14
2	Edwards 2002, Takemura, Klimiuk, Ulfgren, and Curd	§ 103	6
3	Edwards 2001, Rituxan Label, Takemura, Klimiuk, and Ulfgren	§ 103	1–3, 7, and 8
4	Edwards 2001, Rituxan Label, Takemura, Klimiuk, Ulfgren, and Curd	§ 103	4–6, 9–14

F. Abbreviations

Throughout this Decision, we use the following abbreviations.

2x1000 mg	Two infusions of 1000 mg
ACR20	American College of Rheumatology 20% improvement criteria ⁴
ACR50	American College of Rheumatology 50% improvement criteria ⁵

⁴The patient must have an improvement of twenty percent in the signs and symptoms of rheumatoid arthritis to be considered an ACR20 responder. Ex. 2087 ¶ 47.

⁵The patient must have an improvement of fifty percent in the signs and

ACR70	American College of Rheumatology 70% improvement criteria ⁶
IND	Investigational New Drug
FDA	Food and Drug Administration
PDP	Product Development Plan
POC	Proof of Concept
RA	Rheumatoid Arthritis
TNF α	Tumor Necrosis Factor-alpha
TNFi	TNF α -inhibitor
TNFIR	TNF α -inhibitor Inadequate-Responder

II. ANALYSIS

A. Claim Interpretation

The Board interprets claims in an unexpired patent using the “broadest reasonable construction in light of the specification of the patent.” 37 C.F.R. § 42.100(b) (2017).⁷ 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. 2007). Any

symptoms of rheumatoid arthritis to be considered an ACR50 responder. Ex. 2087 ¶ 47.

⁶ The patient must have an improvement of seventy percent in the signs and symptoms of rheumatoid arthritis to be considered an ACR70 responder. Ex. 2087 ¶ 47.

⁷ A recent amendment to this rule does not apply here, because the Petition was filed before November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018).

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; PO Resp. 7–16. We interpret the following term 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. *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. “*Inadequate Response to a TNF α -Inhibitor*”

Each challenged claim requires treating a “patient who experiences an inadequate response to a TNF α -inhibitor.” The Specification expressly defines the term “inadequate response to a TNF α -inhibitor” as “an inadequate response to previous or current treatment with a TNF α -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 Paulsen*, 30 F.3d at 1480, so as not to require further construction. The parties do not dispute this construction. *See* Pet. 26; PO Resp. 7–8.

B. Petitioner’s Obviousness Challenges

1. *Summary of Asserted Prior Art*

a. Edwards 2002 (Ex. 1003)

Edwards discloses the results of a study involving 161 patients with

RA. Ex. 1003. The patients, who were receiving methotrexate treatment when the study began, 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.*

b. Edwards 2001 (Ex. 1004)

Edwards 2001 discloses the results of an open study of B-lymphocyte depletion in five RA patients “to test the hypothesis that B lymphocytes may be essential to disease perpetuation.” Ex. 1004, Abstract. Edwards 2001 concludes that the “findings are consistent with the concept that RA is critically dependent on B lymphocyte depletion and suggest that B-lymphocyte depletion may be a safe and effective therapy.” *Id.*

“The chosen B-lymphocytes protocol combined rituximab with corticosteroid and cyclophosphamide in a single 3-week course.” *Id.* at 2. The treatment protocol included the following: (i) rituximab as four i.v. infusions on days 2, 8, 15, and 22 of 300, 600, 600, and 600 mg, respectively; (ii) oral prednisolone 60 mg on days 1–22; and (iii) cyclophosphamide 750 mg as i.v. infusions on days 4 and 17. *Id.*

Edwards 2001 discloses that the results obtained suggest that the treatment protocol “may be of major benefit to subjects with RA.” *Id.* at 3.

Edwards 2001 discloses that “all patients achieved ACR50” responses and 3 patients “achieved ACR70 [responses] without introduction of further therapy.” *Id.* Edwards 2001 further discloses that

despite the small number of patients . . . similar cases treated in the same way can be expected with 95% confidence to have a minimum chance of 47.8% of achieving ARC50 6 months after B-lymphocyte depletion. If the current status of subjects is taken as the end-point and the option of repeat treatment is included, the same percentage figures can be applied to ACR70 at 18 months.

Id.

After considering several competing hypotheses regarding the mechanism of action for the treatment protocol, the authors conclude that “there remains a strong indication that B-lymphocyte depletion was a necessary component of the therapeutic action.” *Id.* at 6.

c. 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. *Id.* 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 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, . . . [are] 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.*

d. 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-1 β , and TNF α . *Id.* at 2. Relevant to the cytokine TNF α , Klimiuk discloses that each RA phenotype correlates to different levels of TNF α , where (1) granulomatous synovitis has high levels of TNF α , (2) follicular synovitis has intermediate levels of TNF α , and (3) diffuse synovitis has low levels of TNF α . *Id.* at 5 (Fig. 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.

e. Ulfgren (Ex. 1007)

Ulfgren discloses the results of a study investigating the effects of infliximab, a TNF α -inhibitor, on cytokine levels in the synovial tissue of 8

RA patients. Ex. 1007, 1. Ulfgren reports that “[s]ynovial TNF α 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 TNF α the image analysis methods.” *Id.* at 5. Ulfgren further discloses “a highly significant correlation between baseline TNF α expression and the change in expression in response to anti-TNF α .” Ex. 1007, 5.

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

f. Curd (Ex. 1008)

Curd discloses the intravenous administration of rituximab to patients with a clinical diagnosis of RA. Ex. 1008, 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 . . .”).

g. Rituxan Label (Ex. 1009)

The Rituxan Label describes Rituxan (rituximab) as a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Ex. 1009, 1070. The product is formulated for intravenous administration and is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell Non-Hodgkin's lymphoma ("NHL") *Id.* at 1070–71. The reference reports results from various clinical trials in which 375 mg/m² of Rituxan was administered intravenously weekly for four doses to patients having relapsed or refractory NHL, including relapsed or refractory LG-NHL. *Id.* at 1071.

*2. Petitioner's Obviousness Challenge of Claims 1–3 and 7–9
Relying on Edwards 2002 (Subset of Challenged Claims in
Ground 1)*

For Ground 1, Petitioner contends that claims 1–5 and 7–14 of the '838 patent would have been obvious over the combination of Edwards 2002, Takemura, Klimiuk, and Ulfgren. Pet. 36–45. Petitioner relies heavily on Edwards 2002 and its disclosure of the successful treatment of RA with 2x1000 mg of rituximab. Pet. 36–37, 46–47; Ex. 1003.

Patent Owner presents evidence of an actual reduction to practice of the invention recited in claims 1–3 and 7–9 prior to October 11, 2002, the earliest effective date of Edwards 2002. PO Resp. 16–25; Ex. 1034 ¶¶ 57, 60, Attachment 2a; Pet. 31. Without Edwards 2002, Petitioner's challenge of claims 1–3 and 7–9 in Ground 1 fails as Petitioner relies on no other reference disclosing the successful treatment of RA using the claimed dose of 2x1000 mg of rituximab. Thus, a dispositive issue before us as to

claims 1–3 and 7–9 in the context of Ground 1 is whether there was an actual reduction to practice of a method of treating RA in patients considered inadequate responders to a TNF α -inhibitor using 2x1000 mg of rituximab according to those claims.

For the reasons set forth below, we determine that the evidence of record establishes that there was an actual reduction to practice of the subject matter of claims 1–3 and 7–9 at least by September 4, 2002, which is prior to the earliest effective date of Edwards 2002, October 11, 2002. Accordingly, Edwards 2002 is not prior art to claims 1–3 and 7–9.

a. Patent Owner's Response

Patent Owner contends that the claimed method for using 2x1000 mg of rituximab for treating RA patients who are TNFIRs is the result of a joint collaboration between Patent Owner and F. Hoffmann-La Roche (“Roche”). PO Resp. 16–17; Ex. 2087 ¶ 8; Ex. 2070, 1. Patent Owner credits Dr. Stevens of Roche with the idea of using 2x1000 mg of rituximab to treat rheumatoid arthritis. PO Resp. 16–18. Dr. Benyunes of Genentech is credited with the idea of using Dr. Stevens' 2x1000 mg rituximab dosing regimen to treat TNFIRs. *Id.* at 18–24.

Patent Owner contends that “Edwards 2002 is not prior art to at least claims 1–3 and 7–9 because . . . those claims were reduced to practice by at least July 2002, and no later than September 2002,” and therefore before the publication of Edwards 2002 on October 11, 2002.⁸ PO Resp. 16, 24–25.

⁸ Edwards 2002 includes a date stamp on the title page of October 14, 2002. Dr. Bennett provides a copy of Edwards 2002 that includes a date stamp on

Specifically, Patent Owner contends that Dr. Stevens' conception of using 2x1000 mg of rituximab to treat rheumatoid arthritis is documented in a 2000 Product Development Plan ("2000 PDP"). PO Resp. 17 (citing Ex. 2087 ¶¶ 18, 21–28; Ex. 2018, 8, 14–16; Ex. 2085 ¶¶ 9–11). The 2000 PDP describes the design of a randomized Phase II, "Proof of Concept" (POC) study. Ex. 2018, 15. The 2000 PDP identifies as a "Preferred Scenario" a four-arm trial involving active RA patients categorized as methotrexate partial responders. Ex. 2018, 15; Ex. 2087 ¶¶ 15–25. Patients in the first arm would receive methotrexate plus placebo, and patients in the other three arms would receive 2x1000 mg of rituximab either as monotherapy, or in combination with methotrexate or cyclophosphamide. Ex. 2018, 15; Ex. 2087 ¶¶ 15–25.

Thereafter, the Phase II/POC study was conducted and the interim results of the study were reported in May 2002. Ex. 2087 ¶¶ 30, 38, 44–46. Subsequently, the interim results were analyzed separately by Dr. Quan, working under the direction of Dr. Benyunes, to determine whether the 2x1000 mg rituximab dosing regimen was efficacious in treating TNFIRs. Ex. 2084 ¶¶ 5, 11–15. Dr. Quan's email dated July 2, 2002, provides a summary of the response rate of TNFIRs and states that the "limited data do support efficacy of Rituxan in the anti-TNF failure population." Ex. 2067.⁹

the title page indicating that the document was processed at the University of Illinois at Chicago Library on 11 October 2002.

⁹ Ex. 2067, Email from Dr. Joanne Quan regarding Update on Phase 2 RA/Interim Data – July 2, 2002; *see also id.* ("14 of the 122 subjects in the interim data set had previous treatment with etanercept or infliximab. Of these 14 patients, 3 were randomized to MTX, and the remaining 11 to

On September 4, 2002, substantially the same results reporting the successful treatment of TNFIRs with the 2x1000mg dosing regimen were submitted to the FDA in a 2002 Pre-IND Meeting Package. *See* Ex. 2070,¹⁰ 24 (“Post-hoc analysis was conducted using data from patients who have used anti-TNF therapy during their experience with RA at any time [These data] suggest the possible positive clinical application of rituximab in a patient population who have had an inadequate response to anti-TNF therapies. The control group (MTX only) showed no response while the combined active rituximab groups showed combined positive responses of ACR20 (64%), ACR50 (36%) and ACR70 (18%).”).¹¹

b. Petitioner’s Reply

In its Reply, Petitioner first contends Patent Owner has failed to show that it is entitled to an earlier invention date primarily because that there was no joint conception of the claimed invention by the named inventors, Dr. Benyunes and Dr. Stevens. Reply 2–6; *see also* Ex. 2007, 533–37 (certificate of correction naming Dr. Stevens as a co-inventor). In particular, Petitioner contends that Patent Owner has not presented any evidence to

Rituxan arms. [A]cross all Rituxan arms, 7/11 (64%) achieved an ACR 20; 4/11 (36%) achieved an ACR 50; and 2/11 (18%) achieved an ACR 70.”).

¹⁰ Ex. 2070, Pre-IND/Pre-Phase III Meeting Package for Rituxan (Rituximab) in Rheumatoid Arthritis (Patients with Inadequate Response to TNF Inhibitors) – September 4, 2002 (“2002 Pre-IND Meeting Package”).

¹¹ Petitioner acknowledges that the data relied on by Patent Owner in “Ex. 2070 is no different from Dr. Quan’s email summary [(Ex. 2067)].” Reply, 12.

establish collaboration or direct communication between the two named inventors. *Id.* at 6. Thus, according to Petitioner, “there could not have been any engagement among the inventors to contribute to a joint conception.” *Id.* (citing *Vanderbilt Univ. v. ICOS Corp.*, 601 F.3d 1297, 1303 (Fed. Cir. 2010) (“The interplay between conception and collaboration requires that each co-inventor engage with the other co-inventors to contribute to a joint conception.”)).

Second, Petitioner contends that Patent Owner has not produced any independent evidence to corroborate Dr. Stevens’ conception of the claimed dosing regimen. *Id.* at 6–9. For example, Petitioner notes that the 2000 PDP, documenting the use of 2x1000 mg of rituximab to treat rheumatoid arthritis, does not identify Dr. Stevens as an author. *Id.* at 7 (citing Ex. 2018, 1). Petitioner also notes that the 2000 PDP and 2002 Pre-IND Meeting Package both suggest that the rationale for the dosing regimen originated from the open label study disclosed by Edwards 2001, a study in which Dr. Stevens allegedly had no active involvement. *Id.* at 8 (citing Ex. 2018, 7; Ex. 2070, 35, 19–21 (“The rationale for the dose of rituximab selected to treat RA was based upon safety and efficacy in RA patients reported in an open label trial (see section 3.2.1).”); Ex.1061, 32:23–33:10).

Third, Petitioner contends that Patent Owner’s “alleged reduction to practice on July 3, 2002 by Dr. Benyunes, see Exs. 2067; 2068, was nothing more than an email from his colleague, Dr. Quan, describing her post-hoc analysis of the summary of interim results of the [Phase II/POC] trial received from Roche.” *Id.* at 10. According to Petitioner, however, Dr. Benyunes was not involved in the design of the Phase II/POC trial and the fact that some of the patients that took part in the study turned out to be

TNFIRs was not the result of any request or direction by Dr. Benyunes. *Id.* at 10–11. Thus, according to Petitioner, the results of Roche’s Phase II/POC trial cannot inure to the benefit of Dr. Benyunes because “it was independently designed and commenced at least a year before Dr. Benyunes purportedly conceived of his clinical trial idea to target only those RA patients who had failed TNF α -inhibitors.” *Id.* at 9 (citing *Genentech, Inc. v. Chiron Corp.*, 220 F.3d 1345, 1354 (Fed. Cir. 2000) (for inurement, inventor must have submitted the embodiment for testing for the intended purpose of the invention)).

Fourth, Petitioner contends that the post-hoc realization that some subjects in Roche’s Phase II/POC trial had previously been treated with TNF α -inhibitors cannot inure to the benefit of Dr. Stevens because “[t]esting Dr. Benyunes’ idea was not the intended purpose of Roche’s [Phase II/POC] trial, and no one at Genentech or Roche even knew that the patient pool included anyone previously treated with TNF α -inhibitors until after the interim results were reviewed.” *Id.* at 12–14 (citing *Genentech*, 220 F.3d at 1354 (“[B]efore a non-inventor’s recognition of the utility of the invention can inure to the benefit of the inventor First, the inventor must have conceived of the invention. Second, the inventor must have had an expectation that the embodiment tested would work for the intended purpose of the invention. Third, the inventor must have submitted the embodiment for testing for the intended purpose of the invention.”))).

c. Patent Owner’s Sur-Reply

Patent Owner responds with the following:

Petitioner does not dispute that by July 2002, and no later than September 4, 2002, the claimed invention was reduced to

practice. PO Resp., 19–24. Nor does Petitioner dispute the inventors recognized this reduction to practice. Ex. 2080, ¶¶ 58–63; Ex. 2087, ¶¶ 54–57; Ex. 2086, ¶¶ 27–33; Ex. 2084, ¶¶ 11–16. Instead, Petitioner alleges that neither Dr. Stevens nor Dr. Benyunes should be credited with the invention. In doing so, Petitioner improperly asks the Board to decide inventorship. 35 U.S.C. §311; *see also Int’l Bus. Machs. Corp. v. Intellectual Ventures II, LLC*, IPR2014-00587, Pap. 57, 5–6 (Nov. 6, 2015) (patent owner not required to address inventorship to successfully show prior reduction to practice); *Google LLC v. Space Data Corp.*, IPR2018-00944, Pap. 20, 6 (Nov. 7, 2018). Petitioner’s arguments should be rejected on this basis alone.

Sur-Reply, 23.

Patent Owner further contends that “[i]t is *not* necessary’ that joint inventors ‘should physically work on the project together. One may take a step at one time, the other an approach at different times.’” Sur-Reply, 19 (quoting *Vanderbilt*, 601 F.3d at 1302). Patent Owner also contends that joint inventors “need not have their own contemporaneous picture of the final claimed invention in order to qualify as joint inventors.” *Id.* (citing *Vanderbilt*, 601 F.3d at 1303; *Chai v. Frame Capacitance Switch*, 10 USPQ2d 1460, 1462 (BPAI 1988) (“no absolute requirement in the law for direct collaboration between joint inventors”)).

Patent Owner contends that the evidence of record shows that

- 1) Dr. Stevens and Dr. Benyunes conceived and reduced to practice the claimed methods as part of a global collaboration between their respective companies that included regular communication (PO Resp., 16–24; Ex. 1060, 37:17–38:5; Ex. 2036; Ex. 2039; Ex. 2042; Ex. 1065, 20:15–21:16);
- 2). Dr. Stevens first conceived the idea to treat RA using two 1000mg doses of rituximab (PO Resp., 16–18; Ex. 2018, 1, 8, 15, 24; Ex. 2085 ¶¶ 10–11;

Ex. 1065, 51:19–22, 2:15–22); and 3) “[i]t was only after Dr. Benyunes shared his idea that the POC protocol was amended to identify TNFIRs in the study and to separately analyze whether TNFIRs could be successfully treated with 2x1000mg rituximab” (Ex. 2057; Ex. 2065, 69–70; Ex. 2081 ¶¶ 10–12). Sur-Reply, 19–22.

d. Discussion

Demonstrating a reduction to practice of an inventive process requires showing that the inventors (1) performed a process that met all the limitations and (2) determined that the invention would work for its intended purpose.¹² *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1373 (Fed. Cir. 2008). Here, the record shows that a method for treating RA with 2x1000 mg rituximab in patients who experience an inadequate response to a TNF α -inhibitor was performed at least by September 4, 2002. The invention was made as a result of Roche’s Phase II/POC trial in which Dr. Stevens and Dr. Benyunes participated as part of a global team. PO Resp., 16–24; Ex. 1060, 37:17–38:5; Ex. 2036; Ex. 2039; Ex. 2042; Ex. 1065, 20:15–21:16. The record shows that Dr. Stevens contributed the idea of dosing RA patients with 2x1000 mg of rituximab. PO Resp., 16–18; Ex. 2018, 1, 8, 15, 24; Ex. 2085 ¶¶ 10–11; Ex. 1061, 94:10–12, 84:23–85:23; Ex. 2087 ¶¶ 14–

¹² We note that the relevant burden here is Patent Owner’s “burden of production . . . to argue or produce evidence that . . . [Edwards 2002] is not prior art because the asserted claims . . . are entitled to the benefit of a filing date (constructive or otherwise) prior to the filing date of [Edwards 2002].” *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F. 1375, 1380 (Fed. Cir. 2015).

28; *see also* Ex. 1065, 51:19–22, 52:15–22 (Dr. Schleuniger providing corroborating testimony that it was Dr. Stevens who proposed the dosing regimen); Ex. 2085 ¶¶ 9–11 (same).¹³ The record also shows that Dr. Benyunes contributed the idea of treating TNFIRs with 2x1000 mg of rituximab. Ex. 2080 ¶¶ 11, 15, 23–25; Ex. 1060, 15:17–22, 19:10–20:2, 28:15–29:5; Ex. 2084 ¶¶ 4–5, 6–9; Ex. 1063, 27:8–15; Ex. 2086 ¶¶ 13–15.

Although Patent Owner admits that Roche’s Phase II/POC trial was not conducted specifically to test the TNFIR subset of patients (PO Resp. 20), once the interim results for that trial were made available, a post-hoc analysis of the data performed by Dr. Quan showed that TNFIRs took part in the study and were successfully treated. Ex. 2067; *see also* Ex. 2084 ¶ 15 (Dr. Quan testifying that the idea for targeting patients who experience an inadequate response to a TNF α -inhibitor with rituximab came from Dr. Benyunes). That successful result was reported to the FDA in the 2002 Pre-IND Meeting Package on September 4, 2002. Ex. 2070, 1, 24. Furthermore, the record shows that the inventors understood that the invention would work for its intended purpose. Here, we credit the undisputed testimony of Dr. Stevens and Dr. Benyunes that each realized their invention successfully treated TNFIRs prior to the submission of the results to the FDA. Ex. 2087 ¶ 57; Ex. 2080 ¶ 61.¹⁴

¹³ Dr. Schleuniger was a colleague of Dr. Stevens, who lead the development and commercial team for rituximab at Roche. Ex. 1065, 11:18–21.

¹⁴ Petitioner does not dispute that Drs. Stevens and Benyunes realized their invention successfully treated TNFIRs by September 4, 2002. Reply, 1 (“What Patent Owner’s proffer does show is that the alleged inventors analyzed the Edwards 2002 pre-publication data and realized that some of

We have considered Petitioner's contentions that there was no joint collaboration and no joint conception between Dr. Benyunes or Dr. Stevens, but are not persuaded by them. Reply 4–6. That Dr. Stevens and Dr. Benyunes made sequential, non-contemporaneous contributions to the claimed subject matter does not negate findings of actual reduction to practice or joint inventorship. As explained above, Dr. Benyunes and Dr. Stevens performed a process that met all the limitations of claims 1–3 and 7–9, and determined that the invention would work for its intended purpose. The statutory requirements for joint inventorship are found in 35 U.S.C. § 116, which states, in relevant part, that “[i]nventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent.” *See also Vanderbilt*, 601 F.3d at 1302 (same). The court in *Vanderbilt* further explained that

A primary focus of section 116 has thus always been on collaboration and joint behavior. A person must contribute to the conception of the claimed invention to qualify as a joint inventor. *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1359 (Fed. Cir. 2004). Yet, each contributor need not have their own contemporaneous picture of the final claimed invention in order to qualify as joint inventors. *See Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (“One need not alone conceive of the entire invention, for this would obviate the concept of joint invention.”). Rather, “the qualitative contribution of each collaborator is the key—each inventor must

the subjects who were successfully treated with rituximab had previously used TNF α -inhibitors.”).

contribute to the joint arrival at a definite and permanent idea of the invention as it will be used in practice.” *Burroughs Wellcome Co. v. Barr Labs. Inc.*, 40 F.3d 1223, 1229 (Fed. Cir. 1994). The interplay between conception and collaboration requires that each co-inventor engage with the other co-inventors to contribute to a joint conception.

601 F.3d at 1303 (underline added). Here, the parties do not dispute that Dr. Stevens is credited¹⁵ with the idea to treat RA patients with 2x1000 mg rituximab and that Dr. Benyunes, after the submission of the 2000 PDP, later conceived treating TNFIRs. Thus, each of the inventors is credited by Patent Owner for an element of the claims and there is no dispute between the parties that Dr. Stevens and Dr. Benyunes were each aware that the 2002 Pre-IND Meeting Package submitted to the FDA on September 4, 2002, disclosed data showing successful treatment of TNFIRs. Reply 1.

Another argument raised by Petitioner against actual reduction to practice and joint inventorship appears to concern to what extent Dr. Stevens and Dr. Benyunes worked together to develop the claimed invention. Reply, 4–5. Here, we find the evidence showing that Dr. Benyunes or Dr. Stevens worked together as part of a global team during Roche’s Phase II/POC trial, which involved regular communications between team members, sufficient to establish that the inventors “work[ed] toward the same end and produc[ed] an invention by their aggregate efforts.” *Vanderbilt*, 601 F.3d at

¹⁵ We address below Petitioner’s argument suggesting that the record does not establish that Dr. Stevens conceived of the idea of dosing RA patients with 2x1000 mg rituximab, the portion of the invention for which he is given credit by Patent Owner.

1302 (quoting *Monsanto Co. v. Kamp*, 269 F. Supp. 818, 824 (D.D.C. 1967)); Ex.1060, 37:17–38:5; Ex.1065, 20:15–21:16; Ex. 2036; Sur-Reply, 19–20. Taken together, we are not persuaded by Petitioner’s arguments that there was no joint collaboration or no joint conception between Dr. Benyunes and Dr. Stevens for the purpose of determining either actual reduction to practice or joint inventorship.

In its Reply, Petitioner suggests that it was Dr. Edwards and not Dr. Stevens that should be given credit for conceiving the claimed dosage. Reply 6–9; Tr. 18:1–12. To the extent that Petitioner is arguing that either Dr. Stevens or Dr. Benyunes is not the true inventors of the claimed subject matter, however, we agree with Patent Owner that we need not resolve this issue in order to find Edwards 2002 is not prior art. Reply, 6–9; Sur-reply, 23; *Int’l Bus. Machs. Corp. v. Intellectual Ventures II, LLC*, Case IPR2014-00587, slip op. at 5–6 (PTAB Nov. 6, 2015) (Paper 57) (patent owner not required to address inventorship to show reduction to practice to antedate prior art reference). Rather, our determination is predicated on our finding that Dr. Benyunes and Dr. Stevens performed a process that met all the limitations of claims 1–3 and 7–9, and determined that the invention would work for its intended purpose.

Accordingly, in view of the above, we determine that the evidence of record establishes that there was an actual reduction to practice of the claimed subject matter at least by September 4, 2002, which is prior to the earliest effective date of Edwards 2002, October 11, 2002. Because Edwards 2002 was not publicly available until October 11, 2002, it is not prior art to claims 1–3 and 7–9. Consequently, without the benefit of Edwards 2002, Petitioner fails to establish that claims 1–3 and 7–9 of the

'838 patent would have been obvious over the combination of Edwards 2002, Takemura, Klimiuk, and Ulfgren.

3. Petitioner's Obviousness Challenge of Claims 1–14 Relying on the Combination of Takemura, Klimiuk, and Ulfgren

In each of Grounds 1–4, Petitioner combines either Edwards 2001 or 2002 with at least the combination of Takemura, Klimiuk, and Ulfgren. Petitioner relies on the combination of Takemura, Klimiuk, and Ulfgren for its contention that a person of ordinary skill in the art would have understood that RA patients expressing low levels of TNF α would not respond adequately to TNF α -inhibitors, but would respond to rituximab due to its distinct mechanism of action. See *e.g.*, Pet. 2 (“[B]ased on rituximab’s well-known mechanism of action described in Takemura—a mechanism that does not inhibit TNF α but instead targets immune cells called “Bcells”—a POSA would have reasonably expected the regimen of Edwards 2002 to treat RA in patients who respond inadequately to TNFis.”).

For the reasons below, however, we determine that Petitioner has failed to establish by a preponderance of evidence that a person of ordinary skill in the art would have had a reasonable expectation of success for successfully treating RA in TNFIRs with rituximab based on the discloses in Takemura, Klimiuk, and Ulfgren.

a. Petitioner's Contentions

(1) Grounds 1 and 2

For Ground 1, Petitioner contends that claims 1–5 and 7–14 of the '838 patent would have been obvious over the combination of Edwards 2002, Takemura, Klimiuk, and Ulfgren. Pet. 36–45. First, Petitioner

contends that Edwards 2002 expressly discloses every limitation of claims 1–5 and 7–14 with the exception of treating a TNF α -inhibitor inadequate-responder. *Id.* at 36–37. 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).

Second, 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 TNF α , and as such, would not respond adequately to a TNF α -inhibitor. *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 TNF α ; Ulfgren taught that RA patients with low levels of TNF α respond inadequately to TNFis; and Takemura taught that rituximab is nevertheless an effective treatment for RA patients with diffuse synovitis. Ex. 1002 ¶95.

Id. at 40. Petitioner asserts further that “TNFis work by inhibiting a specific proinflammatory cytokine—TNF α —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 TNF α .” *Id.* (citing Ex. 1005, 6; Ex. 1002 ¶¶ 96–98).

Moreover, Petitioner argues that

there was no known relationship between a patient's TNF α 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 TNF α) 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.*

Pet. 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-TNF α 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”).

In Ground 2, 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. Claim 6 further requires the treatment with methotrexate and a corticosteroid regimen, and specifically, a regimen of methylprednisolone and prednisone. 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).

(2) Grounds 3 and 4

For Ground 3, Petitioner relies on the combination of Edwards 2001, Rituxan Label, Takemura, Klimiuk, and Ulfgren to support its position that claims 1–3, 7, and 8 would have been obvious. Pet. 47–56. For Ground 4, Petitioner relies on the combination of Edwards 2001, Rituxan Label, Takemura, Klimiuk, Ulfgren, and Curd to support its position that claims 4–6 and 9–14 would have been obvious. *Id.* at 56–59.

In each of Grounds 3 and 4, Petitioner relies on Edwards 2001 for its disclosure of "the successful treatment of patients with severe RA by administering rituximab in combination with cyclophosphamide and prednisolone (a corticosteroid)." *Id.* at 47. Edwards discloses the treatment of five RA patients who previously failed numerous disease modifying anti-rheumatic drugs ("DMARDs") (Ex. 1002 ¶ 13), but not patients who previously failed TNF α -inhibitors. Each challenged claim, however, requires treating RA in inadequate responders to a TNF α -inhibitor, a specific patient population. For that element, Petitioner combines Edwards 2001 with the disclosures of Takemura, Klimiuk, and Ulfgren.

As in Grounds 1 and 2, 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 TNF α , and as such, would not respond adequately to a TNF α -inhibitor. Pet. 54–56. Briefly, Petitioner contends that "Takemura taught that, by depleting B-cells,

rituximab effectively treated patients with both follicular and diffuse synovitis.” *Id.* at 54 (citing Ex. 1005, 8–9). Petitioner further contends that “a POSA reading Takemura in view of Klimiuk and Ulfgren would have reasonably expected that a dosing regimen of rituximab that was effective for RA patients generally would also be effective in patients who, because they have diffuse synovitis (and therefore low levels of TNF α), respond poorly to TNFis.” *Id.* at 54 (citing Ex. 1005, 8–9; Ex. 1006, 5; Ex. 1007, 5–6; Ex. 1002 ¶¶ 143–144).

b. Discussion

Having considered the parties’ positions and evidence of record, we are persuaded for the reasons stated by Patent Owner, which we adopt, that the record does not support a finding that a person of ordinary skill in the art would have equated diffuse synovitis patients with TNFIRs, a link that is required to support Petitioner’s obviousness rationale. PO Resp. 26–29; Sur-Reply, 3–6. In particular, we determine that the evidence of record does not support a finding that Takemura teaches or suggests that diffuse synovitis is a condition that would respond adequately to B-cell depletion therapy. *See* PO Resp. 30–32 (providing a detailed synopsis of the experiments performed and discussed in Takemura). Here, we credit the un rebutted testimony of Dr. Silverman that Takemura characterized the tissues from patients with diffuse synovitis as “lacking B cells” and “B cell-poor.” Ex. 2095 ¶ 104 (citing Ex. 1005, 6–7); *see also* Ex. 2094, 110:1–4 (Dr. Massarotti confirming that Takemura does not report any B-cell depletion results for diffuse synovitis tissue samples). Specifically, Dr. Silverman testifies as follows:

A POSITA would not read Takemura as recommending the use of a B-cell targeting antibody in patients it characterized as lacking B-cells in the synovial tissue and for which Takemura itself reports no data from B-cell depletion experiments. Nor would Takemura provide a POSITA with a reasonable expectation of success in treating such patients with an anti-CD20 antibody/rituximab. Indeed, . . . when Takemura identifies the use of B-cell depleting agents in RA patients, it does so only with respect to follicular synovitis patients, “this subset with GCs” which have “tertiary lymphoid microstructures in the synovium.” Ex. 1005 at 8–9. Takemura contains no such teaching for diffuse synovitis patients.

Ex. 2095 ¶ 104. As Patent Owner points out, Petitioner fails to explain why a person of ordinary skill in the art would have expected patients with diffuse synovitis lacking B-cells to respond to B-cell depletion therapy. PO Resp., 35 (citing Ex. 2095 ¶ 104).

Neither Klimiuk nor Ulfgren cures that deficiency of Takemura. With regard to Klimiuk, Petitioner relies on Klimiuk for disclosing that diffuse synovitis patients have lower TNF α levels, thereby suggesting that such patients would not respond adequately to TNFis. Pet. 37–40. However, diffuse synovitis is also considered a “milder disease that is responsive to nonaggressive treatment” (PO Resp., 28; Ex. 1006, 7; Ex. 2095 ¶ 73–74), whereas TNFIRs are “the most significant group of [RA] patients that remained challenging to treat” (Ex. 2094, 19:18–22:5; Ex. 1002 ¶ 50; *see also* Ex. 2008, 1, 12 (“difficult-to-treat”)). Furthermore, Klimiuk characterizes diffuse synovitis patients as having less B-cell activity than follicular and granulomatous synovitis patients. PO Resp., 28–31; Ex. 2095 ¶¶ 73–77, 102; Sur-Reply, 4. In this manner, Klimiuk also does not clearly support a relationship between diffuse synovitis and TNFIRs.

Ulfgren too is relied on by the Petitioner to tie diffuse synovitis patients and lower TNF α levels. Pet. 39. Even if such a relationship could be established, we find no persuasive evidence on record linking lower TNF α levels to TNFIRs, as discussed above. Accordingly, the art relied upon by Petitioner does not support a finding that a person of ordinary skill in the art would have understood that “a dosing regimen of rituximab that was effective for RA patients generally would also be effective in patients who, because they have diffuse synovitis (and therefore low levels of TNF α), respond poorly to TNFis.” *Id.* at 54

Having considered the parties positions and evidence of record, summarized above, we conclude that Petitioner has failed to establish 1) obviousness of claims 1–5 and 7–14 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; 3) obviousness of claims 1–3, 7, and 8 over the combination of Edwards 2001, Rituxan Label, Takemura, Klimiuk, and Ulfgren; or 4) obviousness of claims 4–6 and 9–14 over the combination of Edwards 2001, Rituxan Label, Takemura, Klimiuk, Ulfgren, and Curd.

III. MOTIONS TO EXCLUDE

A. Petitioner’s Motion to Exclude

Petitioner filed a motion to exclude evidence. Paper 81. Patent Owner opposed (Paper 91) and Petitioner submitted a reply in support of its motion (Paper 95). Petitioner moves to exclude Ex. 2014 and Ex. 2314 for lack of authenticity under Federal Rule of Evidence 901 or moves to exclude as hearsay under Federal Rule of Evidence 802. Paper 81, 1–9. Because we

do not rely on either Ex. 2014 or Ex. 2314 to reach the final decision, we dismiss the Petitioner's motion to exclude as moot.

B. Patent Owner's Motion to Exclude

Patent Owner filed a motion to exclude evidence. Paper 82. Petitioner opposed (Paper 92) and Patent Owner submitted a reply in support of its motion (Paper 94). Patent Owner moves to exclude 1) the Edwards Declaration (Ex. 1059); 2) paragraphs 10, 11, 13–15, and 18 of the Massarotti Reply Declaration (Ex. 1067), which cite Ex. 1059, directly or indirectly; and 3) the portions of Petitioner's Reply (pp. 15–18) that cite Ex. 1059, directly or indirectly. Paper 82, 1. Patent Owner contends that the Edwards Declaration constitutes inadmissible hearsay and that reliance on the Edwards Declaration in the Massarotti Reply Declaration and Petitioner's Reply also constitutes inadmissible hearsay. Patent Owner further contends that Dr. Edwards was not made available for cross-examination and therefore should receive little to no weight. *Id.* at 2.

We have reviewed the testimony provided by Dr. Edwards and see no credible basis that would warrant its exclusion. Patent Owner's objections go to the weight and sufficiency of the testimony, rather than its admissibility. We are capable of discerning from the testimony, and the evidence presented, whether the witness's testimony should be entitled to any weight, either as a whole or with regard to specific issues. We weigh such testimony on an issue-by-issue basis, as appropriate. Furthermore, Patent Owner has had the opportunity to address any alleged deficiencies in the testimony of Dr. Edwards in its multiple filings throughout this proceeding, and we recognize that Dr. Edwards was not made available for

cross-examination for this proceeding. Paper 103. In this regard, Patent Owner, in its Sur-Reply, has already provided argument on the weight that the Edwards Declaration should be given in this proceeding. See Paper 85, 16–17 (“absent cross-examination it should receive little to no weight”). Thus, we deny Patent Owner’s motion seeking to exclude the testimony of Dr. Edwards in this proceeding.

IV. MOTIONS TO SEAL

In Paper 61, we granted-in-part Patent Owner’s unopposed motion to seal (Paper 43) and ordered that the Modified Stipulated Standing Protective Order set forth in Exhibit 2100 shall govern the conduct of this proceeding. Paper 61. The parties have since submitted five unopposed motions to seal: Papers 63, 64, 84, and 97 (Patent Owner), and Paper 71 (Petitioner).

The Board’s standards for granting motions to seal are discussed in *Garmin International v. Cuozzo Speed Technologies, LLC*, Case IPR2012-00001 (PTAB Mar. 14, 2013) (Paper 34). In summary, there is a strong public policy for making all information filed in *inter partes* review proceedings open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. *Garmin*, slip op. at 1–2. Under 35 U.S.C. § 316(a)(1) and 37 C.F.R. § 42.14, the default rule is that all papers filed in an *inter partes* review are open and available for access by the public; a party, however, may file a concurrent motion to seal and the information at issue is sealed pending the outcome of the motion. It is only “confidential information” that is protected from disclosure. 35 U.S.C. § 316(a)(7); see Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14,

2012). The standard for granting a motion to seal is “for good cause.” 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof in showing entitlement to the requested relief, and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

We remind the parties of the expectation that confidential information relied upon or identified in a final written decision will be made public. See Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,761. Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

A. Patent Owner’s Motions to Seal (Papers 63, 64, 84 and 97) and Modification of Previous Order on Patent Owner’s Motion to Seal (Paper 61)

1. Denying Patent Owner’s Motion to Seal (Paper 63)

Patent Owner requests that the non-redacted versions of its Patent Owner Response and non-redacted versions of Exhibits 2080–2082, 2084–2087, 2089, and 2090 remain under seal pursuant to the Stipulated Standing Protective Order (Exhibit 2100). Paper 63. As justification for its motion, Patent Owner merely states that the redacted portions contain confidential business information for which redactions have been maintained, including (1) non-public research and development information in the form of proprietary clinical and scientific data concerning rituximab, and (2) confidential information about drug development and regulatory approval

strategies, together with related internal processes and structures).” Paper 43, 2–3.

Patent Owner’s motion is denied without prejudice. Having reviewed the redacted portions of the parties’ respective demonstrative exhibits, we are not persuaded that the redactions are narrowly tailored to protect non-public business information. Patent Owner may file a renewed motion to seal subject to the conditions stated in section IV(A)(5), hereinbelow.

2. Granting Patent Owner’s Motion to Seal (Paper 64)

Patent Owner’s requests that the non-redacted version of its Patent Owner Preliminary Response and non-redacted versions of Exhibits 2080–2082, 2084–2087, 2089, and 2090 filed in IPR2018-01019, now joined to this case, remain under seal pursuant to the Stipulated Standing Protective Order (Exhibit 2100). Paper 64. We grant Patent Owner’s request. The documents that Patent Owner seeks to protect in IPR2018-01019 are the same or substantially the same as the documents that are now of record in this case. Thus, granting Patent Owner’s request would not impact our aim to strike a balance between the public’s interest in maintaining a complete and understandable file history and the parties’ interest in protecting truly sensitive information. Accordingly, we do so.

3. Denying Patent Owner’s Motion to Seal (Paper 84)

Patent Owner requests that the non-redacted version of its Patent Owner Sur-Reply remain under seal pursuant to the Stipulated Standing Protective Order. Paper 84. Patent Owner states that the redacted portions contain confidential business information and that “only the most ‘truly sensitive’ non-public confidential information has been redacted, and these

redactions are narrowly tailored to redact non-public business information of Genentech and its two development partners for rituximab.” *Id.* at 2–3.

Patent Owner’s motion is denied without prejudice. Having reviewed the redacted portions of Patent Owner’s Sur-Reply, we are not persuaded that the redactions are narrowly tailored to the most “truly sensitive” non-public confidential information. For example, several redacted portions do not appear to contain confidential information but rather merely mention the existence of confidential information. Sur-Reply, 13. Patent Owner may file a renewed motion to seal subject to the conditions stated in section IV(A)(5), hereinbelow.

4. Denying Patent Owner’s Motion to Seal (Paper 97)

Patent Owner requests that “the parties’ respective demonstrative exhibits (Patent Owner’s Exhibit 2115, and Petitioner’s Exhibit 1074) and the redacted portion of Patent Owner’s Objections to Petitioner’s Demonstratives” (Paper 102) remain under seal pursuant to the Stipulated Standing Protective Order. Paper 97. Patent Owner states that the redacted portions contain confidential business information and are “narrowly tailored to protect non-public business information of Genentech and its two development partners for rituximab.” *Id.* at 2–3

Patent Owner’s motion is denied without prejudice. Having reviewed the redacted portions of the parties’ respective demonstrative exhibits, we are not persuaded that the redactions are narrowly tailored to protect non-public business information. For example, certain redacted portions do not appear to contain confidential information, but rather merely mention the existence of confidential information. Ex. 2115, slide 51. Patent Owner

may file a renewed motion to seal subject to the conditions stated in section IV(A)(5), hereinbelow.

5. Modification of Previous Order on Patent Owner's Motion to Seal (Paper 61) and Patent Owner's Renewed Motion to Seal

To the extent we rely on any of the material sought to be protected in this Decision, we modify our previous Order (Paper 61) in accord with this Decision. For example, Patent Owner affirmatively relies upon the declaration of Urs Schleuniger (Ex. 2085) and certain other exhibits corroborating its position of joint inventorship for Dr. Stevens and Dr. Benyunes (e.g., Ex. 2036), which we address in this Decision. Accordingly, Patent Owner may, within 14 days of this Decision, renew its motion(s) to seal any portion of its Patent Owner Response, Sur-Reply, and the presently protected exhibits that are discussed in this Decision. Because the public has a heightened interest in understanding the basis for our decision on patentability, any renewed motion shall attest that the material sought to be protected is not directly or indirectly relied on in this Decision, or to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the renewed motion to seal, Patent Owner shall file narrowly redacted public versions of any exhibits sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the exhibits at issue will be made available to the public.

B. Denying Petitioner's Motion to Seal (Paper 71)

Petitioner moves to seal the non-redacted versions of Petitioner's Reply (Paper 69), the Deposition Transcript of Mark C. Benyunes, M.D., (Ex. 1060), the Deposition Transcript of Randall M. Stevens (Ex. 1061), the Deposition Transcript of Timothy Mark Shaw (Ex. 1062), the Deposition Transcript of Joanne Moon Quan (Ex. 1063), the Deposition Transcript of Eva Hessey (Ex. 1064), the Deposition Transcript of Urs Schleuniger, Ph.D. (Ex. 1065), the Deposition Transcript of Gregg J. Silverman (Ex. 1066), and the Supplemental Declaration of Elena M. Massarotti, M.D. (Ex. 1067) because they refer to Patent Owner's confidential information as noted in the Stipulated Protective Order (Ex. 2100). Paper 71, 1–2. Petitioner provides no other justification for why the redacted portions of the cited documents should be kept confidential and, thus, fails to satisfy the good cause requirement.

Petitioner's motion is denied without prejudice to Patent Owner. Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently confidential portion of Exhibits 1060 through 1067 and Paper 69. The motion shall attest that the material sought to be protected is not directly or indirectly relied on in this Decision, or to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the motion to seal, Patent Owner shall file narrowly redacted public versions of any documents sought to be sealed.

C. Redaction of the Final Written Decision

Subject to the same conditions as in sections IV(A)(5) and (B), above, the parties may, within 21 days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such proposal, at the expiration of 21 days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

V. CONCLUSION

Having considered all the evidence, Petitioner has not demonstrated by a preponderance of the evidence the unpatentability of claims 1–14 of the '838 patent. The parties' motions to exclude evidence and to seal are addressed in the following Order.

VI. ORDER

For the reasons given, it is

ORDERED that claims 1–14 of the '838 patent have not been shown to be unpatentable.

FURTHER ORDERED that Petitioner's motion to exclude Ex. 2014 and Ex. 2314 is dismissed as moot.

FURTHER ORDERED that Patent Owner's motion to exclude Ex. 1059, paragraphs 10–11, 13–15, and 18 of Ex. 1067, and certain portions of Petitioner's Reply is denied.

FURTHER ORDERED that we modify our prior order on Patent Owner's motion to seal (Paper 61) in accord with the following: Within 14 days of this Decision, Patent Owner may file/renew its motion to seal any presently redacted or otherwise confidential portions of Paper 85, Exhibits

1074, 2080–2082, 2084–2087, 2089, 2090, and 2115. Any such motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in this Decision. Petitioner may file a response within one week of Patent Owner’s motion. The Exhibits and Papers will remain designated Board and Parties Only for 21 days from the date of this Decision or until consideration of any such motion and reply.

FURTHER ORDERED that Patent Owner may file/renew its request to seal any confidential information as instructed in this Decision.

FURTHER ORDERED that Patent Owner’s motion to seal set forth in Paper 64 is granted.

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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