UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner

v.

GENENTECH, INC.,
Patent Owner

Inter Partes Review No. IPR2017-01923
Patent No. 7,976,838 B2
Issued: July 12, 2011
Filed: March 20, 2008

Title: THERAPY OF AUTOIMMUNE DISEASE IN A PATIENT WITH AN INADEQUATE RESPONSE TO A TNFα-INHIBITOR

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of claims 1–14 of U.S. Patent No. 7,976,838 ("the '838 patent"). These claims are directed to: (1) methods of treating rheumatoid arthritis ("RA") in a patient who experiences an inadequate response to a TNFα-inhibitor ("TNFi"), which inhibits the pro-inflammatory protein TNFα; (2) by administering the antibody rituximab; (3) as two intravenous doses of 1000mg; and, for some claims, (4) with methotrexate and/or corticosteroids. As shown below, the claimed methods would have been obvious to a person of ordinary skill in the art ("POSA") at any time between the filing date in April 2003 and the critical date in April 2002—for two independent reasons.

First, all claims are obvious variants of an abstract published in 2002 by Dr. Jonathan Edwards ("Edwards 2002"), which is prior art to the '838 patent under 35 U.S.C. §102(a), and disclosed every element of the claimed invention except the treatment of a patient who experiences an inadequate response to a TNFi. EX1003, 3. Although the Board recently declined to institute review of the '838 patent over Edwards 2002 because of that missing limitation, the petitioner in that proceeding did not cite certain key references relied on in this Petition—references that neither the Board nor the Examiner ever considered—teaching that rituximab's mechanism of action made it an ideal therapy for RA patients who did not respond to TNFis.

Specifically, as explained by Petitioner's declarant and expert rheumatologist, Dr. Elena Massarotti, two prior art articles by Klimiuk (EX1006) and Ulfgren (EX1007) taught that RA patients who respond poorly to TNFis have "diffuse synovitis," which is characterized by low levels of TNFα. EX1002 ¶92. A third prior art article by Takemura (EX1005) taught that rituximab—unlike TNFis—effectively treats RA patients with normal *and* diffuse synovitis. EX1002 ¶94. Thus, based on rituximab's well-known mechanism of action described in Takemura—a mechanism that does not inhibit TNFα but instead targets immune cells called "B-cells"—a POSA would have reasonably expected the regimen of Edwards 2002 to treat RA in patients who respond inadequately to TNFis. *Id.* ¶¶96–98.

Second, and independently, all claims are obvious variants of Edwards 2001—an earlier article by the same author that also taught a method of treating RA with rituximab, and is prior art to the '838 patent under 35 U.S.C. §102(b). EX1004. Although Edwards 2001 did not use the precise claimed regimen of two 1000mg doses, that regimen was an obvious modification of the rituximab dosing that was FDA-approved at the time for treating relapsed non-Hodgkin's lymphoma ("NHL")—i.e., four weekly doses totaling an average of 2400mg—in view of pharmacokinetic data published in the Rituxan™ label.

As Patent Owner acknowledged in a related proceeding, and as Petitioner's declarant and expert oncologist Dr. Michael Grossbard confirms, a POSA

optimizing the approved NHL dosing for a disease that did not involve active tumors (e.g., RA, which is not a cancer but an autoimmune disorder) "would have used less rituximab, either by decreasing the frequency (less than four doses) or the amount (mg/m^2)." EX1035, 50; EX1041 ¶25. In light of rituximab's known pharmacokinetics, a POSA would have arrived at the claimed dosing regimen with a reasonable expectation of success. EX1002 ¶¶125–127. Moreover, a POSA would have known that RA patients treated with rituximab could "optionally further be treated with … methotrexate and corticosteroids." EX1008, 25:9-16.

All challenged claims are thus unpatentable as obvious under 35 U.S.C. §103.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. §42.8(b), Petitioner states as follows:

1. ***Real parties-in-interest.*** Petitioner Pfizer, Inc. is the real party-in-interest for this Petition. No other parties exercised or could have exercised control over this petition; no other parties funded or directed this Petition. *Office Patent Trial Practice Guide*, 77 Fed. Reg. 48756, 48759–60 (Aug. 14, 2012).

2. ***Related matters.*** The '838 patent was previously challenged by another petitioner in *Boehringer Ingelheim Int'l GMBH v. Genentech, Inc.*, IPR2015-00417, which was filed on December 15, 2014. In that proceeding, the Board instituted IPR of claims 1–14 of the '838 patent. EX1037, 27–28. The *Boehringer* proceeding was

terminated on October 1, 2015, following petitioner Boehringer's Request for Adverse Judgment. IPR2015-00417, Paper 18 (Oct. 1, 2015).

A different petitioner, Celltrion, previously joined Boehringer's IPR proceeding in *Celltrion, Inc. v. Genentech, Inc.*, IPR2015-01733, which was filed on August 14, 2015. Before the Board issued a decision on Celltrion's joinder motion, Celltrion also requested the Board's permission to dismiss its petition and motion for joinder without prejudice. IPR2015-01733, Paper 10 (Oct. 1, 2015). The Board granted petitioner Celltrion's motion to dismiss without prejudice.

Celltrion challenged the '838 patent again in *Celltrion v. Biogen Inc.*, IPR2016-01667, which was filed on August 24, 2016. The Board denied institution of IPR of the challenged claims based upon the grounds asserted by Celltrion. IPR2016-01667, Paper 15 (Mar. 2, 2017). EX1039. The Board denied Celltrion's Request for Rehearing of the denial of institution on August 18, 2017.

The grounds of unpatentability asserted in IPR2015-00417, IPR2015-01733, and IPR2016-01667 are different than the grounds asserted in this Petition, which rely on prior art references (e.g., Takemura, Klimiuk, and Ulfgren) that were not relied upon by the petitioners in the *Boehringer* and *Celltrion* petitions or by the Examiner during prosecution of the '838 patent.

Petitioner here has also joined an instituted IPR of U.S. Patent No. 7,820,161 ("the '161 patent") filed by Celltrion (IPR2016-01614) after filing an identical

challenge to the ’161 patent and a motion for joinder in IPR2017-01115. Similar to the ’838 patent, the ’161 patent is directed to a method of treating rheumatoid arthritis using rituximab in combination with methotrexate.

3. ***Lead and back-up counsel.*** Petitioner identifies the following:

- *Lead counsel*: Jovial Wong (Reg. No. 60,115)
- *Back-up counsel*: Charles B. Klein*
- *Back-up counsel*: Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. ***Service information.*** Petitioner identifies the following:

- *Email address*: rituximabIPR@winston.com
- *Mailing address*: WINSTON & STRAWN LLP
  1700 K Street, NW
  Washington, DC 20006
- *Telephone number*: (202) 282-5000
- *Fax number*: (202) 282-5100

Please address all correspondence to lead counsel at the address shown above. Petitioner consents to electronic service at the above listed email address.

III. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. §42.104, Petitioner states as follows:

a. ***Grounds for standing*.** Petitioner certifies that (i) the ’838 patent is available for IPR; and (ii) Petitioner is not barred or estopped from requesting review of the ’838 patent on the grounds identified in this Petition. The required fee is paid through the Patent Review Processing System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 50-1814.

b. ***Identification of challenge*.** Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1–14 of the ’838 patent pursuant to the following statement of precise relief requested:

Ground	Claims	Basis	References
I.A	1–5, 7–14	§103	Edwards 2002 (EX1003); Takemura (EX1005); Klimiuk (EX1006); Ulfgren (EX1007)
I.B	6	§103	Edwards 2002 (EX1003); Takemura (EX1005); Klimiuk (EX1006); Ulfgren (EX1007); Curd (EX1008)
II.A	1–3, 7–8	§103	Edwards 2001 (EX1004); Rituxan™ label (EX1009); Takemura (EX1005); Klimiuk (EX1006); Ulfgren (EX1007)

II.B	4–6, 9–14	§103	Edwards 2001 (EX1004); Rituxan™ label (EX1009); Takemura (EX1005); Klimiuk (EX1006); Ulfgren (EX1007); Curd (EX1008)

IV. LEVEL OF ORDINARY SKILL IN THE ART

In light of the specification, the prosecution history, and the prior art, a POSA for purposes of the '838 patent would include a practicing rheumatologist with at least an M.D. degree and five years of experience treating patients with RA and/or researching treatments for RA, including with disease modifying anti-rheumatic drugs ("DMARDs") and biologics. EX1002 ¶13. Such a person would have access to, and seek input from, as appropriate, individuals with other specialties besides rheumatology, including an oncologist or hematologist having knowledge of or experience with the use of rituximab to treat diseases including NHL. *Id.*

V. BACKGROUND

A. The state of the art for treating RA

As of April 2003 (and also as of the critical date in April 2002), the preferred initial therapy for RA was methotrexate. However, while initially effective, methotrexate lost efficacy over time, requiring combinations with additional therapies. TNFis emerged as a potent second-line therapy, but a substantial number of patients did not respond to them. For these patients, a need for improved treatment remained.

1. Methotrexate was the preferred first-line therapy for RA, but its effectiveness over time was limited.

RA is an autoimmune disease characterized by chronic inflammation of the joints, causing "irreversible destruction of cartilage, tendons, and bones." EX1005, 2; EX1002 ¶21. As of 2002, the guidelines of the American College of Rheumatology ("ACR") taught that "[t]he ultimate goals in managing RA are to prevent or control joint damage, prevent loss of function and decrease pain." EX1010, 1.

Following a diagnosis of RA, patients were generally prescribed a DMARD. *Id.* at 2; EX1001, 4:17–22. By 2002, the most commonly used DMARD for initial therapy was methotrexate. EX1020, 3; EX1002 ¶¶22–23. "As of the year 2000, the question for rheumatologists was not whether to use methotrexate, but rather … whether there were any reasons *not* to use methotrexate." EX1015, 60 (emphasis added). "Because of its favorable efficacy and toxicity profile, low cost, and established track record in the treatment of RA, [methotrexate] ha[d] become the standard by which new DMARDs [we]re evaluated." EX1010, 10.

Even though methotrexate was successful in treating RA, "approximately one-third of patients fail to respond to oral [methotrexate] and will require additional therapy." EX1020, 2. The ACR guidelines taught that even if a DMARD was initially effective, "[r]epetitive flares, unacceptable disease activity …, or progressive joint damage" often occurred. EX1010, 3. For that reason, methotrexate

monotherapy was unlikely to remain effective for significant periods of time. *Id.* When a patient no longer responded to methotrexate, it was "standard practice" to combine it with another DMARD. EX. 1020, 3. Recognizing that individual "DMARD[s] lose their efficacy over time," there was "a growing body of data supporting the relative safety and enhanced efficacy of multiple DMARD therapy as compared with monotherapy." *Id.* at 4; EX1002 ¶24.

To evaluate when to change therapies, the ACR guidelines developed a metric to assess disease progression in terms of "ACR" scores. EX1010, 5. "ACR20" refers to a 20% improvement in a patient's "tender and swollen joint count," and in three of five factors: (i) patient's global assessment; (ii) physician's global assessment; (iii) patient's assessment of pain; (iv) degree of disability; and (v) level of acute-phase reactant. *Id.*; EX1019, 6. "ACR50" and "ACR70" refer to 50% and 70% improvement, respectively, in these same metrics. EX1010, 5. If there is no improvement or the scores continue to decline for three months, a change in DMARD therapy is warranted. *Id.* at 3; EX1002 ¶25.

2. TNFα-inhibitors were the next line of treatment once methotrexate monotherapy and similar therapies failed, but a third of patients did not adequately respond.

After initial DMARD therapy failed, many rheumatologists turned to biologic TNFis combined with methotrexate. EX1021, 10–11; EX1002 ¶26. By 2002, three TNFis were FDA-approved for RA: etanercept (ENBREL®), infliximab

(REMICADE®), and adalimumab (HUMIRA™). EX1001, 5:21–24. "The development of genetically engineered biologic agents that selectively block cytokines (anticytokine therapy) in the short term represent[ed] a major advance in the treatment of RA." EX1010, 10. "Patients with early RA and those with active RA in whom previous DMARD therapy had failed showed improvement with etanercept therapy," and "[b]oth etanercept and infliximab have been shown to be beneficial when used in combination with [methotrexate] in patients with ongoing active RA despite adequate doses of [methotrexate] alone." *Id.*

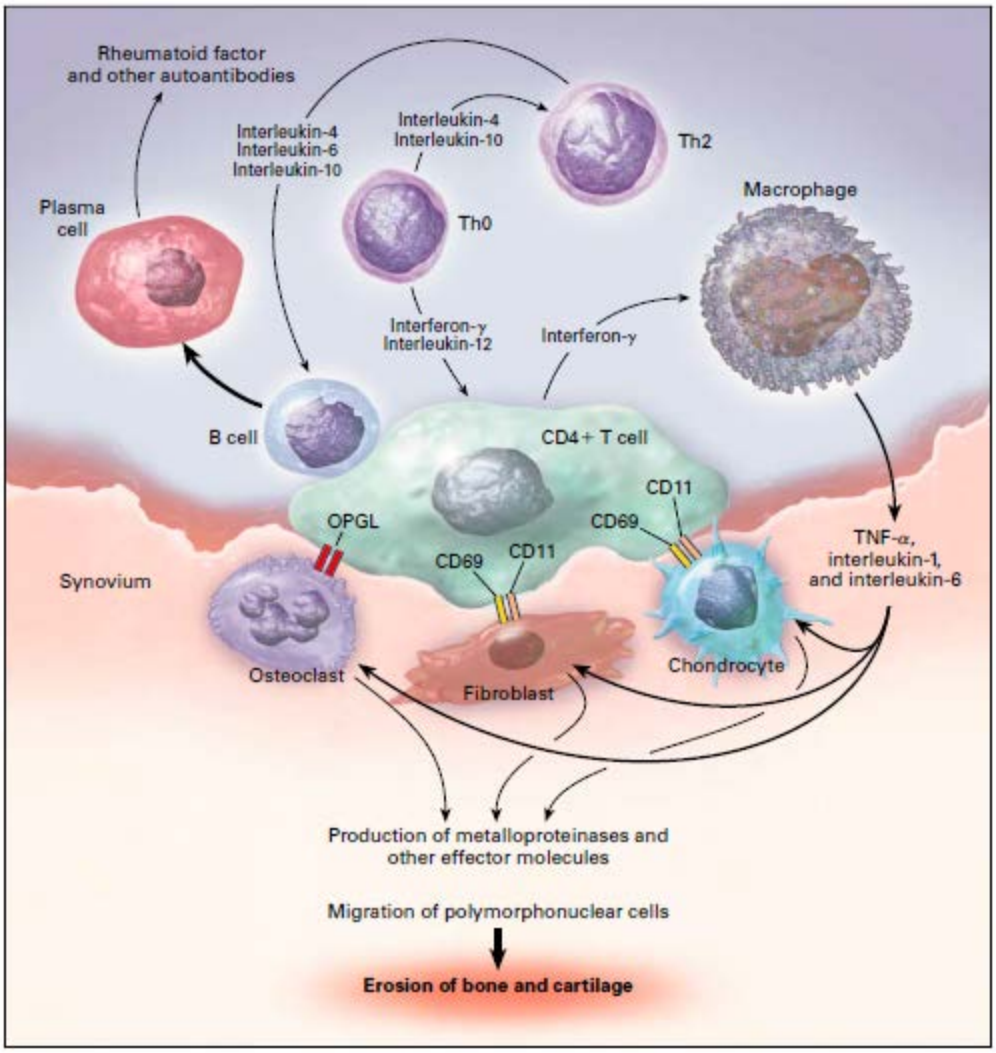
Yet TNFis also had their shortcomings. Because TNFα "plays an important role in host protection against infection and tumor genesis," TNFis should "be used with caution in patients with any susceptibility to infection or a history of tuberculosis." EX1010, 11. Some patients also had severe toxic reactions. *Id.* Moreover, "[n]ot all patients with RA respond to anti-TNFα therapy, and disease flares occur after therapy is discontinued." *Id.* One study reported that as many as 25–38% of etanercept patients and 21–42% of infliximab patients do not respond to treatment. EX1022, 1. The art thus recommended that if "improvement has not occurred within [8–12 weeks], alternative treatments or regimens should be considered." EX1028, 1; EX1015, 63; EX1002 ¶¶27–28.

3. Known differences among RA patient populations revealed why some patients did not adequately respond to TNFis—they have low levels of TNFα.

The success of DMARD combination therapies and biologics resulted from the progress rheumatologists "made in understanding basic mechanisms that underlie the development of RA and its perpetuation within joints." EX1015, 46–47; EX1011, 1. Treatments had long been designed based on the understanding of RA's pathogenesis. EX1015, 46–47. As rheumatologists gained new insights into RA's etiology, new treatments emerged. *Id.* at 47–48; EX1002 ¶29.

By 2002, rheumatologists had a working model of the immune response that causes permanent joint destruction. EX1011, 2, Figure 1. It was well understood that immune cells, cytokines[1], and other proteins in the synovium (i.e., joint tissue) were responsible for the joint damage that characterizes RA. EX1015, 32. As the diagram below illustrates, it was known that the mechanisms underlying RA involve many types of cellular responses. EX1011, 2, Figure 1; EX1002 ¶30.

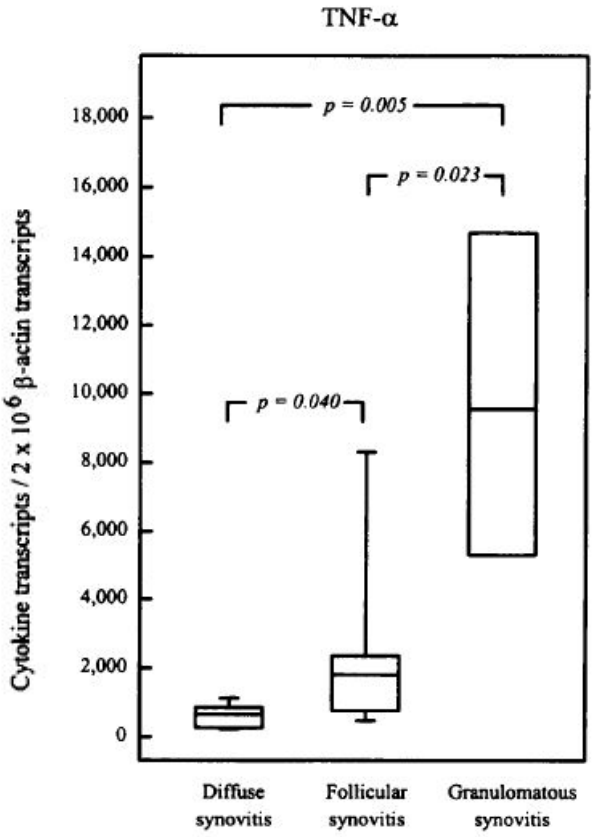
[1] A cytokine is a protein enzyme that immune cells use to communicate with one another. EX1015, 10.



The hallmark of RA is infiltration of the synovium by activated CD4+ T-cells. EX1011, 1. "Activated" T-cells "are the main orchestrator of cell-mediated immune responses" and draw other immune cells into the synovium. *Id.* These cells "release numerous cytokines"—particularly TNFα, IL-1, and IL-6—which cause inflammation. *Id.* at 3–4. This inflammation, coupled with the release of cytokines, causes the release of enzymes that erode joints, bone, and cartilage. *Id.* at 4.

While it was understood that cytokines contributed to RA, it was equally understood that not all patients have the same levels of cytokines that are involved in inflammatory reactions. EX1002 ¶¶32–37. In 2001, Klimiuk observed that "multiple mechanisms regulate the synovial inflammation and the contribution of T cells and macrophages may be different in individual patients," which "may correlate with different disease manifestations as well as outcomes." EX1006, 1.

In a study of joint tissues obtained from 21 RA patients, Klimiuk reported that "rheumatoid synovitis is a heterogeneous entity with three distinct histologically defined phenotypes." *Id.* at 2. Klimiuk classified the synovitis as either (i) *diffuse*, (ii) *follicular*, or (iii) *granulomatous*. *Id.* at 3; EX1025, 5. Each synovitis type "displayed a unique cytokine profile." EX1006, 1. In particular, each type expressed significantly different levels of TNFα: The highest were found in granulomatous synovitis; intermediate levels were found in follicular synovitis; and the lowest levels were found in diffuse synovitis. *Id.* at 5. The chart below illustrates the different TNFα levels in each type of synovitis. *Id.* at 5, Figure 3.



Klimiuk concluded "that patients display considerable differences in the organization and the functional commitment of the inflammatory infiltrates." *Id.* at 7. These variable types of synovitis "correlated with the combination and the amount of cytokines produced in the tissue," which "should be considered in the design of treatment trials and in the application of therapeutic agents in individual patients." *Id.* at 7, 8; EX1002 ¶¶43–45.

Klimiuk's findings explained why many patients did not respond to TNFis. Indeed, it was known by 2002 that TNFα levels affect a patient's ability to respond to TNFis. EX1007, 5. In 2001, Ulfgren observed "a highly significant correlation

between baseline TNFα expression and the change in expression in response to anti-TNFα." *Id.* For patients with high TNFα levels, a response to TNFis is likely. *Id.* Conversely, "patients with low levels of synovial TNFα production prior to treatment may be least likely to benefit from anti-TNFα therapy." *Id.* at 5–6. As such, "the only clear mechanism that could account for non-responsiveness has been documented by the use of synovial biopsy, in which patients with low levels of synovial TNF at the time of treatment were poor responders." EX1018, 6; EX1002 ¶¶49–51.

B. The promise of improving RA therapy with rituximab

By 2002, a recently approved biologic—rituximab—quickly became the focus of efforts to improve RA treatment for patients who responded inadequately to TNFis. Based on the biological traits of poor responders and rituximab's independent mechanism of action, rheumatologists began to adapt the approved dosing of rituximab for NHL to the particular needs of RA.

1. Rituximab, which acts by depleting B-cells instead of inhibiting TNFα, emerged as a logical therapy for patients who responded inadequately to TNFis.

The FDA approved Rituxan™—the commercial form of rituximab—in 1997 for the treatment of relapsed or refractory NHL. EX1009, 7. The Rituxan™ label taught that rituximab is an "antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes." *Id.* at 6. Rituximab thus binds to

the CD20 antigen on B-cells, enabling their destruction—including in patients who do not have cancer. EX1002 ¶66.

Rheumatologists soon became increasingly interested in using rituximab to treat RA. *Id.* ¶¶39–40. While rheumatologists had traditionally thought of RA as a T-cell and cytokine-mediated disease, researchers including Takemura showed that B-cells play a role in sustaining the presence of activated T-cells in the synovium, which trigger the release of pro-inflammatory cytokines. Thus, Takemura postulated that "B cells may be uniquely situated to stimulate proinflammatory T cells in rheumatoid synovitis." EX1005, 2.

Takemura's results supported that hypothesis. Synovial tissue samples were obtained from RA patients and implanted into mice, which were injected with rituximab. *Id.* at 2–3. After treatment, the tissues had a marked decrease in T-cells. *Id.* at 6. Takemura concluded that "T cell activation in rheumatoid synovitis [is linked] to the presence of B cells." *Id.* In other words, activated T-cells could function only when surrounded by B-cells, "but could not be triggered in tissues lacking" them. *Id.* Takemura also disclosed that "elimination of B cells from the synovial tissue disrupted T cell activation and the production of proinflammatory monokines." *Id.* When rituximab was administered, "the frequency of tissue-infiltrating T cells and macrophages decreased markedly, to the extent of abrogating

synovial inflammation. This observation supported a direct contribution of B cells in maintaining stimulation of proinflammatory T cells." *Id.* at 9.

The tissues studied in Takemura included both diffuse and follicular synovitis. *Id.* at 8. As Klimiuk had shown, these two types express significantly different levels of TNFα—follicular synovitis expresses intermediate levels of TNFα, whereas diffuse synovitis expresses particularly low levels. EX1006, 5. Nevertheless, in Takemura's study, this marked difference in TNFα levels had no effect on the depletion of RA-inducing T-cells by rituximab: "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." EX1005, 9. That is, rituximab treated RA both in tissues with normal levels of TNFα (which are responsive to TNFis) *and* in tissues that express especially *low* levels of TNFα (which are not). *Id.*; EX1002 ¶¶54–55.

Takemura confirmed that because rituximab does not target TNFα, but instead treats RA synovitis by a different mechanism of action (i.e., depleting the B-cells that support the presence of activated T-cells), rituximab's effectiveness for RA is unrelated to a patient's TNFα levels. EX1002 ¶93. Takemura concluded that because "T cell activation and its downstream effects, such as production of the proinflammatory monokines … [was] suppressed by depleting $CD20^+$ B cells," the

"elimination of B cells [by using rituximab] could be developed into a potent immunosuppressive therapy" for RA. EX1005, 9.

2. Acting on evidence of rituximab's low toxicity and ability to deplete B-cells, rheumatologists began to explore off-label uses of rituximab to treat RA in clinical studies.

Armed with the dosage recommendations and safety profile described in the Rituxan™ label, rheumatologists began to explore off-label uses of rituximab in autoimmune diseases within two years of the FDA's 1997 approval of Rituxan™. EX1002 ¶58. For example, Edwards published two articles in 1998 and 1999 recommending that rheumatologists use rituximab to treat RA. EX1013, 3–4; EX1014, 8. And in 2001, Edwards published a study demonstrating the successful treatment of severe RA with rituximab. EX1004, 2.

Each patient in Edwards 2001 had failed five DMARD monotherapy treatments. *Id.* "The chosen B-lymphocyte-depleting protocol combined rituximab with corticosteroid and cyclophosphamide in a single 3-week course." *Id.* Edwards 2001's protocol was developed based on "anecdotal evidence, from patients coincidentally receiving both low- and high-dose cytotoxic regimens that RA is about as difficult to cure as non-Hodgkin lymphoma and … that a threshold of B-lymphocyte depletion would need to be reached." *Id.*

Edwards administered four infusions of rituximab over the course of three weeks using a regimen that was similar to the rituximab dosing that was FDA-

approved at the time for NHL—i.e., four infusions of 375mg/m^2, which, based on an average body surface area of 1.6m^2, is equal to a total fixed dose of about 2400mg. EX1002 ¶60. Specifically, on days 2, 8, 15, and 22 of the treatment regimen, Edwards administered fixed doses of rituximab at 300, 600, 600, and 600mg, respectively, for a monthly total of 2100mg. EX1004, 2.

Following the Rituxan™ label's instructions, Edwards also administered prednisolone, a corticosteroid. *Id.* To mitigate "hypersensitivity reactions" to rituximab, which occur in about 80% of patients during their first infusion and 40% during subsequent infusions, the Rituxan™ label recommended co-administration of epinephrine, antihistamines, or corticosteroids. EX1009, 7. Prednisone, prednisolone, methylprednisolone, and dexamethasone were commonly used corticosteroids administered with rituximab. EX1002 ¶112 ; EX1008, 8:29.

Even though the total dose of rituximab administered in Edwards 2001 was lower than the approved dose for NHL, it proved highly effective in treating RA. EX1002 ¶¶60–62. "All patients" receiving the combination of rituximab and corticosteroids "showed rapid improvement in synovitis," including ACR50 or ACR70 responses. EX1004, 3.

Edwards 2001 explained that "the results obtained in this study suggest that the protocol used, or a modification thereof, may be of major benefit to subjects with RA." *Id.* Following a statistical analysis, Edwards 2001 predicted that "similar

cases treated in the same way can be expected with 95% confidence to have a minimum chance of 47.8% of achieving ACR50 6 months after B-lymphocyte depletion …. [T]he same percentage figures can be applied to ACR70 at 18 months." *Id.* Edwards 2001 concluded: "[T]here remains a strong indication that B-lymphocyte depletion was a necessary component of the therapeutic action." *Id.* at 6. Thus, Edwards 2001 showed that a total monthly dose of approximately 2000mg rituximab was effective to treat RA. EX1002 ¶141.

3. Rheumatologists knew how to optimize the dose of rituximab for RA based on its known pharmacokinetic profile and the everyday practical considerations of treating RA.

After the success of his 2001 study, Edwards' next task was to optimize rituximab's dosing regimen for RA so that it would be manageable in clinical practice. EX1002 ¶62. The prior art—including an international patent publication by Curd published in 2000—taught that the dosing of rituximab to treat RA could be either the same or "differ[ent] from that presently recommended for RITUXAN®" to treat NHL. EX1008, 23:28–29. By 2002, a number of practical considerations were known that narrowed the dosing of rituximab to treat RA to a limited number of possibilities. EX1002 ¶¶118–142.

First, rituximab had a known pharmacokinetic profile that informed how it should be dosed for different conditions. *Id.* ¶¶121–125. Rituximab was approved at a single "recommended" dose of 375mg/m^2 in four weekly intravenous infusions

(equal to four infusions averaging 600mg for a monthly total of 2400mg). EX1009, 8. The Rituxan™ label taught that, at this dose, rituximab leads to "a rapid and sustained depletion of circulating and tissue-based B cells." EX1009, 7. The section of the label on pharmacokinetics taught that "[t]he peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden." *Id.*

Because of the phenomenon known as "tumor sink," patients with active lymphoma (who therefore have a greater tumor burden in their bodies, because RA is not associated with tumors) required more frequent doses of rituximab. EX1035, 50 n.11; *see* EX1024, 2. It was known that the increased number of tumor cells in patients with active NHL "would sequester the rituximab and reduce its effective serum concentration." EX1035, 50 n.11.

Unlike active lymphoma, RA is not characterized by tumor bulk. EX1041 ¶25. Thus, the data in the Rituxan™ label suggested that a reduced number of infusions and/or a reduced monthly dose would be effective for treating RA. *Id.* As Patent Owner explained in a related IPR, a POSA reviewing the pharmacokinetic profile on the Rituxan™ label and seeking to develop a dosing regimen for conditions characterized by little to no tumor burden "would have used less rituximab, either by decreasing the frequency (less than four doses) or the amount (mg/m^2) given in each administration." EX1035, 50; EX1041 ¶¶18–21.

Second, the ACR guidelines recommended that rheumatologists consider, among other factors, "convenience of administration, requirements of the monitoring program, costs of the medication and monitoring (including physician visits and laboratory costs), time until expected benefit, and frequency and potential seriousness of adverse reactions." EX1010, 9. In particular, rheumatologists had to consider the "likelihood of compliance" by patients and their "own confidence in administering and monitoring the drug." *Id.* It was well known that patient noncompliance "is increased when patients … need to take the medication in multiple doses." EX1015, 29.

Conversely, a patient's adherence to a regimen could be improved if "[t]he regimen is not disruptive to normal patterns of activities." *Id.* Compliance was often improved by reducing the dosing frequency—particularly for intravenous therapies such as rituximab that required infusions lasting 4–6 hours. EX1002 ¶¶139–140; *see* EX1023, 3–4. Thus, it made sense to reduce the number of infusions required for a previously established dosing regimen. EX1002 ¶¶141–142.

Third, the ACR guidelines taught that the cost of treatment was an important factor. EX1010, 13–14. The average annual medical costs of an RA patient were approximately $8,500, and thus "ignoring financial considerations would inadequately reflect the impact on [patients of] daily treatment decisions." *Id.* This

factor was particularly important for rheumatologists prescribing biologics, which in 2002 and 2003 were generally more expensive than other therapies. EX1021, 10.

To alleviate the high cost of biologics, rheumatologists such as Kremer discouraged variable weight-based dosing, which was only approved for infliximab and was similar to the body-surface-area dosing indicated in the Rituxan™ label for NHL. *Id.* at 9–10. "Because of the differing costs for patients of different weight, it is possible that infliximab may be less cost-effective for large patients than for small patients." *Id.* at 10. To avoid wasting an expensive drug by administering only a portion of a vial based on a patient's weight, Kremer recommended fixed doses—and that "no portion of a vial be discarded." *Id.*; EX1002 ¶¶132–133.

As of 2002, rituximab was only commercially available in "100mg and 500mg of sterile, preservative-free, single-use vials." EX1009, 8. Moreover, the label instructed practitioners to "[d]iscard any unused portion left in the vial." *Id.* Thus, the most convenient way to administer half of a monthly dose of 2000mg—approximately the total monthly dose that Edwards 2001 had shown was effective to treat RA—was to avoid wasting any amount of rituximab by administering two whole vials of 500mg in one sitting totaling 1000mg. EX1002 ¶¶134–135.

C. In line with rituximab's known pharmacokinetics, Edwards 2002 confirmed that rituximab treats RA in two intravenous doses of 1000mg in combination with methotrexate.

Consistent with these known practical considerations, Edwards arrived at an optimized dose of rituximab to treat RA in Edwards 2002, which disclosed the results of a randomized, double-blinded study assessing the use of rituximab for treating RA, including in combination with methotrexate and corticosteroids. EX1003, 3. Edwards 2002 involved 161 patients divided into four treatment groups, all of which had received ≥10mg per week of methotrexate. *Id.* Group A received only continuing methotrexate as a control; Group B received rituximab monotherapy in two intravenous infusions of 1000mg; Group C received rituximab in combination with cyclophosphamide; and Group D received rituximab—again as two intravenous infusions of 1000mg—with methotrexate. *Id.*

Edwards 2002 determined that "[t]he safety profile indicates that all 3 rituximab regimens were well tolerated." *Id.* Moreover, patients receiving rituximab with either cyclophosphamide or methotrexate experienced a "substantial clinical benefit," and "the highest levels of ACR20, 50 and 70 responses." *Id.* As shown below, the highest numbers of ACR50 and ACR70 responders were in patients taking rituximab with methotrexate:

	MTX (n=30)	Rituximab (n=31)	Rituximab + CTX (n=31)	Rituximab + MTX (n=30)
ACR20	10 (33%) *na*	18 (58%) *p=0.073*	26 (84%) *p<0.001*	24 (80%) *p=0.001*
ACR50	3 (10%) *na*	10 (32%) *p 0.059*	14 (45%) *p=0.004*	15 (50%) *p=0.002*
ACR70	0 (0%) *na*	4 (13%) *ns*	5 (16%) *p=0.053*	7 (23%) *p=0.01*

Edwards' decision to administer methotrexate in combination with rituximab followed the recommendations and practices of previous rheumatologists. EX1002 ¶¶26, 71. Not only was methotrexate considered the standard DMARD for treating RA at the time—including for use in combination therapy with biologics (*supra* Part V.A)—but Curd taught that methotrexate could be combined with rituximab to treat RA. EX1008, 25:10–15 (patients given rituximab can be "optionally further treated with any one or more agents employed for treating RA … [using DMARDs] such as methotrexate and corticosteroids").

VI. THE '838 PATENT

The '838 patent has 14 claims. Claim 1 is reproduced below and is illustrative of the claimed invention:

> 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 1000mg.

The specification includes a single prophetic example describing a "therapeutically effective" dose of an anti-CD20 antibody in "[a] patient with active rheumatoid arthritis who has an inadequate response to one or more TNFα-inhibitor therapies." EX1001, 37:7–31. Patients "are treated with a therapeutically effective dose of the CD20 antibody, for instance, 1000mg i.v. on Days 1 and 15, or 375mg/m^2 i.v. weekly x 4." *Id.* at 31:29–31. These regimens are "[e]xemplary." *Id.* at 29:32–33. Following the administration of the "exemplary dosage regimens," the example hypothesizes (without reporting any data) that results "may" include certain responses: "Exploratory endpoints and analysis *may* involve: ACR(20/50/70 and ACR n) and change in [ACR] responses over Weeks 8, 12, 16, 20, 24 and beyond will be assessed using a binary or continuous repeated measures model, as appropriate … [N]o erosive progression *may* be assessed at weeks 24 and beyond." *Id.* at 32:28–35 (emphasis added).

VII. CLAIM CONSTRUCTION

A. "an inadequate response to a TNFα-inhibitor" (all claims)

For purposes of this Petition, Petitioner does not contest the Board's construction of this term in IPR2016-01667 as "an inadequate response to previous or current treatment with a TNFα-inhibitor because of toxicity and/or inadequate efficacy." EX1039, 7.

B. "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" (claims 2–7)

This term merely recites the intended result of a specific and fixed amount already recited in the claims—i.e., "two intravenous doses of 1000mg"—and is therefore non-limiting and entitled to no patentable weight.

Where, as here, a method claim requires "express dosage amounts," the recited amounts "are material claim limitations; the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). Because "[t]he steps of [administering two intravenous 1000mg doses] are performed in the same way regardless of whether or not the patient experiences a reduction in [ACR response or erosive progression]," the intended clinical result recited in the claims is "non-limiting." *Id.* at 1381.

"Such a construction is even more appropriate here … [under] the broadest reasonable interpretation consistent with the specification," which "does not describe any studies that show that [the recited clinical results were actually obtained], thus also suggesting that the claims do not incorporate such a requirement." *In re Montgomery*, 677 F.3d 1375, 1380–81 (Fed. Cir. 2012) (citation and quotation omitted). At most, the recited language indicates that "efficacy [was] inherent in carrying out the claim steps." *Id.*

Accordingly, claim 2's recitation of clinical outcomes obtained by administering a specifically recited dose is not a separate limitation of the claim.

C. "wherein" clauses reciting intended results (claims 10, 12–14)

Claims 10 and 12–14 recite the following clauses: "wherein the patient has no erosive progression at weeks 24 and beyond"; "wherein the clinical response is ACR50 response at week 24"; "wherein the clinical response is ACR70 response at week 24"; and "wherein the clinical response is no erosive progression at weeks 24 and beyond," respectively. None of these clauses is limiting.

"A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim"—such clauses "merely describe the result of arranging the components of the claims [or performing the recited steps] in the manner recited in the claims." *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed. Cir. 1993) (citation omitted); MPEP §2111.04 ("wherein" and "whereby" clauses "raise a question as to the limiting effect of the language in a claim"); *Ben Venue*, 246 F.3d at 1375.

Here, the specification makes clear that the recited responses are merely the intended result of a dosing regimen that is expressly required. EX1001, 32:28–34 ("Exploratory endpoints and analysis *may* involve: ACR(20/50/70 … over Weeks 8, 12, 16, 20, 24 and beyond …. [N]o erosive progression *may* be assessed at weeks 24 and beyond.") (emphasis added).

It is no answer for Patent Owner to invoke "the doctrine of claim differentiation to distinguish between claims [12–14]," which are identical other than the "wherein" clauses, because that "doctrine only creates a presumption that each claim in a patent has a different scope; it is not a 'hard and fast' rule of construction." *Ben Venue*, 246 F.3d at 1376. Because claims 12–14 are "limited only to the actual steps of those claims, without regard to the result of performing the claimed steps," the Board should "decline to blindly apply the doctrine [of claim differentiation] in this case to supplant other canons of claim construction that compel [the] conclusion that [these] claims [] have identical scope." *Id.*

Accordingly, the "wherein" clauses of claims 10 and 12–14 are non-limiting and are not separately material limitations.

D. "[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" (claim 11)

This preamble merely states the intended effect of the claim and is therefore non-limiting and not entitled to any patentable weight.

"Generally, the preamble does not limit the claims." *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). This presumption is overcome only if the preamble "recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

A preamble is not limiting "when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention." *Id.* at 809. That is the case here.

As with the claims discussed above, the recited method steps of claim 11—i.e., administering rituximab as two intravenous doses of 1000mg with methotrexate—must be performed the same way regardless of whether the intended result in the preamble is achieved. Thus, the preamble is not limiting. *See Ben Venue*, 246 F.3d at 1375 (holding that the preamble, "[a] method for reducing hematologic activity," was non-limiting because the steps in the body of the claim "are performed in the same way regardless whether or not the patient experiences a reduction in hematologic toxicity").

Accordingly, the preamble language of claim 11 is non-limiting and is entitled to no patentable weight.

VIII. PRIOR ART STATUS OF CITED REFERENCES

As shown below and in the Declaration of Petitioner's expert librarian, Dr. Scott Bennett (EX1034), the references Petitioner relies upon for the grounds of unpatentability in this Petition are printed publications that were publicly accessible before April 9, 2003 and/or 2002, and therefore qualify as prior art to the '838 patent under 35 U.S.C. §§ 102(a) and/or 102(b), respectively.

All of the references described below were published in journals or books that have long been cataloged or indexed in a meaningful way. EX1034 ¶¶ 41–97. Thus, each reference was sufficiently accessible to the public, and ordinarily skilled artisans, exercising reasonable diligence, would have no difficulty finding copies of it. *Id.* ¶101. Moreover, each date stamp on each of the references has the general appearance of date stamps that libraries have long affixed to periodicals, and there is no reason to believe it was affixed by anyone other than library personnel, or on any other date than the date stamped on the reference. *Id.* ¶¶ 41–97.

A. Edwards 2002 (EX1003)

Edwards 2002 is an authentic copy of an abstract from *Arthritis & Rheumatism*—a periodical first published in 1958 and held by 831 libraries worldwide. *Id.* ¶56. A date stamp from the University of Illinois at Chicago Library indicates that the journal containing Edwards 2002 was processed on October 11, 2002. *Id.* ¶57. Therefore, Edwards 2002 was available to the public before April 9, 2003 (*id.* ¶60), and is a prior art printed publication under §102(a).

In IPR2016-01667, Patent Owner attempted to remove Edwards 2002 as prior art under §102(a) by arguing that the claimed invention "was conceived and actually reduced to practice by the inventors … before the alleged October 2002 publication date of Edwards 2002." EX1038, 12. The Board, however, chose "not [to] reach Patent Owner's prior invention contentions." EX1039, 9 n.7.

As an initial matter, the ’838 patent’s “Background of the Invention” section includes Edwards 2002 in a list of prior art “[p]ublications” (EX1001, 3:33, 53–57), and “[a] statement in a patent that something is in the prior art is binding on the applicant and patentee.” *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988); *see also Intri-Plex Techs., Inc. v. Saint-Gobain Performance Plastics Rencol Ltd.*, IPR2014-00309, Paper 83 at 21 (PTAB Mar. 23, 2014) (“we have long treated a patent applicant’s admissions as prior art”).

Even apart from that admission, Patent Owner bears the burden “to prove entitlement to an earlier invention date” by producing evidence of “(1) a conception and reduction to practice before the filing date of the [’838] patent or (2) a conception before the filing date of the [’838] patent combined with diligence and reduction to practice after that date.” *Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1322–23 (Fed. Cir. 2013). While the “[t]he issue of the conception date of an invention is a legal conclusion,” it must be “based on underlying factual findings.” *Id.* at 1322.

At the institution stage, any dispute over such factual issues must “be viewed in the light most favorable to the petitioner … for purposes of deciding whether to institute an *inter partes* review.” 37 C.F.R. §42.108(c). That is especially true where, as in IPR2016-01667, a patent owner relies on declaratory testimony to support factual allegations of prior conception and/or reduction to practice. *JDS*

Uniphase Corp. v. Fiber, LLC, IPR2013-00318, Paper 12 at 14 (PTAB Dec. 6, 2013) (declining to rely on "declaration [] testimony" to swear behind a reference because "the witness [] may be subject to cross-examination," and "[t]he time for such cross-examination is after the Board institutes a trial, not beforehand").

Accordingly, at this stage of the proceeding, the Board should decline to weigh any evidence of prior invention submitted by Patent Owner and instead find a reasonable likelihood that Edwards 2002 is prior art to the '838 patent.

B. Edwards 2001 (EX1004)

Edwards 2001 is an authentic copy of an article from *Rheumatology*—a periodical first published in 1999 and held by 316 libraries worldwide. EX1034 ¶46. A date stamp from the Southern Illinois University Library indicates that the journal containing Edwards 2001 was processed on March 22, 2001. *Id.* ¶47. Therefore, Edwards 2001 was available to the public before April 9, 2002 (*id.* ¶50), and is a prior art printed publication under §102(b).

C. Takemura (EX1005)

Takemura is an authentic copy of an article from the *Journal of Immunology*—a periodical first published in 1950 and held by 871 libraries worldwide. *Id.* ¶84. A date stamp from the University of Illinois at Urbana-Champaign Library indicates that the journal containing Takemura was processed on October 20, 2001. *Id.* ¶85.

Therefore, Takemura was available to the public before April 9, 2002 (*id.* ¶87), and is a prior art printed publication under §102(b).

D. Klimiuk (EX1006)

Klimiuk is an authentic copy of an article from the *American Journal of Pathology*—a periodical first published in 1925 and held by 916 libraries worldwide. *Id.* ¶66. A date stamp from the University of Illinois at Urbana-Champaign Library indicates that the journal containing Klimiuk was processed on November 7, 1997. *Id.* ¶67. Therefore, Klimiuk was available to the public before April 9, 2002 (*id.* ¶70), and is a prior art printed publication under §102(b).

E. Ulfgren (EX1007)

Ulfgren is an authentic copy of an article from *Arthritis & Rheumatism*. *Id.* ¶88. A date stamp from the National Library of Medicine indicates that the journal containing Ulfgren was processed on November 14, 2000. *Id.* ¶94. Therefore, Ulfgren was available to the public before April 9, 2002 (*id.* ¶97), and is a prior art printed publication under §102(b).

F. Curd (EX1008)

Curd is a PCT application that was published by the World Intellectual Property Organization on November 16, 2000. EX1008. Accordingly, Curd is a prior art printed publication under §102(b).

G. Rituxan™ label (EX1009)

The Rituxan™ label is an authentic copy of an excerpt from the 1999 *Physician's Desk Reference* ("PDR")—a periodical first published in 1974 and held by 3,844 libraries worldwide. *Id.* ¶76. A date stamp from the University of Illinois at Urbana-Champaign Library indicates that the PDR containing the Rituxan™ label was circulated to a library patron on May 7, 2001. *Id.* ¶77. Therefore, the Rituxan™ label was available to the public before April 9, 2001 (*id.* ¶78), and is a prior art printed publication under §102(b).[2]

IX. ANALYSIS OF GROUNDS FOR TRIAL

Claims 1–14 of the '838 patent are unpatentable as obvious under §103(a).

[2] In IPR2016-01614, Patent Owner is challenging the authenticity and prior art status of a different exhibit that the parties in that proceeding also call "the Rituxan™ label." Here, however, "the Rituxan™ label" is an excerpt of the 1999 PDR, whose authenticity and public accessibility as of the critical date cannot be disputed. *See Frontier Therapeutics, LLC v. Medac Gesellschaft fur klinische Spezialpraparate mbH*, IPR2016-00649, Paper 10 at 21–22 & 6 n.4 (PTAB Sept. 1, 2016) (excerpts from "the PDR" are "portions of a reference book that were published on the dates indicated on the documents" and "sufficiently establish that they constitute printed publication prior art, absent additional evidence indicating otherwise").

A. Ground I: Obviousness over Edwards 2002—§102(a) prior art

First, all claims are obvious variants of the method disclosed in Edwards 2002, in view of additional references that qualify as prior art under §102(b), which were not before the Board or the Examiner in any previous proceeding involving the '838 patent. Claims 1–5 and 7–14 would have been obvious over Edwards 2002 in view of Takemura as evidenced by Klimiuk and Ulfgren, and claim 6 would have been obvious over those same references in further view of Curd.

1. Ground I.A: Claims 1–5 and 7–14 would have been obvious over Edwards 2002 in view of Takemura as evidenced by Klimiuk and Ulfgren.

a. Claims 1 and 8

Claim 1 is directed to "[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 1000mg." Claim 8 is identical except that the antibody that binds to CD20 is limited to rituximab. As the Board has twice confirmed, with the exception of treating a patient who experiences an inadequate response to a TNFi, Edwards 2002 expressly discloses every limitation of these claims. EX1037, 12–13, 17–18; EX1039, 8, 11–13. In view of Takemura, Klimiuk, and Ulfgren, a POSA would have been motivated, with a reasonable expectation of success, to use the method of Edwards 2002 to treat RA in patients who inadequately respond to TNFis, rendering claims 1 and 8 obvious. EX1002 ¶86.

i. Edwards 2002 taught a method of treating RA in a human patient by administering two intravenous doses of 1000mg rituximab.

Edwards 2002 disclosed a randomized, double-blind study on 161 RA patients who were separated into four groups—including three receiving rituximab in two intravenous 1000mg doses. EX1003, 3. One of these groups received this dose of rituximab in combination with methotrexate, and all patients received corticosteroids. *Id.*

Edwards 2002 concluded that "all 3 rituximab regimens were well tolerated," and the patients taking rituximab experienced a "substantial clinical benefit" in the treatment of their RA. *Id.* In particular, patients receiving the combination therapy of rituximab and methotrexate experienced "the highest levels of ACR20, 50 and 70 responses." *Id.* Accordingly, Edwards 2002 taught an effective method of treating RA in a human patient comprising administering to the patient rituximab (an antibody that binds to CD20), wherein the rituximab is administered as two intravenous doses of 1000mg. EX1002 ¶87.

ii. Klimiuk taught that RA patients with diffuse synovitis have the lowest levels of TNFα.

Based on rituximab's known mechanism of action and the known differences in cytokine profiles among the RA patient population, a POSA would have reasonably expected the method of Edwards 2002 to effectively treat RA patients who experienced an inadequate response to a TNFi. *Id.* ¶88.

As shown by Klimiuk, a POSA would have known that RA "synovitis is a heterogeneous entity with three distinct histologically defined phenotypes." EX1006, 2. In particular, patients with RA were known to have one of three types of synovial tissues (or synovitis), each of which expresses different levels of TNFα: (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 5–6. Thus, a POSA would have understood that some RA patients had particularly low levels of TNFα—a cytokine well known to contribute to the pathogenesis of RA. *Id.*; EX1002 ¶89. Given this known variability, a POSA designing a new RA treatment would have been motivated to improve the treatment options for patients with *all* types of synovitis—including patients with diffuse synovitis who expressed the lowest levels of TNFα. EX1002 ¶89.

iii. Ulfgren taught that RA patients with lower levels of TNFα respond poorly to a TNFi.

A POSA would have understood that the patients studied in Klimiuk with diffuse synovitis—i.e., those with the lowest levels of TNFα—did not adequately respond to TNFis such as infliximab. *Id.* ¶90. Ulfgren observed "a highly significant correlation between baseline TNFα expression and the change in expression in response to anti-TNFα." EX1007, 5. Ulfgren thus taught 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; EX1026, 9.[3]

Accordingly, in view of Klimiuk and Ulfgren, a POSA would have understood that (i) RA patients with diffuse synovitis have low levels of TNFα (as taught by Klimiuk); (ii) RA patients with low levels of TNFα respond inadequately to TNFis (as taught by Ulfgren); and, therefore, (iii) RA patients with diffuse synovitis respond inadequately to TNFis. EX1002 ¶¶91–92.

iv. Takemura taught that rituximab, by depleting B-cells instead of inhibiting TNFα, effectively treats RA patients with diffuse synovitis.

Although it was known that RA patients with low levels of TNFα respond inadequately to TNFis, a POSA would have understood that rituximab, which does *not* treat RA by inhibiting TNFα, was equally effective in patients with normal levels of TNFα *and* in patients who, because they have diffuse synovitis, have particularly *low* levels of TNFα. *Id.* ¶¶93–94. In other words, rituximab was used effectively to treat RA patients regardless of their TNFα levels.

As Takemura explained, unlike TNFis, rituximab's therapeutic effect results from its targeted "elimination of B cells from the synovial tissue," which "disrupt[s]

[3] Other authors confirmed that Ulfgren "has shown low synovial TNFα production in nonresponder patients." EX1026, 9; *accord* EX1027, 2; EX1018, 6.

T cell activation and the production of proinflammatory monokines." EX1005, 6. Takemura observed this effect in tissues with both follicular (normal TNFα) and diffuse (low TNFα) synovitis, noting 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.* at 9 (emphasis added). Encouraged by these results, Takemura predicted that the use of rituximab to treat RA patients with either type of synovitis "could be developed into a potent immunosuppressive therapy." *Id.*

v. Thus, a POSA would have reasonably expected Edwards 2002's method to treat RA in a human patient who experiences an inadequate response to a TNFi.

In summary, 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. Thus, a POSA would have understood that rituximab is an effective treatment for RA patients who, because they have diffuse synovitis—and therefore express low levels of TNFα—experience an inadequate response to a TNFi. *Id.* ¶96.

In view of this understanding, a POSA would have been motivated, with a reasonable expectation of success, to use the dosing regimen of Edwards 2002—i.e.,

administering rituximab in two intravenous doses of 1000mg—to treat a human patient who experiences an inadequate response to a TNFi. *Id.* ¶¶96–98. While Edwards 2002 did not explicitly state whether any of its 161 patients experienced such an inadequate response, a POSA would have reasonably expected that the effectiveness of rituximab demonstrated by Edwards 2002 would remain unaffected by a patient's responsiveness to a TNFi. *Id.* That is, a POSA would have understood that Edwards 2002's method would be equally effective in RA patients with different types of synovitis—including patients with low levels of TNFα who, therefore, do not adequately respond to TNFis. *Id.*

That expectation was supported by the known and unrelated mechanisms of action of TNFis and rituximab. *Id.* ¶98. TNFis work by inhibiting a specific pro-inflammatory cytokine—TNFα—that is produced downstream from a sequence of cellular reactions starting with the "activation" of T-cells. *Id.* TNFα, however, is just one of the three primary inflammatory cytokines (along with IL-1 and IL-6) that are ultimately produced by activated T-cells. EX1011, 4. Unlike TNFis, rituximab 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.*; EX1005, 6; EX1002 ¶¶96–98.

As of 2002 and 2003, 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.*

Claims 1 and 8 thus would have been obvious. *Id.*

b. Claims 2 and 3

Claim 2 is identical to claim 1 except that it requires that the anti-CD20 antibody (e.g., rituximab) is administered "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." *Id.* ¶99.

As discussed in Part VII.B above, claim 2's recitation that the patient achieves an ACR50 or ACR70 response, or the absence of erosive progression, is non-limiting because it merely recites the intended results of the claimed steps of administering an anti-CD20 antibody "as two intravenous doses of 1000mg." *See, e.g.*, *Ben Venue*, 246 F.3d at 1375.

In any event, Edwards 2002 expressly disclosed that numerous patients who were administered this exact regimen achieved ACR50 and ACR70 responses.

EX1003, 3; EX1002 ¶101. Accordingly, for the same reasons explained above for claim 1, claim 2 would have been obvious. EX1002 ¶101.

Claim 3 depends from claim 2 and requires that the anti-CD20 antibody is rituximab, which is the antibody administered in Edwards 2002. EX1003, 3. Thus, claim 3 also would have been obvious. EX1002 ¶102.

c. Claims 4, 9, and 10–14

Claims 4 and 9 depend from claims 3 and 8, respectively, and further require treating the patient with methotrexate. In Edwards 2002, "[a]ll patients were receiving methotrexate (MTX)" initially, and patient Group D received the combination of rituximab (as two intravenous doses of 1000mg) "plus continuing MTX," i.e., methotrexate. EX1003, 3. This group receiving combination therapy with rituximab and methotrexate saw a "substantial clinical benefit," and "the highest levels of ACR20, 50 and 70 responses." *Id.*

A POSA thus would have been motivated, with a reasonable expectation of success, to maintain the concomitant methotrexate administered in combination with the regimen of rituximab in Edwards 2002. EX1002 ¶104. Accordingly, for the same reasons that claims 3 and 8 are obvious variants of Edwards 2002, claims 4 and 9 also would have been obvious. *Id.*

Similarly, claim 10 is identical to claim 8 except that it requires the administration of methotrexate and adds the clause, "wherein the patient has no

erosive progression at weeks 24 and beyond." Again, Edwards 2002 expressly encouraged the combination of rituximab and methotrexate. Moreover, as discussed above, the "wherein" clause regarding the lack of erosive progression recites only an intended result of the claimed regimen, and is thus entitled to no patentable weight. *Tex. Instruments*, 988 F.2d at 1172. Accordingly, claim 10 would have been obvious. EX1002 ¶105.

Likewise, claim 11 is identical to claim 8 except that it also requires the administration of methotrexate, and is directed to "[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." As with the "wherein" limitations discussed above, this preamble recites only the intended result of the dosing limitations in the body of the claim, and is thus nonlimiting. *Ben Venue*, 246 F.3d at 1375. In any event, the patients in Edwards 2002 who were administered this dosing regimen achieved ACR50 and ACR70 responses. EX1003, 3; EX1002 ¶106. Accordingly, claim 11 would have been obvious. EX1002 ¶106.

Claims 12–14 depend from claim 11 and add "wherein" clauses reciting that the clinical response is "ACR50 response at week 24," "ACR70 response at week 24," and "no erosive progression at weeks 24 and beyond," respectively. For the same reasons discussed above, these "wherein" clauses merely describe the intended result of the claims and are non-limiting. *Tex. Instruments*, 988 F.2d at 1172.

Moreover, Edwards 2002 taught that patients who were administered the same exact regimen achieved ACR50 and ACR70 responses. EX1003, 3; EX1002 ¶107. Accordingly, claims 12–14 would have been obvious. EX1002 ¶107.

d. Claim 5

Claim 5 depends from claim 4 and requires that "the patient is further treated with a corticosteroid regimen." In Edwards 2002, "[a]ll groups also received a 17 day course of corticosteroids (total dose of 960mg)," and, therefore, were all treated with a corticosteroid regimen. EX1003, 3; EX1002 ¶108. Accordingly, for the same reasons that claim 4 is an obvious variant of Edwards 2002, claim 5 also would have been obvious. EX1002 ¶108.

e. Claim 7

Claim 7 depends from claim 2 and further requires that "the CD20 antibody is the only B-cell surface marker antibody administered to the patient." In Edwards 2002, three groups of patients—Groups B, C, and D—received two intravenous doses of 1000mg rituximab, as required by claim 2, and no other B-cell surface marker antibody. EX1003, 3; EX1002 ¶109.

Accordingly, for the same reasons that claim 2 is an obvious variant of Edwards 2002, claim 7 also would have been obvious. *Id.* ¶110.

2. Ground I.B: Claim 6 would have been obvious over Edwards 2002 in view of Takemura as evidenced by Klimiuk and Ulfgren, and further in view of Curd.

Claim 6 depends from claim 5 and limits the corticosteroid regimen to one that "consists of methylprednisolone and prednisone." Although 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.* ¶¶112–115.

In particular, Curd included an example in which "[p]atients with clinical diagnosis of rheumatoid arthritis (RA) are treated with rituximab (RITUXAN®)," and "the patient is optionally further treated with any *one or more* agents employed for treating RA such as … immunosuppressive agents such as methotrexate or corticosteroids." EX1008, 25:9–16 (emphasis added). Curd further described the use of "steroids such as glucocorticosteroids, e.g., *prednisone*, *methylprednisolone*, and dexamethasone." *Id.* at 8:28–29 (emphasis added).

As Dr. Massarotti explains, a POSA would have used these corticosteroids to mitigate any hypersensitivity reactions to rituximab both during the rituximab infusion (e.g., intravenous methylprednisolone) and by prescription following treatment (e.g., oral prednisone). EX1002 ¶¶113–114; *see* EX1009, 7, 10; EX1001, 31:33–37 (defining "corticosteroid regimen" to include non-simultaneous dosing).

Thus, it would have been obvious to administer the specific corticosteroids prednisone and methylprednisolone in combination with rituximab and methotrexate. EX1002 ¶115. Accordingly, claim 6 would have been obvious. *Id.*

B. Ground II: Obviousness over Edwards 2001—§102(b) prior art

Independently, all claims are obvious variants of Edwards 2001—which is prior art under 35 U.S.C. §102(b) and cannot be antedated by Patent Owner—in view of additional §102(b) references that were not before the Board or the Examiner in any prior proceeding involving the '838 patent.

1. Ground II.A: Claims 1–3 and 7–8 would have been obvious over Edwards 2001 in view of the Rituxan™ label and Takemura as evidenced by Klimiuk and Ulfgren.

a. Claims 1 and 8

As discussed in Ground I, claim 1 requires "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 1000mg," and claim 8 limits the same method to rituximab. These claims would have been obvious.

i. Edwards 2001 taught a method of treating RA in a human patient by administering a total monthly dose of about 2000mg rituximab.

Edwards 2001 disclosed the successful treatment of patients with severe RA by administering rituximab in combination with cyclophosphamide and prednisolone (a corticosteroid). EX1004, 2. "All patients" in Edwards 2001

"showed rapid improvement in synovitis." *Id.* at 3. Moreover, "all patients achieved ACR50" responses, and more than half "achieved ACR70 [responses] without introduction of further therapy." *Id.* Thus, Edwards 2001 taught a method of treating RA in a human patient comprising administering to the patient rituximab (i.e., an antibody that binds to CD20). EX1002 ¶118.

Edwards 2001 disclosed a four-dose regimen of rituximab that resulted in a total monthly dose of ≈2100mg. EX1004, 2. This regimen was similar to the four-dose regimen for NHL that was FDA-approved at the time, except that Edwards 2001 used fixed doses (instead of varying the dose based on each patient's body surface area) and a lower monthly total than the average of 2400mg for NHL. EX1002 ¶119. As the authors explained, this dosing regimen was "based on the type of combination therapy used in B-cell lymphoma." EX1004, 2. In their conclusion, however, having confirmed that rituximab "may be of major benefit to subjects with RA," the authors suggested that future studies on the use of rituximab in RA should adopt either "the protocol used, *or a modification* thereof." *Id.* at 3 (emphasis added). Indeed, a POSA would have been motivated to optimize the dose of rituximab that was approved for NHL to the particular needs of RA. EX1002 ¶120; EX1008, 23:19–20, 28–29 ("In one embodiment, the dosage of the antibody [to treat autoimmune disorders] differs from that presently recommended for RITUXAN®.").

ii. The Rituxan™ label would have motivated a POSA to titrate the approved dosing regimen to use fewer infusions and a lower total dose.

As of 2002, the only FDA-approved dosing regimen of rituximab was the "recommended" regimen in the Rituxan™ label for low-grade NHL—i.e., four weekly doses of 375mg/m^2. EX1009, 11. Based on the average human body surface area of 1.6 m^2, this regimen is approximately equal to four weekly doses of 600mg, totaling 2400mg per month. EX1002 ¶121; EX1041 ¶17. Importantly, a POSA would have understood that this dose had been specifically designed to treat NHL—a type of cancer—and thus a POSA would not have assumed that it was also necessarily the optimal dose to treat RA. EX1002 ¶¶122–127; EX1041 ¶¶17–18.

In fact, a POSA would have understood from the Rituxan™ label that the recommended number of infusions and recommended total dose for treating NHL could be *reduced* when treating RA. EX1002 ¶127; EX1041 ¶¶19–25. The section titled "Human Pharmacokinetics/Pharmacodynamics" taught that "[t]he peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden," which the label called "the variable tumor burden among patients." EX1009, 9.

As Patent Owner explained in another IPR involving the Ritxuan™ label, "the data presented in the label affirmatively suggests not using the relapsed dosing regimen in a disease setting where there will be a lower tumor burden and fewer

circulating B-cells in the patient." EX1035, 49. "In such a setting, the label suggests use of a *lower* dose," because not as much rituximab is needed in patients with no (or less) tumor burden. *Id.* Patent Owner thus argued that a POSA "would have used less rituximab, either by decreasing the frequency (less than four doses) or the amount (mg/m^2)…." *Id.* at 50.

Here, as Drs. Massarotti and Grossbard confirm, a POSA would have known that, since RA is not a type of cancer, it involves no "tumor burden." EX1002 ¶123; EX1041 ¶25. Thus, in line with Patent Owner's interpretation of the Rituxan™ label, a POSA optimizing the dose of rituximab for RA would have been motivated to reduce the approved frequency and/or amount for administration. EX1002 ¶127; EX1041 ¶25.

Moreover, a POSA would have maintained the fixed dosing of Edwards 2001—i.e., giving the same dose to all patients—rather than reverting to the body-surface-area dosing used for NHL. EX1002 ¶¶128–131. No variable dosing was needed for RA because there was no direct correlation between body surface area and synovium volume. *Id.* And a POSA would have preferred to use a fixed dose, which is much easier to administer because it is the same for every patient and does not require the extra steps of measuring a patient's body surface area and calculating a patient-specific dose. *Id.* Indeed, nearly every RA therapy at the time used fixed

dosing; the only exception was infliximab, which was dosed based on body weight—an approach that had been criticized by rheumatologists. *Id.* ¶131; EX1021, 10.

A POSA also would have been motivated to reduce the number of infusions used to treat NHL—i.e., administer fewer than four doses in a month—to improve patient compliance. EX1002 ¶129–130. Indeed, the "likelihood of compliance" by patients was an important consideration for RA treatments in general (EX1010, 9), and the likelihood that patients will fail to comply "is increased when patients … need to take the medication in multiple doses" (EX1015, 29). *See Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance.").

iii. Given the commercially available 500mg single-use vial, a POSA would have arrived at two doses of 1000mg through routine optimization.

Another important consideration for a POSA seeking to develop an optimized dosing regimen would have been the vials of rituximab that were available for preparing an infusion. *Id.* ¶¶132–133. As of 2002, rituximab was only supplied in single-use vials of 100mg and 500mg. EX1009, 11. In seeking to reduce the number of infusions and the total dose from the approved regimen for NHL, a POSA would have opted to use entire vials of rituximab, because the Rituxan™ label warned to "[d]iscard any unused portion left in the vial" (EX1009, 8), and using anything less

than an entire vial would thus result in wasting an expensive therapy. EX1002 ¶133; *see* EX1021, 10 (encouraging fixed dosing such that "no portion of a vial be discarded" to reduce costs); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1127–28 (Fed. Cir. 2000) (finding "a motivation to combine" because modifying an existing method would "cost less to produce").

A POSA developing a new dosing regimen with a reduced frequency and/or amount relative to the dosing regimen used for NHL would have faced a limited set of options with the commercially available 100mg and 500mg single-use vials of Rituxan™. EX1002 ¶¶134–137. Titrating down from the frequency (four doses) and amount (approximately 2400mg) used for NHL—and attempting to recreate the successful results of Edwards 2001 with a monthly total of 2100mg—a POSA would have considered two infusions totaling 2000mg as the simplest option to try using whole vials of 500mg. *Id.* Thus, arriving at two doses per month of 1000mg would have required no more than routine optimization. *Id.*; *see Hoffmann-La Roche*, 748 F.3d at 1333 (holding claimed dose obvious where a POSA "looking to scale to a monthly dose of oral ibandronate from a known-effective daily dose was [] faced with a very limited set of possibilities").

At the very least, the 1000mg dose was "obvious to try": In addition to the titration suggested by rituximab's known pharmacokinetics, "[t]here was a need to solve the problem of patient compliance by looking to less-frequent dosing

regimens. And … there were only a 'finite number of identified, predictable solutions'" in view of the two single-use vials that were commercially available. *Id.* (quoting *KSR Int'l Co. v. Teleflex*, 550 U.S. 398, 421 (2007)); *see also Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (finding obviousness where, "though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine"); EX1002 ¶137.

Moreover, a POSA reducing the number of infusions to improve patient compliance would have reasonably expected that administering two doses of 1000mg for a monthly total of 2000mg—i.e., approximately the same total amount that successfully treated RA in Edwards 2001 (2100mg)—would be equally as effective as an already proven regimen with more frequent administrations. EX1002 ¶¶138–141; *see also Hoffmann*, 748 F.3d at 1332 ("it was reasonable to expect that a once monthly dose of 150mg would have roughly the same efficacy as a daily dose of 5mg"); *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) ("Obviousness does not require absolute predictability of success…. [A]ll that is required is a reasonable expectation of success.") (citation omitted).

Accordingly, it would have been obvious in view of the Rituxan™ label to optimize the dose of rituximab to treat RA as used in Edwards 2001 to two intravenous doses of 1000mg. EX1002 ¶142.

iv. A POSA would have reasonably expected the optimized dose of rituximab to treat RA patients who responded inadequately to a TNFi.

For the same reasons discussed in Ground I, a POSA would have been motivated, with a reasonable expectation of success, to use the optimized dose of rituximab for RA—i.e., two intravenous doses of 1000mg—in the specific population of patients who had experienced an inadequate response to a TNFi. *Id.* ¶¶143–144. Again, Takemura taught that, by depleting B-cells, rituximab effectively treated patients with both follicular *and diffuse* synovitis. EX1005, 8–9. A POSA would have understood the significance of that teaching in view of Klimiuk, which taught that patients with diffuse synovitis have low levels of TNFα (EX1006, 5), and in view of Ulfgren, which taught that patients with low levels of TNFα respond inadequately to TNFis (EX1007, 5–6). EX1002 ¶¶143–144.

Accordingly, 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 TNFα), respond poorly to TNFis. *Id.* Because rituximab does not inhibit TNFα, but instead was known to act by a different mechanism of action that is unrelated to the inter-patient variability that causes disparate responses to TNFis, a POSA would not have expected that a

different dosing regimen of rituximab was necessary to effectively treat patients who experienced an inadequate response to a TNFi. *Id.*

Claims 1 and 8 thus would have been obvious. *Id.* ¶¶117–144.

b. Claims 2 and 3

Claim 2 is identical to claim 1 except it requires that the anti-CD20 antibody (e.g., rituximab) is administered "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." *Id.* ¶145.

As discussed in Part VII.B, claim 2's recitation that the patient achieves an ACR50 or ACR70 response, or the absence of erosive progression, is entitled to no patentable weight because it merely recites the intended results of the claimed regimen—i.e., administering an anti-CD20 antibody "as two intravenous doses of 1000mg." *See Ben Venue*, 246 F.3d at 1375.

Moreover, Edwards 2001 disclosed that "all patients achieved ACR50" responses, and more than half "achieved ACR70" responses. EX1004, 3. Thus, claim 2 would have been obvious. EX1002 ¶146.

Claim 3 depends from claim 2 and requires that the anti-CD20 antibody is rituximab, which was the antibody administered in Edwards 2001. EX1004, 2. Accordingly, claim 3 also would have been obvious. EX1002 ¶147.

c. Claim 7

Claim 7 depends from claim 2 and further requires that "the CD20 antibody is the only B-cell surface marker antibody administered to the patient." In Edwards 2001, all patients received rituximab—and no other B-cell surface marker antibody. EX1004, 2; EX1002 ¶148. Accordingly, for the same reasons that claim 2 is an obvious variant of Edwards 2001, claim 7 also would have been obvious. *Id*. ¶149.

2. Ground II.B: Claims 4–6 and 9–14 would have been obvious over Edwards 2001 in view of the Rituxan™ label and Takemura as evidenced by Klimiuk and Ulfgren, and further in view of Curd.

a. Claims 4 and 9

Claims 4 and 9 depend from claims 2 and 8, respectively, and further require treating the patient with methotrexate. Although methotrexate was not used in Edwards 2001, as discussed above in Part V.B.2, methotrexate was a commonly used DMARD that was considered the initial standard of care for treating RA, and was frequently used in combination therapy with biologics. EX1002 ¶151.

Moreover, Curd expressly included an example in which "[p]atients with clinical diagnosis of rheumatoid arthritis (RA) are treated with rituximab (RITUXAN®)," and "the patient is optionally further treated with … immunosuppressive agents such as methotrexate." EX1008, 25:9–16. Thus, the combination therapy of rituximab and methotrexate to treat RA was not only obvious—it was already known and in use. EX1002 ¶¶152–153.

Claims 4 and 9 thus would have been obvious. *Id.*

b. Claims 5–6

Claim 5 depends from claim 4 and requires that "the patient is further treated with a corticosteroid regimen." Claim 6 depends from claim 5 and limits that regimen to one that "consists of methylprednisolone and prednisone."

All patients in Edwards 2001 received "[o]ral prednisolone 60mg on days 1–22, reducing in the three older subjects (perceived to be at higher risk of toxicity) to 30mg on days 11–22 and then withdrawn over 3 weeks in subjects not previously taking steroids and, in the other cases, to 5mg daily over 6 weeks." EX1004, 2. Thus, Edwards 2001 expressly taught the combination of rituximab and corticosteroids, rendering claim 5 an obvious variant. EX1002 ¶155.

Curd additionally taught the use of corticosteroids, including both prednisone and methylprednisolone, in combination with rituximab. *Id.* ¶156. Specifically, the example in which "[p]atients with clinical diagnosis of rheumatoid arthritis (RA) are treated with rituximab (RITUXAN®)" provided that "the patient is optionally further treated with any one or more … corticosteroids," which Curd defined to include "prednisone[and] methylprednisolone." EX1008, 25:9–16, 8:28–29.

Thus, it would have been obvious in view of Curd to administer these specific corticosteroids, rendering claim 6 obvious. EX1002 ¶157.

c. Claims 10–14

Claim 10 is identical to claim 9 (which depends from claim 8 and adds co-administration with methotrexate), except that claim 10 adds the clause, "wherein the patient has no erosive progression at weeks 24 and beyond."

For the reasons discussed in Part VII.C, the "wherein" clause in claim 10 regarding the absence of erosive progression recites only an intended result of the claimed therapeutic regimen, and is thus entitled to no patentable weight. *See Tex. Instruments*, 988 F.2d at 1172. Accordingly, for the same reasons discussed above for claim 9, claim 10 also would have been obvious. EX1002 ¶¶158–159.

Likewise, claim 11 is identical to claim 9 except that it is directed to "[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." As with the "wherein" clauses discussed above, this preamble recites only the intended result of the dosing limitations in the body of the claim, and is thus non-limiting. *Ben Venue*, 246 F.3d at 1375.

In any event, all patients in Edwards 2001 achieved ACR50 responses, and most achieved ACR70 responses. EX1004, 3; EX1002 ¶160. A POSA would have reasonably expected that administering two rituximab doses of 1000mg, totaling 2000mg in a month, would achieve the same clinical results as the regimen of Edwards 2001, which involved more frequent administrations but amounted to

almost the same total monthly dose. EX1002 ¶161; *see Hoffmann*, 748 F.3d at 1333 ("it was reasonable to expect that a once monthly dose of 150mg would have roughly the same efficacy as a daily dose of 5mg"). Accordingly, claim 11 would have been obvious. EX1002 ¶161.

Claims 12–14 depend from claim 11 and add "wherein" clauses reciting that the clinical response is "ACR50 response at week 24," "ACR70 response at week 24," and "no erosive progression at weeks 24 and beyond," respectively. These "wherein" clauses merely describe the intended result of the claims and are entitled to no patentable weight. *Tex. Instruments*, 988 F.2d at 1172. In any event, Edwards 2001 taught that patients taking a regimen totaling the same monthly dose achieved ACR50 and ACR70 responses. EX1004, 3; EX1002 ¶162.

Accordingly, claims 12–14 would have been obvious. EX1002 ¶162.

C. There are no probative secondary considerations.

Petitioner is not aware of any probative evidence of secondary considerations that would undermine the evidence of *prima facie* obviousness discussed above. EX1002 ¶163. In any event, "objective evidence of nonobviousness simply cannot overcome such a strong *prima facie* case of obviousness." *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008).

At this stage, moreover, Petitioner has no burden to identify and rebut secondary considerations. Patent Owner must first present a *prima facie* case for

such considerations, which Petitioner may then rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2014-01453, Paper 11 at 20 (PTAB Mar. 10, 2015). Thus, panels routinely reject arguments against institution based on secondary considerations. *E.g.*, *Petroleum Geo-Services Inc. v. WesternGeco LLC*, IPR2014-01478, Paper 18 at 36 (PTAB Mar. 17, 2015).

Nevertheless, in an abundance of caution, Petitioner preliminarily addresses the alleged secondary considerations that Patent Owner asserted in IPR2015-00417—i.e., (a) teaching away; (b) unexpected results; (c) long-felt need; and (d) commercial success—all of which the Board rejected. EX1036, 62–68; EX1037, 23–25. Petitioner reserves the right to address any other evidence of secondary considerations that Patent Owner may present in this proceeding.

1. De Vita and Curd did not teach away.

Both during prosecution and in IPR2015-00417, Patent Owner argued that a 2001 article by De Vita et al. "taught away" from the claimed methods by reporting that, in a five-person study, "two patients who had not responded to anti-TNF alpha therapy exhibited little or no improvement" when receiving the standard dose of rituximab for NHL. EX1036, 47 (citing EX1016, 2). Patent Owner contrasted this result with the remaining three patients in De Vita's study, who "showed major improvement with ACR70 and ACR50 responses," whereas patients who did not

respond to TNFis "experienced an *increase* in the number of eroded joints." *Id.* These results, however, do not teach away.

"A reference does not teach away if it does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (alteration and citation omitted). Nothing in De Vita meets that standard. Where, as here, references do not "expressly teach away from the claimed invention," "inferr[ing] that these references taught away" by merely reporting unsuccessful results is improper. *Id.* at 738 ("articles show[ing] increased side effects associated with" higher concentrations did not teach away "from a further tripling of the [drug] concentration").

Moreover, unsuccessful results fail to teach away if "it was unknown *why* [the study] was unsuccessful"—"speculat[ion] that the [claimed method] was to blame for the inconclusive results" is insufficient. *Hoffmann-La Roche*, 748 F.3d at 1330. Here, De Vita itself offers an alternative explanation: "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." EX1016, 5. In other words, one of the two patients who did not respond to TNFis *also* could not adequately respond to rituximab. EX1002 ¶¶166–167. Thus, "especially in the face of [De Vita's own] competing explanation of the

[unsuccessful] results," Patent Owner's "speculation d[oes] not amount to an affirmative teaching away." *Hoffman La-Roche*, 748 F.3d at 1330–31.

Equally flawed is Patent Owner's argument in IPR2015-00417 that "the Curd PCT Publication expressly teaches away from administering anything else with rituximab when it states that '[p]referably however, the patient is *only* treated with RITUXAN®.'" EX1036, 62 (quoting EX1008, 25:10–16) (emphasis by Patent Owner). As the Board correctly found, Curd's general preference for rituximab monotherapy does not "criticize, discredit, or otherwise discourage" the alternative combinations of rituximab with methotrexate and/or corticosteroids. EX1037, 23; *Galderma Labs.*, 737 F.3d at 738 ("A reference does not teach away, however, if it merely expresses a general preference for an alternative invention."); EX1002 ¶¶168–169.

2. The claimed methods do not produce unexpected results.

The Board also correctly rejected Patent Owner's argument that rituximab's use "in patients who did not respond to anti-TNFα therapy is supported by evidence of unexpected results." EX1037, 24–25. As the Board explained, "the treatment of rheumatoid arthritis in patients who did not respond to anti-TNFα therapy was known" in the art. EX1037, 25 (citing EX1017, 3). This fact alone is fatal: Patent Owner "[can]not otherwise identif[y] what novel elements in the claims anchor its objective evidence." *Id.* (citing *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed.

Cir. 2011) ("Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention.")).

Additional evidence that was not before the Board in IPR2015-00417 supports that conclusion. "[B]y definition, any superior property must be *unexpected* to be considered as evidence of non-obviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Yet here, in view of Takemura, Klimiuk, and Ulfgren, rituximab's effectiveness for treating RA in patients who did not respond adequately to TNFis was entirely expected. *Supra* IX.A.1.a.ii–IX.A.1.a.iv.

3. The claimed invention did not satisfy a long-felt need.

Likewise, the Board rejected Patent Owner's argument that the '838 patent met a "need for an effective alternative treatment for anti-TNFα nonresponders [that] persisted for years." EX1036, 63. Again, the prior art disclosed the use of "rituximab alone for the treatment of erosive RA in patients that have previously failed treatment with an anti-TNFα antibody." EX1037, 25 (alteration omitted) (citing EX1017). There is no evidence that any of the obvious variants of that known use claimed in the '838 patent satisfied any other "need." *See Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010) ("Where the differences between the prior art and the claimed invention are as minimal as they are here [], it cannot be said that any long-felt need was unsolved.").

Long-felt need is also irrelevant because a key element of the claimed method—rituximab—had only recently become available when the '838 patent was filed. EX1002 ¶173. Given that rituximab was not commercially available before the FDA's approval of Rituxan™ in late 1997, any "long-felt need" before that time cannot suggest that methods of using rituximab to treat RA in TNFi non-responders were nonobvious. "[O]nce another supplied the key element [of the combination], there was no long-felt need," and "unsuccessful attempts to reach a solution … before that time became wholly irrelevant." *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) (quotation omitted).

Moreover, the patent claiming the genetic sequence for rituximab—U.S. Patent No. 5,736,137 ("the '137 patent")—issued in 1998 and did not expire until 2015. EX1032; EX1001, 2:34–36. This patent, which was assigned to Patent Owner, legally precluded others from developing the methods claimed in the '838 patent as of April 2002 and 2003. Thus, any "evidence relating to the 'failure of others,' a[nd] 'long-felt but unsolved need,' … is undermined by the fact that those phenomena—to the extent they exist in this case—could have been derived from [Patent Owner's] ownership of the ['137] patent as much as from the nonobviousness of the [claimed invention]." *Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 392 (S.D.N.Y. 2007), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008).

4. Any commercial success lacks a nexus to the claims.

Lastly, the Board correctly rejected "Patent Owner['s] assert[ion] that the claimed methods have led to significant commercial success, based on worldwide sales of rituximab." EX1037, 25. As the Board observed, Rituxan™'s sales are largely "attributable to the use of rituximab in oncology, e.g., to treat non-Hodgkin's lymphoma"—not RA—and Patent Owner admitted that it is "'difficult to precisely determine the sales split between Rituxan use in oncology and immunology settings.'" *Id.* (quoting EX1033, 54). Thus, "Patent Owner has failed … to establish sufficient nexus between the commercial success of the product and any element recited in the claims" of the '838 patent. *Id.*

Since then, moreover, Patent Owner has represented that the same methods claimed by the '838 patent—i.e., administering "rituximab … along with methotrexate" in "two infusions of 1000mg"—"are embodiments of the *'161 patent* claims." EX1040, 59–60 (emphasis added). That admission precludes any finding of nexus here. Even assuming Patent Owner can isolate the sales of rituximab to treat RA, "[t]his is not a situation where the success of a product can be attributed to a single patent, because [rituximab's approved use for RA] embodied at least two patents: the ['838] patent *and* the ['161] patent," and thus "there is no presumption that the product's success was due *only* to the ['838] patent." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010), *vacated on other*

grounds, 649 F.3d 1276, 1296 (Fed. Cir. 2011); *see Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 838–39 (Fed. Cir. 2015) ("evidence of licensing should not be afforded much weight" where there were "other patents involved").

Independently, any commercial success fails to show nonobviousness because the '137 patent, which claimed rituximab, precluded others from commercializing the method claimed in the '838 patent as of 2002–2003. And where, as here, "market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma Labs.*, 737 F.3d at 740 (alterations and quotation omitted).

X. CONCLUSION

The Board should institute *inter partes* review and cancel claims 1–14 of the '838 patent as unpatentable.

Dated: August 29, 2017

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. §42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,999 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on August 29, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on Patent Owner at the correspondence address of record for U.S. Patent No. 7,976,838 B2, and at another address known as likely to effect service, as follows:

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