UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.
Petitioner,

v.

GENENTECH, INC.
Patent Owner

Patent No. 7,976,838 B2
Issued: July 12, 2011
Filed: March 20, 2008
Inventors: Mark C. Benyunes and Randall M. Stevens

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

Inter Partes Review No. 2017-02042

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,976,838 UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 42.100

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1165	Declaration of Siegmund Gutman

I. PRELIMINARY STATEMENT

Pursuant to 35 U.S.C. § 311 and 37 C.F.R. § 42.100, Petitioner, Sandoz, Inc., respectfully requests *inter partes* review ("IPR") of claims 1–14 ("the Challenged Claims") of U.S. Patent No. 7,976,838 ("the '838 patent"). USPTO assignment records state that the '838 patent is assigned to Genentech, Inc. Ex. 1102.

The '838 patent claims methods of treating rheumatoid arthritis ("RA") using two intravenous doses of 1,000 mg of an anti-CD20 antibody—*e.g.*, rituximab—in a human patient who "experiences an inadequate response" to a tumor necrosis factor alpha ("TNFα") inhibitor.

Rituximab was well known before the Earliest Possible Priority Date[1] of the '838 patent as a safe and effective treatment for both non-Hodgkin's lymphoma ("NHL") and RA because it targets and kills B-cells. In 2002, Dr. Jonathan Edwards published results of a clinical trial treating patients with RA using the exact same dosing regimen claimed in the '838 patent—two intravenous 1,000 mg doses of rituximab. Ex. 1138 at S197. The regimen combined rituximab with methotrexate and corticosteroids as recited in dependent claims of the '838 patent.

[1] The '838 patent claims priority to U.S. Provisional Application No. 60/461,481, filed April 9, 2003.

Id. Other prior art—*e.g.*, Patel, Tuscano, and DeVita 2002 (referenced in Patel)—demonstrated the therapeutic effectiveness of rituximab in patients with refractory RA, including patients who did not respond to prior treatment with multiple disease modifying anti-rheumatic drugs ("DMARDs"), such as TNFα inhibitors. Ex. 1159 at 1984; Ex. 1136 at 3420; Ex. 1160 at 2029. Accordingly, all the elements of the Challenged Claims are expressly disclosed in, and are obvious over, the prior art.

A person of ordinary skill in the field of rheumatology ("POSITA") would have had a strong motivation to use rituximab as disclosed in Edwards 2002 in patients who experienced an inadequate response to TNFα inhibitors ("TNFIRs") with a reasonable expectation of success.

A POSITA would have been motivated to use the Edwards 2002 dosing regimen because it was more convenient and simpler than those already used to treat TNFIRs and therefore, would improve patient compliance. Additionally, Edwards 2002 and other studies (*e.g.*, DeVita 2002) treated patients that received rituximab with the same dosing regimen without regard to prior treatment successes or failures. Accordingly, a POSITA would have expected to succeed in treating TNFIRs with the Edwards 2002 dosing regimen because the Edwards 2002 dosing regimen had, in fact, succeeded in treating RA. This makes sense given that

rituximab works through a different mechanism of action—B-cell depletion—than TNFα inhibitors.

In addition, for therapeutic purposes, the Edwards 2002 dosing regimen would have been considered equivalent to the dosing regimens that had already been used to successfully treat RA in TNFIRs, including the dosing regimens of De Vita 2002 and Tuscano. The interchangeability between the Edwards 2002 dosing regimen and the De Vita 2002 dosing regimen is confirmed by the ’838 patent specification.

Additional claim limitations directed to combination therapies involving prior art drugs commonly used to treat RA, like methotrexate and corticosteroids, do not confer patentability to the ’838 patent claims. The PTAB should institute trial on all claims.

II. MANDATORY NOTICES – 37 C.F.R. § 42.8(A)(1) AND (B)

A. 37 C.F.R. § 42.8(b)(1): Real Party In Interest

Sandoz, Inc. (“Sandoz” or “Petitioner”) is the real party-in-interest for Petitioner.

B. 37 C.F.R. § 42.8(b)(2): Related Matters

A European counterpart to the '838 patent, EP 1,613,350 (the "EP '350 patent", Ex. 1103),[2] was revoked as obvious in light of one or more of the references asserted here. Ex. 1104; Ex. 1144 (dismissing patentee's appeal of the decision to revoke the EP '350 patent). The '838 patent has been the subject of four prior IPR petitions; IPR2016-01667, IPR2015-01733, IPR2015-00417, and IPR2017-01923. The PTAB instituted review of all claims of the '838 patent in *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc.*, IPR2015-00417, Paper No. 11, at 26–27 (P.T.A.B. July 14, 2015). Another petition, *Pfizer, Inc. v. Genentech, Inc.*, IPR2017-01923, is currently pending before the Board. Petitioner concurrently files one additional IPR petition for the claims of the '838 patent. Petitioner is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in this Proceeding. The grounds, evidence, and/or arguments relied upon in this Petition are different than what was relied upon in IPR2016-01667, IPR2015-01733, IPR2015-00417, and IPR2017-01923, and during prosecution of the '838 patent.

[2] The '838 patent claims priority to U.S. Provisional Application No. 60/461,481 (the "'481 provisional application"); the EP '350 patent claims priority to PCT/US2004/010509, which claims priority to the '481 provisional application.

C. 37 C.F.R. § 42.8(b)(3): Lead and Back-Up Counsel

Petitioner designates the following counsel:

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D. 37 C.F.R. § 42.8(b)(4): Service Information

Please address all correspondence to lead counsel at the contact information above. Petitioner consents to service by electronic mail at sgutmanptabmatters@proskauer.com. A Power of Attorney is being filed concurrently herewith. 37 C.F.R. § 42.10(b).

III. PAYMENT OF FEES – 37 C.F.R. § 42.103

The undersigned authorizes the PTO to charge the fees set forth in 37 C.F.R. § 42.15(a) and any additional fees that may be due for this Petition to Deposit Account No. 50-3081.

IV. GROUNDS FOR STANDING – 37 C.F.R. § 42.104(A)

Petitioner certifies the ’838 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR. 35 U.S.C. § 315.

V. IDENTIFICATION OF CHALLENGE – 37 C.F.R. § 42.104(B)

The ’838 patent issued on July 12, 2011, from U.S. Patent Application No. 12/052,606, and claims priority to the ’481 provisional application (filed April 9, 2003, the “Earliest Possible Priority Date”). This Petition is governed by pre-AIA 35 U.S.C. § 103. *See* MPEP § 2159.01. Petitioner requests review of the Challenged Claims of the ’838 patent on the following grounds:

Ground	Claims	Prior Art References	Statutory Basis
1	1–14	Edwards 2002 in view of Patel and Curd	35 U.S.C. § 103
2	1–14	Edwards 2002 in view of Tuscano and Curd	35 U.S.C. § 103

The cited prior art is as follows:

- Edwards JCW *et al.*, *Efficacy and Safety of Rituximab, a B-Cell Targeted Chimeric Monoclonal Antibody: A Randomized, Placebo-Controlled Trial in Patients with Rheumatoid Arthritis*, 46(9) ARTHRITIS & RHEUMATISM S197 (2002) (“Edwards 2002,” Ex. 1138). Edwards 2002 is prior art under at least 35 U.S.C. § 102(a). Edwards 2002 is a “printed publication” that published at least by October 14, 2002. In a previous IPR, Genentech did not dispute that Edwards 2002 was accessible to the public prior to the Earliest Possible Priority Date. *See Boehringer Ingelheim Int’l GmbH v. Genentech, Inc.*, IPR2015-00417, Paper No. 9, at 37–44 (P.T.A.B. April 15, 2015).

- Patel DD, *B Cell–Ablative Therapy for the Treatment of Autoimmune Diseases*, 46(8) Arthritis & Rheumatism 1984–1985 (August 2002) ("Patel," Ex. 1159). Patel is prior art under at least 35 U.S.C. § 102(a). Patel is a "printed publication" that published at least by August 21, 2002.

- Tuscano JM, *Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis With Rituximab*, 46(12) ARTHRITIS & RHEUMATISM 3420 (December 2002) ("Tuscano," Ex. 1136). Tuscano is prior art under at least 35 U.S.C. § 102(a). Tuscano is a "printed publication" that published at least by December 18, 2002. In a previous IPR, Genentech did not dispute that Tuscano was accessible to the public prior to the Earliest Possible Priority Date. *See Boehringer*, IPR2015-00417, Paper No. 9, at 41–45, 47–49.

- International Application Publication No. WO 00/67796 ("Curd," Ex. 1116) is prior art under at least 35 U.S.C. § 102(b). Curd is a "printed publication" that published on November 16, 2000. As an international patent application filed under the Patent Cooperation Treaty, it became publicly available on the date of its publication.

Below is a detailed explanation of the statutory grounds for the unpatentability of each claim. Additional evidence is provided in the Declarations of David Fox, M.D. (Ex. 1107), William J. Jusko, Ph.D. (Ex. 1108), and other supporting exhibits. 37 C.F.R. § 1.68. The discussion below and supporting

evidence establish that it is reasonably likely Petitioner will prevail with respect to at least one claim.

VI. THE CLAIMS OF THE '838 PATENT ARE UNPATENTABLE

A. Level of Ordinary Skill

A POSITA is presumed aware of all pertinent art, employs conventional wisdom, and possesses ordinary creativity in the pertinent field. Doctors in the field of rheumatology tend to be well informed about current trends and developing therapies for treating rheumatoid arthritis. This was true by the Earliest Possible Priority Date and remains true today. Ex. 1107 ¶ 38.

A POSITA as of the Earliest Possible Priority Date would have been a practicing rheumatologist with (i) at least 2–3 years of experience treating RA patients, (ii) knowledge about the available methods of treating RA, including on-going clinical trials, (iii) an understanding of the pathophysiology of RA, and (iv) an understanding of the design of clinical trials, including those directed to new dosing regimens. *Id.* ¶ 39.

B. The State of the Prior Art

1. Background on Rheumatoid Arthritis

RA is a chronic autoimmune disease that causes pain, stiffness, swelling, limited motion, and function in joints. Ex. 1107 ¶ 40. While RA can affect any joint, small joints of the hands and feet are involved most often. *Id.* Effective

treatments for RA—*e.g.*, DMARDs, non-steroidal anti-inflammatory drugs ("NSAIDs"), and TNFα inhibitors—were available long before the Earliest Possible Priority Date. *Id.* ¶¶ 40–41; *see also* Ex. 1109 at 1682 (listing prior patients' prior DMARD exposure). However, patients often failed to respond adequately or sustain an initial response to treatment, or suffered significant toxicity. Ex. 1107 ¶ 41. When a patient experiences an inadequate response or toxicity, doctors typically prescribe an alternative treatment, or combination of treatments, that work based on a different mechanism of action than the failed therapy. *Id.* ¶ 42–44; Ex. 1110 at 329 (Figure 1). Remission from RA is rare and there is no cure. Ex. 1107 ¶ 41.

2. DMARDs Were Well-Established RA Treatments Before the Earliest Possible Priority Date

Before the Earliest Possible Priority Date, single-agent DMARD therapies were first-line RA treatments. Ex. 1110 at 329 (Figure 1), 331 (Table 2). If the patient response was inadequate, combination therapies involving other DMARDs—including methotrexate—were administered. *Id.* at 329 (Figure 1); Ex. 1107 ¶ 44. Patients who responded inadequately or had side-effects to such combinations were offered other therapies. Ex. 1110 at 329.

In the early 1990s, a committee of the American College of Rheumatology ("ACR") selected a "core set" of measures for assessing a patient's response to RA

treatments. Ex. 1111 at 735 (Table 5); Ex. 1107 ¶ 42. The criteria measure the percent improvement in tender joint count, swollen joint count, and three out of five core set items: (i) physician's global assessment; (ii) patient global assessment; (iii) patient pain; (iv) disability (self-reported via validated survey); and (v) erythrocyte sedimentation rate or C-reactive protein titer. Ex. 1110 at 332. "ACR20" refers to a patient that achieves a 20 percent improvement in tender joint count, swollen joint count, and three of the five core set items. *Id.* "ACR50" and "ACR70" refer to 50 and 70 percent improvements, respectively. *Id.*

Methotrexate is a common DMARD that slows RA's progression by slowing damage to bone and cartilage. Ex. 1107 ¶ 43; *see also* Ex. 1109 at 1682 (Table 1); Ex. 1112 at 780–82. The efficacy and safety of methotrexate for treating RA was well established prior to the Earliest Possible Priority Date. *See* Ex. 1112 at 780 ("The efficacy of methotrexate in the treatment of RA is unquestioned...."); Ex. 1107 ¶¶ 43, 55. Methotrexate was the most commonly used and first prescribed DMARD by most rheumatologists in the United States for treating RA. Ex. 1112 at 779; Ex. 1107 ¶ 43.

Combination therapies for treating RA with methotrexate were common practice before the Earliest Possible Priority Date. By the late 1990s, new RA treatments were generally added to ongoing methotrexate treatment. Ex. 1107 ¶¶ 44, 55–57; *see also, e.g.*, Ex. 1112 at 790. At that time, "most [physicians]

would [have] agree[d], that methotrexate should be the cornerstone of most combinations; it is also the standard against which combinations should be measured." Ex. 1112 at 790; *see* Ex. 1113 at 1548 (stating most new biotechnology-derived therapies, including antibody therapies like some TNFα inhibitors, were combined with methotrexate); Ex. 1114 at 593 (stating that new drugs and biotechnology products "should be tested in combination with methotrexate…, [because] this is how they are likely to be used").

Combination therapies generally targeted inadequate responders to methotrexate—*i.e.*, patients that still experienced symptoms of active disease and needed additional relief. Ex. 1107 ¶¶ 43–44, 55–57; *see also* Ex. 1115 at 209 (disclosing an anti-TNFα antibody and methotrexate combination as "especially effective in RA patients in whom disease control with methotrexate alone is incomplete."). This is because there would be no reason to seek alternative therapies for patients when traditional DMARD therapy was effective. Ex. 1107 ¶ 44. Many new combinations simply built on past treatment regimens—*e.g.*, methotrexate, corticosteroids, and/or NSAIDs were added to newer biologic therapies like TNFα inhibitors or anti-CD20 antibodies. *See*, *e.g.*, Ex. 1116 at 25:10–16 ("[T]he patient is optionally further treated with any one or more agents employed for treating RA such as... methotrexate or corticosteroids….").

3. Corticosteroids Were Used Alone and in Combination with DMARDs, Including Biologic Therapies, to Treat RA

Corticosteroids were used to treat RA long before the Earliest Possible Priority Date. Ex. 1107 ¶ 57; *see also* Ex. 1117 at 142 ("Oral glucocorticoids are widely used to treat patients with [RA]...."). Corticosteroids provide symptomatic relief and can act to reduce the progression of RA when combined with other treatments. *Id.* at 144 (combining corticosteroids with NSAIDs, intra-muscular gold, penicillamine, sulfasalazine, methotrexate, and other agents); Ex. 1118 at 309 (comparing methotrexate, prednisolone, and sulphasalazine versus sulphasalazine alone); Ex. 1106 at 205 (combining prednisolone, rituximab, and cyclophosphamide). Common corticosteroids include "prednisone, methylprednisolone, and dexamethasone…." Ex. 1116 at 8:28–29.

4. TNFα Inhibitors Were a Significant Development for RA Patients Who Inadequately Responded to Other DMARDs

In the mid-1990s, TNFα inhibitors represented a major advance in RA therapies, especially for patients who did not respond adequately to existing DMARDs. Ex. 1107 ¶ 45–46. Before the Earliest Possible Priority Date, at least three TNFα inhibitors were approved by the U.S. Food and Drug Administration ("FDA") for treating RA: (i) etanercept (Enbrel®); (ii) infliximab (Remicade®); and (iii) adalimumab (Humira®). Exs. 1119, 1120, 1121.

It was well understood before the Earliest Possible Priority Date that TNFα inhibitors were not effective in all RA patients. Ex. 1107 ¶ 47. Only about 60% of patients achieve a clinical response to TNFα inhibitors, with or without methotrexate. *Id.*; *see also* Ex. 1122 at 1552. And, failure of any given DMARD therapy is not predictive of whether a patient will respond to TNFα inhibitors. Ex. 1107 ¶ 47; *see also* Ex. 1122 at 1557; Ex. 1123 at 201 ("There are currently no predictors of a good response to anti TNF drugs and a percentage of patients fail to respond to treatment (25% to 38% of etanercept patients; 21% to 42% of infliximab patients)."). It was also well understood that patients who responded inadequately or had toxicity to TNFα inhibitors should seek alternative treatments targeting alternative mechanisms of action. Ex. 1107 ¶ 48; *see also, e.g.*, Ex. 1125 at I129 ("alternative treatments or regimens should be considered" absent improvement in symptoms or laboratory parameters); Ex. 1110 at 332–40 (discussing NSAIDs, DMARDs, glucocorticoids, and biologics, including varying mechanisms of action and successful drug combinations).

The 2002 ACR Guidelines for the Management of RA provides an outline for treating RA. Ex. 1110 at 329 (Figure 1) (reproduced below). Initial treatment involved DMARDs optionally combined with NSAIDs and/or corticosteroids. *Id.* Inadequate responders received additional or different DMARDs. *Id.* Then, suboptimal responses to methotrexate and combination therapies led to biologic

DMARDs, including TNFα inhibitors, alone or combined with methotrexate. *Id.*; *see also* Ex. 1119 at (adalimumab and methotrexate); Ex. 1120 at 12 (etanercept and methotrexate); Ex. 1121 at (infliximab and methotrexate). Following this trajectory, with the development and use of anti-CD20 antibodies to treat RA, TNFIRs would have then received anti-CD20 therapy involving rituximab. Ex. 1107 ¶ 48. At each step, drug dosing was not modified based on toxicity or lack of response to previous therapies involving different mechanisms of action. *Id.*; *see also* Ex. 1119 at 6, 14–15; Ex. 1120 at 12, 23–24; Ex. 1121 at 8, 16.

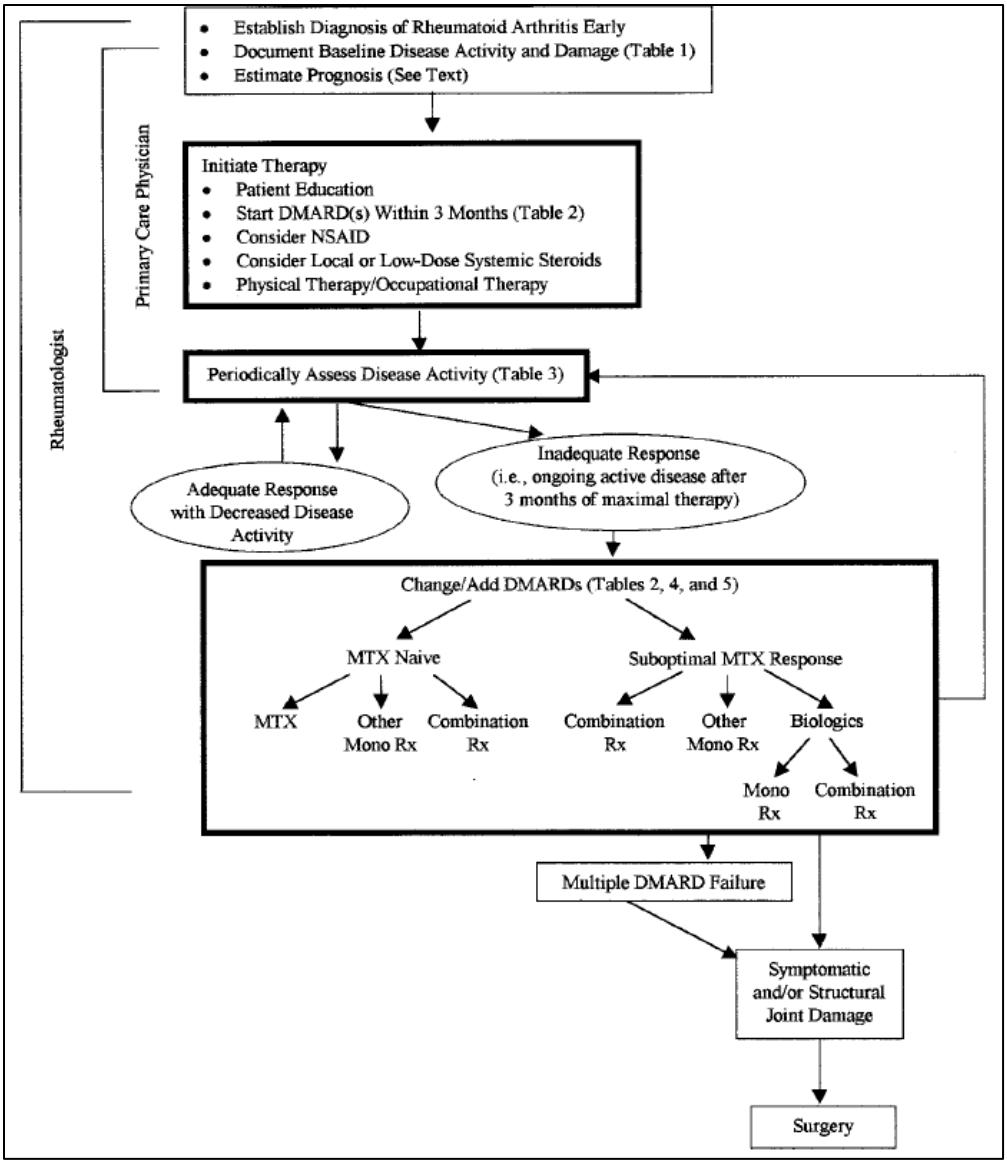

Figure 1: Outline of the management of rheumatoid arthritis.… A suboptimum response to methotrexate (MTX) is defined as intolerance, lack of satisfactory efficacy with a dosage of up to 25 mg/week, or a contraindication to the drug.… [M]ono Rx = monotherapy; combination Rx = combination therapy.

5. Development of Anti-CD20 Antibodies and Their Use to Treat RA, Including in TNFIRs

Rituximab (RITUXAN®, Mabthera®, or IDEC-C2B8) is an antibody that targets B-cells in humans, resulting in B-cell depletion. Ex. 1126 at 1. Rituximab was approved for treating B-cell NHL in 1997. *Id*. at 2. Rituximab was well tolerated and non-toxic, with some patients safely receiving single dose infusions of over 1,000 mg. Ex. 1128 at 2460 Ex. 1107 ¶ 49; *see also* Ex. 1127 at 3268 (maximum total dose of 3,200 mg).

Rituximab was used to effectively treat RA before the Earliest Possible Priority Date. Ex. 1107 ¶¶ 50–51. By 1998, scientists realized rituximab could be useful to treat RA by causing B-cell depletion. *Id.*; *see also* Ex. 1131 at 126; Ex. 1132 at 53 ("at least in early disease anti-CD20 might well be curative in RA.... The treatment would appear to be very safe, and a clinical trial is proposed"). By 1999, early clinical trial results were reported. *E.g.*, Ex. 1133 at Abstract.

In 2001, Dr. Jonathan Edwards reported the results of a promising study treating RA with rituximab. Ex. 1106 at 205 ("Edwards 2001"); Ex. 1107 ¶ 52. Edwards 2001 reports "[f]ive patients with refractory RA were treated with a monoclonal anti-CD20 antibody, cyclophosphamide and prednisolone and followed for 12–17 months." Ex. 1106 at 205. Patients received the same antibody dose regimen irrespective of what therapy they previously received and

irrespective of what the results were for that previous therapy. *Id.* at 206 (Table 1). All patients satisfied the ACR50 or ACR70 criteria without further therapy. Ex. 1106 at 205.

In October 2002, before the Earliest Possible Priority Date, Dr. Edwards and colleagues reported the results of treating 161 RA patients with rituximab alone and in combination with other therapies. Ex. 1138 at S197. Consistent with the routine practice of combining known therapies, patients were treated with (1) methotrexate, (2) rituximab, (3) methotrexate with rituximab, or (4) rituximab and cyclophosphamide. *Id.*; Ex. 1107 ¶ 53; Ex. 1110 at 332–333. All rituximab receiving patients received two intravenous 1,000 mg doses of rituximab separated by two weeks. Ex. 1138 at S197. All patients received corticosteroids. *Id*. The three rituximab regimens were "well tolerated" and resulted in "substantial clinical benefit in RA," including ACR20, ACR50, and ACR70 responses. *Id.* As in Edwards 2001, Edwards 2002 treated all patients with the same antibody dosing regimen irrespective of what therapy they previously received. Ex. 1138 at S197.

The fact that Edwards 2001 and Edwards 2002 treated all patients the same regardless of their prior therapy is notable. It demonstrates that POSITAs expected the prior therapy and, more particularly, any inadequate response to the prior therapy, would not inform the dosing regimen of rituximab that should be used to successfully treat refractory RA patients. Ex. 1107 ¶¶ 54, 135, 142, 147. POSITAs

had known for years that 40% of RA patients treated with TNFα inhibitors inadequately responded. *See* Ex. 1122 at 1557; Ex. 1123 at 201. Despite this knowledge, studies using rituximab in RA did not control for anti-TNF treatment status, and treated all patients alike, including TNFIRs. Ex. 1106 at 205; Ex. 1138 at S197; Ex. 1136 at 3420 ("[T]his data supports the hypothesis that B lymphocytes mediate pathology in RA and that rituximab is a promising agent for patients with DMARD and infliximab-refractory RA"); Ex. 1105 at 323 (treating four patients with rituximab where half "had not responded to anti-TNF alpha therapy"); Ex. 1159 at 1985. All patients were treated the same despite their prior treatment status because POSITAs were well aware that rituximab, an anti-CD20 antibody, operates with a different mechanism of action than other DMARD therapies like TNFα inhibitors. Ex. 1107 ¶¶ 54, 135, 142, 147; *see also* Ex. 1139 at 4 (Fig. 1.1) (showing how B cells act upstream of TNFα during the inflammatory process); Ex. 1141 at 3 (distinguishing rituximab's effect on B-cells from DMARDs that "target the immune system's T-cells or inflammatory signals"). Consequently, an inadequate response to a TNFα inhibitor would not be predictive of the result or dosing regimen necessary to produce an effective response in a patient receiving rituximab. Ex. 1107 ¶¶ 54, 142.

Also by 2002, rituximab had been used to successfully treat RA in TNFIRs, a fact that was expressly disclosed and touted in DeVita 2002, Tuscano, and Patel,

for example. Ex. 1160 at 2030 (successfully treating four of five RA patients "that had not been responsive to therapies targeted to the T cell/macrophage cell-mediated immune response"); Ex. 1136 at 3420 (concluding that "rituximab is a promising agent for [TNFIRs]"); Ex. 1159 at 1985 (discussing RA patient groups that will respond to B cell ablative therapy and concluding that "certainly those whose RA is refractory to conventional therapy (including TNF inhibitors) may respond").

C. The '838 Patent

1. Claims

The '838 patent has 14 claims. Claims 1, 2, 8, 10, and 11 are independent. The claims recite "[a] method of treating [RA] in a [TNFIR], comprising administering… an antibody that binds to CD20 [(*e.g.*, rituximab)], wherein the antibody is administered as two intravenous doses of 1000 mg." *E.g.*, Ex. 1101 at claim 1, 3. Several claims recite administering the antibody "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…." *E.g.*, *id.* at claim 2, 10–14. Dependent claims are directed to "concomitant methotrexate" and "a corticosteroid regimen." *E.g.*, *id.* at 4–6, 9.

2. Specification

The ’838 patent summarizes the claimed invention as: “a method of treating an autoimmune disease in a mammal who experiences an inadequate response to a TNFα inhibitor, comprising administering to the mammal a therapeutically effective amount of an antagonist which binds to a B cell surface marker.” Ex. 1101 at 4:60–65. The majority of the patent disclosure discusses antibody development and production. *See id.* at 15:27–28:43.

The patent defines “inadequate response to a TNFα-inhibitor” as “an inadequate response to previous or current treatment with a TNFα-inhibitor because of toxicity and/or inadequate efficacy.” *Id.* at 5:25–19. But, “the invention is not limited to a prior therapy step with such a TNFα-inhibitor, for instance, the patient may be considered to be prone to experience a toxicity, e.g. cardiac toxicity, with a TNFα-inhibitor before therapy therewith has begun, or the patient may be determined to be one who is unlikely to respond to therapy with a TNFα-inhibitor.” *Id.* at 28:55–61. Nothing in the ’838 patent suggests to a POSITA that TNFIRs should be treated differently from other patients for purposes of receiving anti-CD20 therapy.

The ’838 patent discloses antibody doses from “about 20 mg/m^2 to about 1000 mg/m^2.” *Id.* at 29:23–25. The patent provides “[e]xemplary dosage regimens [that] include 375 mg/m^2 weekly×4; or 1000 mg×2 (e.g. on days 1 and 15).” *Id.* at

29:32–33. The patent states that "these suggested amounts of antagonist are subject to a great deal of therapeutic discretion." *Id.* at 29:42–43.

The specification discloses no experimental data. The only example is a prophetic example involving the same two dosing regimens: "Patients are treated with a therapeutically effective dose of the CD20 antibody, for instance, 1000 mg i.v. on Days 1 and 15, or 375 mg/m^2 i.v. weekly×4." *See* Ex. 1101 at 31:29–31. The specification does not suggest that one dosing regimen is preferable to another. Rather, it refers to them both as exemplary doses and treats 375 mg/m^2 administered weekly for four weeks as interchangeable with two 1,000 mg doses separated by fourteen days.

The patent defines "therapeutically effective amount" as "an amount of the antagonist which is effective for preventing, ameliorating or treating the autoimmune disease in question." *Id.* at 12:62–65. The specification reports no experimental data to demonstrate that the claimed dosage is actually "therapeutically effective." Instead, the patent relies upon its instruction to administer either four 375 mg/m^2 doses or two 1,000 mg doses to enable a POSITA to administer a "therapeutically effective amount."

In the prophetic example, the specification suggests a "primary endpoint may be the proportion of patients with an ACR20 response at Week 24 using a Cochran-Mantel-Haenszel (CMH) test for comparing group differences, adjusted

for rheumatoid factor and region." *Id.* at 31:42–32:2. The example provides a list of possible secondary endpoints including ACR50 and ACR70 at week 24. *Id.* at 32:4–6. Erosive progression at weeks 24 and beyond is an "exploratory endpoint." *Id.* at 32:28–34. The specification concludes: "Therapy of RA with the CD20 antibody in [TNFIRs] as described above ***will result in a beneficial clinical response*** according to ***any one or more*** of the endpoints noted above." *Id.* at 32:40–43.[3] There is no data or other information to support this conclusion.

3. Prosecution History

During prosecution, Genentech submitted one substantive response to a non-final office action before filing a terminal disclaimer and obtaining a Notice of Allowance. *See* Ex. 1142 at 963–64, 981–87. In its response, Genentech repeatedly distinguished the prior art as not disclosing the "inadequate response to a TNFα inhibitor" or the treatment outcome elements. *See, e.g.*, *id.* at 427–31.

Genentech relied on a declaration by Dr. van Vollenhoven that was originally submitted to the European Patent Office in connection with the opposition to the EP '350 patent resulting in its revocation. *See* Ex. 1143; Ex. 1144 at 30–36 (dismissing patentee's appeal thereby affirming that all challenged claims of EP 1613350 were invalid as lacking an inventive step). Genentech argued that

[3] All emphasis is added unless noted otherwise.

Dr. van Vollenhoven's declaration "explains how the invention addresses a significant unmet medical need in April 2003 by providing an effective treatment regimen for particularly hard to treat and drug-refractory anti-TNF inadequate responders...." *See* Ex. 1142 at 429–30. Contrary to the positions Genentech took during prosecution, the instant petition, through expert testimony and other evidence not before the Examiner, demonstrates that a POSITA would not have considered TNFIRs "harder to treat" with respect to rituximab therapy. This is especially true given that, according to the patent, TNFIRs did not need to actually be treated with TNFα inhibitors to be considered TNFIRs. Ex. 1101 at 28:45–61. In fact, POSITAs would have treated TNFIRs the same as any other RA patient for whom rituximab therapy was being considered.

4. The '838 Patent Had a Single Inventor for More Than 13 Years, Until Genentech Petitioned to Add a Co-Inventor After the PTAB Instituted an IPR of the '838 Patent

Mark Benyunes identified himself as the sole inventor when he filed the '481 provisional application. Ex. 1146 at 1. Dr. Benyunes was the lone inventor named on the two non-provisional applications that followed in 2004 and 2008, and was the only inventor listed on the '838 patent when it issued on July 12, 2011. Ex. 1145 at 1; Ex. 1142 at 2. Dr. Benyunes remained the only inventor for over 13 years. Ex. 1142 at 1053–54.

In July 2016, Genentech filed a Petition for Correction of Inventorship adding Randall Stevens as a co-inventor on the ’838 patent. *Id.* at 1053, 1072. Then, in a patent owner preliminary response, Genentech relied on Dr. Stevens’s work to attempt to swear behind Edwards 2002. *See Celltrion, Inc. v. Genentech, Inc.*, IPR2016-01667, Paper No. 13, at 1 (P.T.A.B. Dec. 6, 2016) (“Edwards 2002 does not even qualify as prior art with respect to a number of claims.... Indeed, one inventor of the ’838 patent—Dr. Randall Stevens—describes some of his prior inventive work in Edwards 2002, which he co-authored.”). Notably, a year before Genentech petitioned to correct inventorship, the PTAB instituted trial in a prior IPR proceeding involving the ’838 patent based on Edwards 2002. *See Boehringer*, IPR2015-00417, Paper No. 11, at 18 (instituting IPR of claims 1–5 and 7–14 based on obviousness over Edwards 2002 and Tuscano).

Every indication is that Genentech’s addition of Dr. Stevens as a co-inventor to the ’838 patent—more than 13 years after the purported dates of conception and reduction to practice—was not a genuine effort to correct inventorship, but a legal strategy to attempt to avoid harmful prior art. In fact, it appears Genentech has not sought to add Dr. Stevens to any domestic or foreign counterpart to the ’838 patent, including related U.S. Patent No. 7,708,994.

D. 37 C.F.R. § 42.104(b)(3): Claim Construction

1. Legal Standard

In an IPR, claim terms are given their broadest reasonable interpretation in light of the patent specification. 37 C.F.R. § 42.100(b). "The specification 'is the single best guide to the meaning of a disputed term.'" *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005)). Claim terms are given their ordinary and customary meaning, as would be understood by a POSITA in the context of the entire disclosure. *Id.* Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

2. Claim Elements That Recite Intended Clinical Outcomes Are Not Entitled to Patentable Weight

Claims 2–7 and 10–14 include "clinical outcome" elements that merely recite the intended results of the claimed methods without reciting anything beyond administering rituximab at the claimed dosage: "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." Ex. 1101 at claims 2–7; *see also id.* at claim 10–14 (reciting the clinical outcomes as part of "wherein" clauses or as a Markush group in the preamble).

The claim language directly relates the clinical outcomes to the recited dosing regimen (*i.e.*, two 1,000 mg doses) and demonstrates that these outcomes are the intended results of the administered doses. In the patent's prophetic example, the specification states that two 1,000 mg doses of rituximab administered two weeks apart, or four 375 mg/m^2 doses of rituximab weekly are "therapeutically effective dose[s]" that "***will result***" in the recited clinical outcomes. *Id.* at 31:29–31, 32:40–43. The '838 patent identifies nothing beyond administering two 1,000 mg doses, or four 375 mg/m^2 doses of the drug to TNFIRs to achieve the claimed clinical outcomes. By saying that such administration "***will result***" in the claimed clinical outcomes, the patent characterizes the clinical outcomes as the intended or aspirational result of the administration. Indeed, the claimed methods remain the same even if none of the clinical outcomes occur.

The Federal Circuit has held that clauses in a method claim have no patentable weight when they express the intended result of a process step. *E.g.*, *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (holding a "clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited"); *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed. Cir. 1993) (finding a clause that "merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim"). This is especially so when, as here, the

specification "does not describe any studies that show" the recited clinical outcomes were achieved "thus… suggesting that the claims do not incorporate such a requirement." *In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012).

The PTAB has also consistently found similar claim elements lack patentable weight when they simply recite the intended result of a prior method step. *E.g.*, *Baxter Healthcare Corp. v. Millenium Biologix, LLC*, IPR2013-00590, Paper No. 49, at 7–8, 10–11 (P.T.A.B. Mar. 18, 2015) (holding claim elements were not entitled to patentable weight because they "list various intended results," "do not recite positive acts that are carried out as part of the claimed methods," "[n]or do they specify any limitation on the manner in which the [method] step is to be carried out"); *Fresenius-Kabi USA LLC v. Cubist Pharms., Inc.*, Case No. IPR2015-00227, Paper No. 13, at 5–7 (P.T.A.B. May 14, 2015) (holding that "the requirement of 'minimiz[ing] skeletal muscle toxicity' would be understood as nothing more than the intended result or consequence of administering daptomycin at the specifically recited dosage interval" because it "does not require anything beyond administering daptomycin at the express dosage intervals recited in the claims"); *Ex Parte Berzofsky*, No. 1010-011270, 2011 WL 891756, at *5 (B.P.A.I. Mar. 10, 2011) ("The wherein clauses do not inform the mechanics of how the 'administering' or 'contacting' steps are performed; rather, the wherein clauses

merely characterize the result of that step[, and therefore are] not entitled to weight in construing the claims.").

E. Statement of the Law of Obviousness

The objective analysis under 35 U.S.C. § 103(a) includes several steps: "[T]he scope and content of the prior art are... determined; differences between the prior art and the claims at issue are... ascertained; and the level of ordinary skill in the pertinent art [is] resolved." *KSR Int'l Co. v. Teleflex, Inv.*, 550 U.S. 398, 399 (2007). "Against this background, the obviousness or nonobviousness of the subject matter is determined." *Id.* "[S]econdary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc., [may also] be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.*

A patent claim is invalid as obvious if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a POSITA. *KSR*, 550 U.S. at 406. In addition, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* at 421.

F. Printed Publications Relied Upon

1. Overview of Edwards 2002

Edwards 2002 reports an initial study using "the chimeric monoclonal antibody, rituximab, against the B-cell antigen CD20, in combination with cyclophosphamide (CTX) and corticosteroids." Ex. 1138 at S197. One hundred sixty one patients with RA that were receiving methotrexate were randomized into one of four treatment groups: (1) methotrexate, (2) rituximab, (3) rituximab plus cyclophosphamide, and (4) rituximab plus methotrexate. *Id.* All groups received a 17 day course of corticosteroids. *Id.* The rituximab regimen was two doses of 1,000 mg. *Id.* Edwards 2002 concludes that "a short induction regimen with rituximab alone or in combination with either [methotrexate] or [cyclophosphamide] produced substantial clinical benefit in RA." *Id.* All rituximab receiving groups produced ACR20, 50, and 70 responses that were higher than the control group that received methotrexate alone. *Id.* The groups that received a combination therapy of rituximab plus either methotrexate or cyclophosphamide "produced the highest levels of ACR20, 50 and 70 responses." *Id.*

2. Overview of Patel

Patel is a review article that discusses the results of several studies involving rituximab in RA. Ex. 1159 at 1984 (citing Ex. 1105; Ex. 1106). First, Patel discloses a report by Edwards and Cambridge (Edwards 2001, Ex. 1106) in which

five patients "with refractory RA were given a regimen of anti-CD20 [antibodies (rituximab)] with intravenous cyclophosphamide and high-dose steroids." *Id.* As a result, "[a]ll of the patients achieved responses meeting the American College of Rheumatology 70% improvement criteria (ACR70) after the first or second treatment cycle." *Id.* Next, Patel discusses a report by De Vita (DeVita 2002, Ex. 1160) treating "5 patients with RA that had not been responsive to combination therapy with methotrexate and cyclosporine A, with or without anti-tumor necrosis factor α (anti-TNFα) therapy" using rituximab. *Id.* DeVita 2002 administered "4 weekly intravenous infusions of 375 mg/m^2" rituximab. Ex. 1160 at 2030. De Vita reported ACR20, ACR50, and ACR70 responses. *Id.* Patel states that, "[t]aken together, the studies on anti-CD20 therapy for RA provide compelling evidence that B cells may play an important role in RA pathogenesis." *Id.* Patel concludes that "certainly those whose RA is refractory to conventional therapy (including TNF inhibitors) may respond" to B cell ablative therapies like rituximab. *Id.* at 1985.

3. Overview of Tuscano

Tuscano is an abstract titled: "Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis with Rituximab." Ex. 1136 at 3420. It reports "the initial data of a clinical trial using rituximab alone for the treatment of erosive RA in patients that have previously failed multiple DMARD's including infliximab."

Id. Infliximab is an anti-TNFα antibody (*i.e.*, TNFα inhibitor) therapy. Ex. 1121. Patients were administered 100 mg rituximab on the first week, followed by 375 mg/m^2 the second week, and 500 mg/m^2 on weeks three and four. Ex. 1136 at 3420. "At a median follow-up of 5 months all seven patients had improved joint scores, and 3 met criteria for an ACR 20." *Id.* "Absolute B lymphocyte levels were diminished by 8 weeks post-therapy." *Id.* Tuscano concludes that "this data supports the hypothesis that B lymphocytes mediate pathology in RA, and that rituximab is a promising agent for patients with DMARD and infliximab-refractory RA." *Id.*

4. Overview of Curd

Curd describes the intravenous administration of rituximab for treating RA. *E.g.*, Ex. 1116 at 25:17–18 ("RITUXAN® is administered intravenously (IV) to the RA patient according to any of the following dosing schedules... [showing various doses on days 1, 8, 15 & 22]," including weekly administrations of 375 mg/m^2). The disclosed doses cover a broad range: "Suitable dosages [are] in the range from about 20mg/m^2 to about 1000mg/m^2. In one embodiment, the dosage of the antibody differs from that presently recommended for RITUXAN®. For example, one may administer to the patient one or more doses of substantially less than 375mg/m^2 of the antibody...." *Id.* at 23:18–21. The range of 20 mg/m^2 to about 1,000 mg/m^2 includes fixed doses of 1,000 mg. Ex. 1107 ¶ 59. The

disclosure related to dose in Curd is nearly identical to the disclosure in the ’838 patent. *Compare* Ex. 1116 at 23:14–33 *with* Ex. 1101 at 29:16–51.

Curd also discusses combination therapies involving methotrexate and corticosteroids and provides a list of three potential corticosteroids: “prednisone, methylprednisolone, and dexamethasone.” *See* Ex. 1116 at 8:28–29, 25:10–16 (“[T]he patient is optionally further treated with any one or more agents employed for treating RA such as... immunosuppressive agents such as ***methotrexate*** or ***corticosteroids*** in dosages known for such drugs or reduced dosages.”).

G. Claims 1–14 Are Invalid Based on Edwards 2002 in View of Patel or Tuscano and Curd

1. Claim 1

Edwards 2002 in view of Patel or Tuscano and Curd discloses “[a] method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα inhibitor, comprising administering to the patient an antibody that binds to CD20, wherein the antibody is administered as two intravenous doses of 1000 mg.”

i. Claim 1, preamble: "A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα inhibitor, comprising"

Patel discusses two studies, Edwards 2001 and DeVita 2002, each of which treated RA patients with rituximab in the same way without regard to their prior therapy status. Ex. 1159 at 1984 (citing Ex. 1106; Ex. 1160). DeVita 2002 successfully treated TNFIRs and non-TNFIRs using the same dosing regimen. *Id.*; Ex. 1160 ("5 patients with RA that had not been responsive to therapies targeted to the T cell/macrophage cell-mediated immune response were treated with anti-CD20 monoclonal antibody…. This proved clinically effective in 4 of the 5 patients."). Patel notes that these studies "provide compelling evidence that B cells may play an important role in RA pathogenesis." *Id.* The article concludes that "certainly those whose RA is refractory to conventional therapy (including TNF inhibitors) may respond" to rituximab. *Id.* at 1985; Ex. 1107 ¶¶ 63, 67, 69.

Tuscano "describe[s] the initial data of a clinical trial using rituximab alone for the treatment of erosive RA in patients that have previously failed multiple DMARD's including infliximab." Ex. 1136 at 3420. A patient that previously failed infliximab therapy—an anti-TNFα antibody—is a TNFIR. Ex. 1107 ¶¶ 65, 70. Like Edwards 2002, Edwards 2001, and DeVita 2002, Tuscano treated all

patients with the same dosing regimen of rituximab irrespective of that patient's prior therapies. Ex. 1136 at 3420.

Edwards 2002 discloses treating 161 patients with active RA that were receiving methotrexate. Ex. 1138 at S197. All of the patients who received rituximab were administered the same two 1,000 mg infusions without regard to their prior therapy status. *Id*.; Ex. 1107 ¶ 68. Although it is not necessary that Edwards 2002 included TNFIRs among its patients to demonstrate that the '838 patent claims are obvious, TNFIRs were included. A research report, dated November 2003, confirms Edwards 2002 included TNFIRs, yet they were neither analyzed separately nor treated differently from any other refractory patient in the study. *See* Ex. 1162 at 48–49, 72. Research Report No. 1005599 (Ex. 1162, "Roche Report") provides the results of a clinical trial conducted according to "Protocol WA16291." Ex. 1162 at 1. "Protocol WA16291" refers to the Edwards 2002 clinical trial.[4] The Roche Report discusses the underlying patient data and final results. *Compare* Ex. 1162 at 51 *with* Ex. 1163 at 2572. Like Edwards 2002,

[4] Dr. Edwards reported the final results of WA16291 in 2004. *See* Ex. 1164 at 17 (referencing "Edwards 2004 (WA16291)"); Ex. 1163 at 2572 (disclosing the final report of a clinical trial of 161 patients divided into the same four groups as Edwards 2002 and authored by the same people).

the Roche Report discloses 161 RA patients divided into four groups: (1) methotrexate; (2) rituximab; (3) rituximab plus cyclophosphamide; and (4) rituximab plus methotrexate. *Id.* at 16. Rituximab was administered in two 1,000 mg doses. *Id.* at 15. Patients were given corticosteroids—methylprednisolone and prednisolone—throughout the study. *Id.* at 26. Genentech cannot credibly dispute that the Roche Report is not the same study as Edwards 2002.

As the Roche Report reveals, five patients in the rituximab group and three patients in the rituximab plus methotrexate group were TNFIRs. *Id.* at 49 (Table 8). In the discussion, the Roche Report states that "10-15% of patients had failed anti-TNF therapy." *Id.* at 72. The authors emphasize that despite prior therapy failures with TNFα inhibitors there was a reasonable expectation that rituximab treatment would work because "[t]he novel mechanism of action of rituximab, targeting B cells, may be of advantage in such patients who have failed therapies targeting other arms of the immune response [such as TNFα inhibitors]." *Id.*

ii. Claim 1, element [a]: "administering to the patient an antibody that binds to CD20"

All four references disclose administering rituximab to patients suffering from rheumatoid arthritis. Ex. 1138 at S197 ("Group B: Rituximab alone (2 × 1g i.v. infusions)"); Ex. 1136 at 3420 ("Here we describe the initial data of a clinical

trial using rituximab alone for the treatment of erosive RA in patients that have previously failed multiple DMARD's including infliximab."); Ex. 1159 at 1984 ("5 patients with refractory RA were given a regimen of anti-CD20…."); Ex. 1116 at 25:9–11 ("Patients with clinical diagnosis of rheumatoid arthritis (RA) are treated with rituximab (RITUXAN®) antibody"). Rituximab is a chimeric, monoclonal antibody that binds to CD20. Ex. 1107 ¶¶ 49, 71–75; Ex. 1138 at S197 ("This initial study used the chimeric monoclonal antibody, rituximab, against the B-cell antigen CD20….").

iii. Claim 1, element [b]: "wherein the antibody is administered as two intravenous doses of 1000 mg"

The claim recites two doses of 1,000 mg, and does not require any specific amount of time between the doses. Edwards 2002 gave all patients that received rituximab two intravenous doses of 1,000 mg. Ex. 1138 at S197; Ex. 1107 ¶ 76.

iv. There is Motivation to Combine Edwards 2002, Patel or Tuscano, and Curd with a Reasonable Expectation of Success to Arrive at Claim 1

Edwards 2002, Patel, Tuscano, and Curd are all directed to using the anti-CD20 antibody rituximab to treat RA. Ex. 1107 ¶¶ 71–75. Patel and Tuscano both reference Edwards 2001 (Ex. 1106), an earlier publication by Dr. Edwards. Ex. 1159 at 1984 ("A report last year by Edwards and Cambridge…"); Ex. 1136 at

3420 ("Recent reports have suggested that RA may be successfully treated with the combination of rituximab and cyclophosphamide."); *see also* Ex. 1106 at 205.

A POSITA would have been motivated to use rituximab to treat RA in TNFIRs with a reasonable expectation of success because TNFIRs had already been successfully treated with rituximab in the prior art. Ex. 1136 at 3420 ("***Successful*** Treatment of ***Infliximab-Refractory Rheumatoid Arthritis*** with Rituximab"); *id.* (concluding that "rituximab ***is a promising agent*** for patients with DMARD ***and infliximab-refractory RA***."); *id.* ("all seven [TNFIRs] had improved joint scores, and 3 met criteria for an ACR 20"); Ex 1159 at 1984 (citing Ex. 1160 (demonstrating "clinically effective [treatment] in 4 of the 5 [treated] patients")); *id.* ("***certainly*** those whose RA is refractory to conventional therapy (including ***TNF inhibitors***) may respond"). It was common sense to treat TNFIRs and expect that they, like other RA refractory patients, would be successfully treated. TNFIRs had already failed multiple other DMARD therapies, and rituximab was a non-surgical alternative that exploited a different mechanism of action from TNFα inhibitors. Ex. 1107 ¶¶ 140–41; Ex. 1110 at 329, Figure 1; *see also* Ex. 1139 at 4 (Fig. 1.1) (showing how B cells act upstream of TNFα during the inflammatory process); Ex. 1141 at 3 (distinguishing rituximab's effect on B-cells from DMARDs that "target the immune system's T-cells or inflammatory signals").

Accordingly, an inadequate response to a TNFα inhibitor would not be predictive of how a TNFIR would respond to rituximab. Ex. 1107 ¶¶ 135, 142, 147.

A POSITA would have been further motivated to use the Edwards 2002 rituximab dosing regimen to treat TNFIRs with a reasonable expectation of success. POSITAs understood that less frequent dosing—*i.e.*, two doses as in Edwards 2002, instead of four doses as in Tuscano or DeVita 2002—would improve patient compliance. Ex. 1107 ¶ 138. Rituximab is administered intravenously. Ex. 1138 at S197. Patients cannot self-administer it and, instead, must travel to a facility for treatment. Ex. 1107 ¶ 138. Patients must take time off of work and other obligations to get to a facility and the treatments take upwards of several hours at the facility. *Id*. And, intravenous administrations cause pain and discomfort that can discourage patients from complying with their treatment regimen. *Id*. Therefore, as with many other drugs, POSITAs would have been motivated—and, in fact, were motivated—to find treatment regimens that required fewer drug administrations, and therefore reduced pain and trips to the clinic. *Id*.; Ex. 1138 at S197 (treating RA patients with two 1,000 mg doses).

Moreover, DeVita 2002 (referenced in Patel), Edwards 2002, Edwards 2001, and others, used the same dosing regimen to treat all refractory patients, including TNFIRs, because POSITAs reasonably expected similar results in all patients,

including TNFIRs.[5] Ex. 1107 ¶¶ 135–37, 140–41; *see also* Ex. 1105 at 323; Ex. 1106 at 206; Ex. 1138 at S197; Ex. 1159 at 1984; Ex. 1123 at 201; Ex. 1124 at 725–26. Thus, because Edwards 2002 demonstrated that refractory RA patients could successfully be treated using two doses of 1,000 mg, a POSITA also would have expected to succeed in treating TNFIRs with the same dosing regimen. Ex. 1107 ¶ 135. Accordingly, a POSITA would have been motivated to use the Edwards 2002 dosing regimen in TNFIRs with a reasonable expectation of success, just as a POSITA would have been motivated to use the Edwards 2002 dosing regimen in any other patient in view of the actual success achieved in Edwards 2002. Ex. 1107 ¶¶ 135–37, 140–41.

The pharmacokinetic profiles of the dosing regimens used to successfully treat TNFIRs in DeVita 2002 and Tuscano confirm what a POSITA would have expected. The profiles are equivalent for therapeutic purposes to the dosing regimen used in Edwards 2002 and the ’838 patent claims. *See* Ex. 1108 ¶¶ 23–24. The ’838 patent confirms the equivalence between the DeVita 2002 dosing regimen and the regimen used in Edwards 2002 and the ’838 patent claims.

[5] In fact, there would not have been any need to treat a patient who was not refractory, since presumably such patients were being adequately treated with their current therapy.

According to the prophetic example of the '838 patent, the dosing regimen used in Edwards 2002 (two 1,000 mg doses) is interchangeable with the dosing regimen used in DeVita 2002 (four weekly doses of 375 mg/m^2). Ex. 1101 at 31:29–31 ("Patients are treated with a therapeutically effective dose of the CD20 antibody…, 1000 mg i.v. on Days 1 and 15, or 375 mg/m^2 i.v. weekly×4"); *see also* Ex. 1107 ¶ 139.

The '838 patent specification confirms the obviousness, demonstrated by the prior art, of treating TNFIRs with two 1,000 mg doses of rituximab. The specification defines a TNFIR as someone that experiences "an inadequate response … ***because of toxicity*** and/or inadequate efficacy." Ex. 1101 at 5:25–29. If toxicity was an issue, a POSITA would have been motivated to treat the patient with an alternative therapy using a different mechanism of action, thereby avoiding the same toxicity. Rituximab was known to have low toxicity. Ex. 1107 ¶ 49.

Genentech has previously argued that a POSITA would not reasonably expect success or that the prior art teaches away from the claimed invention because, while DeVita 2002 taught that "ACR50 and ACR70 results were achievable in certain easier-to-treat RA patients, such results were <u>not</u> achieved in the harder-to-treat TNFα-inadequate-responders." *Celltrion*, IPR2016-01667, Paper 13, at 61 (emphasis in original). This argument has no merit.

First, DeVita 2002 demonstrates POSITAs were aware of TNFIRs, and that those patients were treated in the same manner as other patients. Ex. 1107 ¶ 137; Ex. 1160 at 2030 (treating five female patients, including two TNFIRs, with "an anti-CD20 chimeric monoclonal antibody" consisting of "4 weekly intravenous infusions of 375 mg/m^2"). Edwards 2002 confirms the approach of treating all refractory RA patients, including TNFIRs, alike without regard to their prior therapy to which they inadequately responded, including TNFα inhibitors. Ex. 1107 ¶¶ 137, 142–43; Ex. 1138 at S197.

Second, B-cells are a distinct target from TNFα effector cells (*i.e.*, cells that carry out the response to TNFα exposure), implicating a different mechanism of action. Ex. 1107 ¶¶ 140, 145. POSITAs understood as early as 1999 that attacking B cells with rituximab exploited a different mechanism of action from TNFα inhibitors. *See* Ex. 1107 ¶¶ 140–42; Ex. 1139 at 4 (Fig. 1.1) (showing how B cells act upstream of TNFα during the inflammatory process); Ex. 1141 at 3 (distinguishing rituximab's effect on B-cells from DMARDs that "target the immune system's T-cells or inflammatory signals"). Patel, after reviewing Edwards 2001 and DeVita 2002, concluded as much: "certainly those whose RA is refractory to conventional therapy (including TNF inhibitors) may respond" to "B cell-ablative therapy." Ex. 1129 at 1985. In essence, there was no reason to think that a patient responding inadequately to (or even failing) anti-TNFα therapy

would have had any predictive value for whether that same patient would have responded to rituximab. Ex. 1107 ¶¶ 135, 142, 147.

Third, if the '838 patent disclosure is sufficient to enable a POSITA to understand that a TNFIR could be treated with two 1,000 mg doses of rituximab based on a bare instruction to treat such patients in a prophetic example, the prior art is not required to disclose anything more. *See In re Copaxone Consol. Cases*, Civ. No. 14–1171–GMS, 2017 WL 401943, at *17, 18–19 (D. Del. Jan. 30, 2017), *appeal filed*, No. 17–1575 (Feb. 6, 2017) ("***It would constitute clear error*** for the court to discredit the Pinchasi reference for the same lack of dosing frequency clinical data from which the patents-in-suit suffer.") (*citing Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364,1374 (Fed. Cir. 2005)).

Finally, the prior art—*e.g.*, DeVita 2002 and Tuscano—do not teach away as a matter of law. To teach away, a reference must "'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *Galderma Labs. v. Tolmar, Inc.*, 737 F.3d 731, 738–39 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)); *Gator Tail, LLC v. Mud Buddy LLC*, 618 Fed. App'x 992, 999 (Fed. Cir. 2015). Genentech does not, and cannot, point to any statement in DeVita 2002 or Tuscano that criticizes, discredits, or discourages investigation into the claimed invention. To the contrary, DeVita 2002 and Tuscano encourage investigation into the

claimed invention by demonstrating that the RA of TNFIRs could be successfully treated with rituximab. Ex. 1107 ¶ 143; Ex. 1160 at 2030 ("In this study, 5 patients with RA ***that had not been responsive to therapies targeted to the T cell***/macrophage cell-mediated immune response were treated with anti-CD20 monoclonal antibodies…. ***This proved clinically effective in 4 of the 5 patients***."); Ex. 1136 at 3420 (reporting the "***Successful Treatment*** of Infliximab-Refractory Rheumatoid Arthritis with Rituximab" and noting that "rituximab is a promising agent for patients with DMARD and infliximab-refractory RA"). DeVita 2002 and Tuscano's actual clinical demonstrations of treating TNFIRs stand in stark contrast to the absence of clinical data in the '838 patent. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("the expectation of success need only be reasonable, not absolute").

Notably, a POSITA would have expected different patients to experience a spectrum of responses to TNFα inhibitors—and would expect about 40% of such treated patients to be inadequate responders. Ex. 1107 ¶ 47; Ex. 1123 at 201. This did not discourage POSITAs from treating RA with TNFα inhibitors. *Id.*; *see also* Ex. 1138 at S197; Ex. 1159 at 1984–85; Ex. 1136 at 3420. In the same way, rather than be discouraged, a POSITA would have been motivated to treat RA in TNFIRs in view of DeVita 2002 and Tuscano's successful treatment of such patients. Ex. 1107 ¶ 143; *Pfizer*, 480 F.3d at 1364 ("the expectation of success need only be

reasonable, not absolute"). TNFIRs had virtually no drug-based options left after rituximab at that time, providing further motivation to use rituximab in the face of a positive responses like those reported in DeVita 2002 and Tuscano. *See* Ex. 1107 ¶ 143; Ex. 1110 at 329, Figure 1. Accordingly, a POSITA would not have understood the prior art to teach away from the claimed invention.

Controlling authority undercuts any attempt by Genentech to argue that the '838 patent claims were somehow patentable because they were directed to the "hardest-to-treat" patients. *See Abbvie Inc. v. Mathilda and Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379–80 (Fed. Cir. 2014) (holding that a later expiring patent that claimed to treat a subset of patients with more severe RA was an obvious variant of an earlier patent that claimed treatment of RA patients generally); *id.* at 1380 (rejecting argument based on "the unexpected result of improving the health of the 'hardest-to-treat patients'"). The fact is that the prior art, such as Edwards 2002 and DeVita 2002, taught that ***all*** RA patients should receive the same dosing regimen within the same study. Ex. 1107 ¶ 142. There is nothing inventive about discovering a subset of patients that are already being treated, and then claiming that the treatment of those patients will be effective.

2. Claim 2

i. Claim 2, preamble: "A method of treating rheumatoid arthritis in a human patient who

experiences an inadequate response to a TNFα inhibitor, comprising"

Edwards 2002 in view of Patel or Tuscano and Curd discloses the preamble of claim 2 for at least the reasons discussed for the identical preamble of claim 1. *See* Section VI.G.1.

ii. Claim 2, element [a]: "administering to the patient an antibody which binds to CD20"

Edwards 2002 in view of Patel or Tuscano and Curd discloses element [a] of claim 2 for at least the reasons discussed for the identical element [a] of claim 1. *See* Section VI.G.1.

iii. Claim 2, element [b]: "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"

Edwards 2002 in view of Patel or Tuscano and Curd discloses "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." Ex. 1107 ¶¶ 88–91. Edwards 2002 discloses that rituximab therapy resulted in 58% ACR20 responses,

32% ACR50 responses, and 13% ACR70 responses at 24 weeks.[6] Tuscano reports that all seven TNFIR patients treated with rituximab "had improved joint scores, and 3 met criteria for an ACR20" and concludes that "this data supports the hypothesis that B lymphocytes mediate pathology in RA, and that rituximab is a promising agent for patients with DMARD and infliximab-refractory RA." Ex. 1136 at 3420. Similarly, after reviewing Edwards 2001 and DeVita 2002, Patel teaches that "certainly those whose RA is refractory to conventional therapy (including TNF inhibitors) may respond." Ex. 1159 at 1985.

iv. Claim 2, element [c]: "wherein the antibody is administered as two intravenous doses of 1000 mg"

Edwards 2002 in view of Patel or Tuscano and Curd discloses element [c] of claim 2 for at least the reasons discussed above for the identical element [b] of claim 1. *See* Section VI.G.1.

[6] This distribution of responses is similar to the distribution of results that Genentech characterized as successful "in treating [TNFIRs] with rituximab." *Celltrion*, IPR2016-01667, Paper 13, at 29 (citing Ex. 1161); Ex. 1161 at 2793–94.

v. There Is Motivation to Combine Edwards, DeVita, and Curd with a Reasonable Expectation of Success in Rendering Claim 2 Obvious

For at least the reasons discussed above in Section VI.G.1, a POSITA would have been motivated to combine Edwards 2002 in view of Patel or Tuscano and Curd to treat TNFIRs by administering two 1,000 mg doses of rituximab with a reasonable expectation of success.

Claim 2 adds elements related to clinical outcomes in patients treated according to the claimed method. The clinical outcomes express the intended result of the claimed method steps and therefore are not limiting. *See* Section VI.D; *e.g.*, *Minton*, 336 F.3d at 1381. However, should the Board find that the clinical outcomes add patentable weight, they still would have been obvious.

The recited clinical outcomes were already disclosed in the prior art. Ex. 1138 at S197 (reporting 32% ACR50 and 13% ACR70 responses when treating RA patients with rituximab alone). A POSITA would have been motivated to achieve the clinical outcomes disclosed in Edwards 2002 in TNFIRs with a reasonable expectation of success. Ex. 1107 ¶¶ 140–41.

First, all of the patients in at least DeVita 2002, Edwards 2002, and Edwards 2001 were treated the same without regard to their prior therapy status. Ex. 1160 at 2030; Ex. 1138 at S197; Ex. 1136 at 3420; Ex. 1106 at 205 Accordingly, just as

there was a reasonable expectation that TNFIRs would be treated with the Edwards 2002 dosing regimen (*see* Section VI.G.1), a POSITA would have had a reasonable expectation that TNFIRs would achieve the same clinical outcomes as any other patient receiving the same dosing regimen—*i.e.*, ACR50 and ACR70 responses as in Edwards 2002. An inadequate response to TNFα inhibitors would not inform a POSITA about whether the patient would respond to rituximab, and therefore TNFIRs were considered no different than any other multiple DMARD refractory patient. Ex. 1107 ¶¶ 135, 140–43, 147.[7]

Second, Tuscano and Patel disclose the successful treatment of TNFIRs with rituximab. Ex. 1136 at 3420 ("At a median follow-up of 5 months all seven patients had improved joint scores, and 3 met criteria for an ACR20"); Ex. 1159 at 1984 ("DeVita and colleagues present their results on anti-CD20 treatment of 5

[7] The data Genentech characterized as establishing success "in treating [TNFIRs] with rituximab" confirms that the distribution of results in TNFIRs is the same as the population reported in Edwards 2002. *Celltrion*, IPR2016-01667, Paper 13, at 29 (citing Ex. 1161); Ex. 1161 at 2793–94; *compare* Ex. 1138 at S197 (reporting 58% ACR20, 32% ACR50, and 13% ACR70 in the rituximab group) *with* Ex. 1161 at 2793–94 (reporting 51% ACR20, 27% ACR50, and 12% ACR70 in TNFIRs treated with rituximab).

patients with RA that had not been responsive to combination therapy with methotrexate and cyclosporine A, with or without anti-[TNFα] therapy…. Four of the 5 patients achieved ACR20 responses….”). Tuscano concludes that “this data supports the hypothesis that B lymphocytes mediate pathology in RA, and that rituximab is a promising agent for patients with DMARD and infliximab-refractory RA.” Ex. 1136 at 3420. Patel similarly concludes that “certainly those whose RA is refractory to conventional therapy (including TNF inhibitors) may respond” to rituximab therapy. Ex. 1159 at 1985. The successful treatment of TNFIRs with rituximab would have contributed to the reasonable expectation of achieving the recited clinical outcomes, including those expressly disclosed in Edwards 2002, at least because it was consistent with the results obtained in Edwards 2002. Ex. 1107 ¶¶ 136–37, 140–41; *see also* Ex. 1159 at 1984; Ex. 1136 at 3420.

These teachings are sufficient to render the claimed clinical outcomes obvious. *See Pfizer*, 480 F.3d at 1364 (“the expectation of success need only be reasonable, not absolute”).

The ’838 patent expressly provides that the dose recited in the claims—*i.e.*, two intravenous doses of 1,000 mg—is an “amount that is effective” to bring about the clinical responses. *See* Ex. 1101 at claim 2; *id.* at 32:40–43 (“Therapy of RA with the CD20 antibody in patients with an inadequate response to TNFα inhibitor therapy as described above ***will result in a beneficial clinical response*** according

to ***any one or more*** of the endpoints noted above."). And, beyond the bare suggestion to administer rituximab to TNFIRs, the '838 patent provides no data to support the idea that administering two 1,000 mg doses of rituximab would result in anything but the listed clinical outcomes. *See* Ex. 1101 at 31:8–32:37. By contrast, the prior art discloses these clinical features and should not be held to a higher standard than the '838 patent itself. *See Copaxone*, 2017 WL 401943, at *17, 18–19 ("***It would constitute clear error*** for the court to discredit the Pinchasi reference for the same lack of dosing frequency clinical data from which the patents-in-suit suffer.") (*citing Merck*, 395 F.3d at 1374).

3. Claim 3

i. "The method of claim 2 wherein the antibody comprises rituximab"

Edwards 2002 in view of Patel or Tuscano and Curd renders the methods of claim 2 obvious for at least the reasons discussed in Section VI.G.2. Rituximab is the anti-CD20 monoclonal antibody disclosed by each of Edwards 2002, Patel, Tuscano, and Curd. Ex. 1138 at S197 ("Group B: Rituximab alone"); Ex. 1136 at 3420 ("clinical trial using rituximab alone"); Ex. 1159 at 1984 (citing Ex. 1106; Ex. 1160 at 2029); Ex. 1116 at 25:9–10 ("Patients with clinical diagnosis of [RA] are treated with rituximab (RITUXAN®) antibody.").

4. Claim 4

i. "The method of claim 2 wherein the patient is further treated with concomitant methotrexate (MTX)"

Edwards 2002 in view of Patel or Tuscano and Curd renders the methods of claim 2 obvious for at least the reasons discussed in Section VI.G.2. Edwards 2002 discloses treating 30 patients with "Rituximab (2 × 1g i.v. infusions) plus continuing [methotrexate]." Ex. 1138 at S197. The results demonstrated that 80% of these patients achieved ACR20, 50% achieved ACR50, and 23% achieved ACR70. *Id.* Edwards 2002 concludes that "[c]ombination with [methotrexate] or [cyclophosphamide] produced the highest levels of ACR20, 50, and 70 responses." *Id.*

5. Claim 5

i. "The method of claim 4 wherein the patient is further treated with a corticosteroid regimen"

Edwards 2002 in view of Patel or Tuscano and Curd renders the methods of claim 4 obvious for at least the reasons discussed in Section VI.G.4. In Edwards 2002, "***[a]ll groups*** also received a 17 day course of corticosteroids…." Ex. 1138 at S197.

Additionally, combination therapies for treating RA were common before the Earliest Possible Priority Date. Ex. 1107 ¶¶ 55–57, 59, 104, 131, 144–45; Ex.

1117 at 142; Ex. 1110 at 329, Figure 1. This was so even before POSITAs understood how the drugs worked. Ex. 1107 ¶ 104; Ex. 1113 at 1550 (reporting that "biotechnology interventions are… being empirically combined with [methotrexate] while hoping for the best. This approach can and should be advocated because our patients simply do not have time to wait until we determine how all of the new and existing drugs work…."). Methotrexate and corticosteroids were commonly used in combination with monoclonal antibodies to treat RA before the Earliest Possible Priority Date. Ex. 1107 ¶ 131; Ex. 1113 at 1549 (describing the "ideal biotechnology combination study" as including the combination of the biologic, methotrexate, and corticosteroids). Curd confirms and encourages the practice of combining therapies, like rituximab, with "any one or more" immunosuppressive agents, including methotrexate and corticosteroids. Ex. 1107 ¶¶ 144–45; Ex. 1116 at 8:22–29 (defining "immunosuppressive agent" as including "steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone"), 25:9–16 (teaching that the patient may be "further treated with any one or more agents employed for treating RA such as... immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages"). A POSITA reading Edwards 2002 in view of Patel or Tuscano and Curd would be motivated to combine rituximab with both methotrexate and corticosteroids with a reasonable expectation of success

given that methotrexate and corticosteroids are both immunosuppressive and anti-inflammatory agents that can enhance the action of rituximab and relieve residual patient symptoms, and because this is precisely what Edwards 2002 did. *See* Ex. 1116 at 8:22–29, 25:9–16; Ex. 1107 ¶¶ 104, 131, 144–45; Ex. 1138 at S197.

6. Claim 6

i. "The method of claim 5 wherein the corticosteroid regimen consists of methylprednisolone and prednisone"

Edwards 2002 in view of Patel or Tuscano and Curd renders the methods of claim 5 obvious for at least the reasons discussed in Section VI.G.5. Edwards 2002 teaches the combination of rituximab, methotrexate, and corticosteroids and further teaches that this combination was the most potent of all treatments tested. Ex. 1138 at S197. In teaching that rituximab should be combined with immunosuppressive agents including methotrexate and corticosteroids, Curd discloses a list of three corticosteroids that includes both methylprednisolone and prednisone. Ex. 1116 at 8:22–29, 25:9–16. A POSITA would have been motivated to combine rituximab with methotrexate, and the specific corticosteroids methylprednisolone and prednisone with a reasonable expectation of success because methotrexate, methylprednisolone, and prednisone are all immunosuppressive and anti-inflammatory agents that can enhance the action of rituximab and relieve residual

patient symptoms. *See* Ex. 1116 at 8:22–29, 25:9–16; Ex. 1107 ¶¶ 104, 131, 144–45; Ex. 1138 at S197.

7. Claim 7

i. "The method of claim 2 wherein the CD20 antibody is the only B-cell surface marker antibody administered to the patient"

Edwards 2002 in view of Patel or Tuscano and Curd renders the methods of claim 2 obvious for at least the reasons discussed in Section VI.G.2. Edwards 2002, Patel, and Tuscano disclose treating RA patients with a single B-cell surface marker antibody, rituximab. Ex. 1138 at S197; Ex. 1136 at 3420; Ex. 1159 at 1984. Moreover, rituximab was the only such anti-CD20 antibody that had received FDA approval at the time, providing further motivation to treat patients with rituximab as the only B cell surface marker antibody.

8. Claim 8

Claim 8 recites rituximab, a specific anti-CD20 antibody, as opposed to an anti-CD20 antibody generally, as in claim 1. Claim 8 is otherwise identical to claim 1. For at least the reasons disclosed in Section VI.G.1 above, Edwards 2002 in view of Patel or Tuscano and Curd discloses the elements of claim 8.

Similarly, for at least the reasons discussed above in Section VI.G.1, a POSITA would have been motivated to combine Edwards 2002 with Patel or

Tuscano and Curd to treat TNFIRs by administering two 1,000 mg doses of rituximab with a reasonable expectation of success.

9. Claim 9

i. "The method of claim 8 further comprising administering methotrexate to the patient"

Edwards 2002 in view of Patel or Tuscano and Curd renders the methods of claim 8 obvious for at least the reasons discussed in Section VI.G.8. Claim 9 adds methotrexate to the method of claim 8 as claim 4 adds methotrexate to the method of claim 2. Thus, for at least the reasons discussed above in Section VI.G.4, Edwards 2002 in view of Patel or Tuscano and Curd discloses "administering methotrexate to the patient."

10. Claim 10

i. Claim 10, preamble: "A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα inhibitor, comprising"

Edwards 2002 in view of Patel or Tuscano and Curd discloses the preamble of claim 10 for at least the reasons discussed for the identical preamble of claim 1. *See* Section VI.G.1.

ii. Claim 10, element [a]: "administering to the patient rituximab"

Edwards 2002 in view of Patel or Tuscano and Curd discloses element [a] of claim 10 for at least the reasons discussed for the identical element [a] of claim 8. *See* Section VI.G.8.

iii. Claim 10, element [b]: "and methotrexate"

Element [b] of claim 10 adds methotrexate to the claimed method in the same way that claim 4 adds methotrexate to the method of claim 2. Therefore, Edwards 2002 in view of Patel or Tuscano and Curd discloses administering "methotrexate" to the patient for at least the reasons discussed above in Section VI.G.4.

iv. Claim 10, element [c]: "wherein the patient has no erosive progression at weeks 24 and beyond"

Element [c] of claim 10 lists one of the clinical outcomes that is disclosed in claim 2, element [b]. The clinical outcomes express the intended result of the claimed method steps and therefore are not limiting. *See* Section VI.D; *e.g.*, *Minton*, 336 F.3d at 1381. However, should the Board find that the clinical outcomes add patentable weight, element [c] of claim 10 would have been obvious for at least the reasons discussed above in Section VI.G.2.

Claim 10 differs from claim 2 in that claim 10 combines rituximab with methotrexate and lists no erosive progression as the only intended result. Edwards 2002 discloses ACR50 and ACR70 responses, and Patel and Tuscano report clinical responses in TNFIRs. Ex. 1107 ¶¶ 89–91; Ex. 1138 at S197; Ex. 1159 at 1984; Ex. 1136 at 3420. Edwards 2002 further reports that combining rituximab with methotrexate nearly doubled the number of ACR50 (50% versus 32%) and ARC70 responses (23% versus 13%) compared to rituximab alone. Ex. 1138 at S197; Ex. 1107 ¶¶ 105–107. As discussed in greater detail in Section VI.G.2, a POSITA would have a reasonable expectation of achieving similar results in TNFIRs because (1) all patients in at least DeVita 2002, Edwards 2002, and Edwards 2001 were treated the same without regard to their prior therapy status, and (2) Tuscano and Patel disclose successful treatment of TNFIRs with rituximab. Ex. 1107 ¶¶ 135–43. Moreover, a POSITA would have reasonably expected a clinically effective treatment with a biologic, like rituximab, and methotrexate to curb erosive progression such that the net effect in terms of erosive progression would be close to zero at 24 weeks and beyond. Ex. 1107 ¶ 108. These teachings are sufficient to render the claimed clinical outcomes obvious. *See Pfizer*, 480 F.3d at 1364 ("the expectation of success need only be reasonable, not absolute").

The '838 patent specification characterizes "erosive progression" merely as an "exploratory" endpoint. Ex. 1101 at 32:28–34. And, the claims and specification

of the ’838 patent provide that the recited dosing—*i.e.*, two intravenous doses of 1,000 mg—is an “amount that is effective” to achieve the recited clinical outcomes. *See* Ex. 1101 at claim 1; *id.* at 32:40–43 (“Therapy of RA with the CD20 antibody in patients with an inadequate response to TNFα inhibitor therapy as described above ***will result in a beneficial clinical response*** according to ***any one or more*** of the endpoints noted above.”). Beyond the bare suggestion to administer rituximab to TNFIRs, the ’838 patent provides no data to support the idea that administering two 1,000 mg doses of rituximab would result in anything but the listed clinical outcomes. Even the paper that Genentech referenced as purportedly showing a successful use of rituximab in TNFIRs noted only that patients “showed a trend toward less progression in radiographic end points.” Ex. Ex. 1161 at 2793. Since Edwards 2002 in view of Patel or Tuscano and Curd renders obvious a method of treating RA in TNFIRs with two 1,000 mg doses of rituximab, it also renders obvious the inevitable result of administering that dose—*i.e.*, no erosive progression at 24 weeks and beyond. *See Copaxone*, 2017 WL 401943, at *17, 18–19 (“***It would constitute clear error*** for the court to discredit the Pinchasi reference for the same lack of dosing frequency clinical data from which the patents-in-suit suffer.”) (*citing Merck*, 395 F.3d at 1374).

v. Claim 10, element [d]: "and wherein rituximab is administered as two intravenous doses of 1000 mg"

Edwards 2002 in view of Patel or Tuscano and Curd discloses element [d] of claim 10 for at least the reasons discussed for the identical element [b] of claim 8. *See* Section VI.G.8.

vi. There Is Motivation to Combine DeVita, Edwards, and Curd with a Reasonable Expectation of Success in Rendering Claim 10 Obvious

For at least the reasons discussed above in Sections VI.G.1, VI.G.2, and VI.G.5, a POSITA would have been motivated to combine Edwards 2002 with Patel or Tuscano and Curd to treat TNFIRs by administering two 1,000 mg doses of rituximab with methotrexate with a reasonable expectation of success of the patient achieving no erosive progression at weeks 24 and beyond.

11. Claim 11

i. Claim 11, preamble: "A method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences

an inadequate response to a TNFα inhibitor, comprising"

The preamble of claim 11 adds the clinical outcomes discussed in element [b] of claim 2 to the preamble that is contained in claim 1 and 2. Therefore, Edwards 2002 in view of Patel or Tuscano and Curd discloses "[a] method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα inhibitor" for at least the reasons discussed above in Sections VI.G.1, VI.G.2, and VI.G.10.

ii. Claim 11, element [a]: "administering to the patient rituximab"

Edwards 2002 in view of Patel or Tuscano and Curd discloses element [a] of claim 11 for at least the reasons discussed for the identical element [a] of claim 8. *See* Section VI.G.8.

iii. Claim 11, element [b]: "and methotrexate"

Element [b] of claim 11 adds methotrexate to the claimed method in the same way that claim 4 adds methotrexate to the method of claim 2. Therefore, Edwards 2002 in view of Patel or Tuscano and Curd discloses administering

"methotrexate" to the patient for at least the reasons discussed above in Section VI.G.4.

iv. Claim 11, element [c]: "wherein rituximab is administered as two intravenous doses of 1000 mg"

Edwards 2002 in view of Patel or Tuscano and Curd discloses element [c] of claim 11 for at least the reasons discussed for the identical element [b] of claim 8. *See* Section VI.G.8.

i. There Is Motivation to Combine DeVita, Edwards, and Curd with a Reasonable Expectation of Success in Rendering Claim 11 Obvious

For at least the reasons discussed above in Sections VI.G.1, VI.G.2, VI.G.4, and VI.G.10, a POSITA would have been motivated to combine Edwards 2002 with Patel or Tuscano and Curd to treat TNFIRs by administering two 1,000 mg doses of rituximab and methotrexate with a reasonable expectation of success of the patient achieving any one of the three listed clinical outcomes.

12. Claim 12

i. "The method of claim 11 wherein the clinical response is ACR50 response at week 24"

For at least the reasons discussed above in Sections VI.G.2, VI.G.10, and VI.G.11, Edwards 2002 in view of Patel or Tuscano and Curd renders obvious all

three of the claimed clinical outcomes, and therefore renders obvious a clinical response that "is ACR50... at week 24."

13. Claim 13

i. "The method of claim 11 wherein the clinical response is ACR70 response at week 24"

For at least the reasons discussed above in Sections VI.G.2, VI.G.10, and VI.G.11, Edwards 2002 in view of Patel or Tuscano and Curd renders obvious all three of the claimed clinical outcomes, and therefore renders obvious a clinical response that "is ACR70... at week 24."

14. Claim 14

i. "The method of claim 11 wherein the clinical response is no erosive progression at weeks 24 and beyond"

For at least the reasons discussed above in Sections VI.G.2, VI.G.10, and VI.G.11, Edwards 2002 in view of Patel or Tuscano and Curd renders obvious all three of the claimed clinical outcomes, and therefore renders obvious a clinical response that "is no erosive progression at weeks 24 and beyond."

H. Genentech Likely Cannot Antedate Edwards 2002

Genentech has previously attempted to antedate Edwards 2002 by relying on statements and work from alleged co-inventor Randal Stevens to purportedly demonstrate prior conception and reduction to practice. *See Celltrion*, IPR2016-

01667, Paper No. 13, at 1 ("Edwards 2002 does not even qualify as prior art with respect to a number of claims... Indeed, one inventor of the '838 patent—Dr. Randall Stevens—describes some of his prior inventive work in Edwards 2002, which he co-authored."). Genentech's evidence of purported prior conception and reduction to practice was redacted in all material respects and is, therefore, currently unavailable to Petitioner and cannot be substantively addressed herein. Regardless, it is unlikely that Genentech can meet its heavy burden to establish that it can antedate Edwards 2002 based on an earlier inventive contribution made by Dr. Stevens and/or Dr. Benyunes, the named inventors on the '838 patent. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 967 (Fed. Cir. 2014) ("the patentee [] must meet its burden of production to demonstrate an earlier conception date").

In order for Genentech to meet its burden to demonstrate an earlier conception date, its alleged earlier conception "must encompass ***all limitations*** of the claimed invention… and is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Singh v. Brake*, 222 F.3d 1362, 1367 (Fed. Cir. 2000) (citation and quotation omitted); *see also Pfaff v. Wells Elecs, Inc.*, 525 U.S. 55, 66 (1998) ("The word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.'"). In addition, Drs. Benyunes and Stevens must have "appreciate[d] the

claimed inventive features…at the time of alleged conception [and] cannot use [] later recognition of those features to retroactively cure [] imperfect conception." *Hitzeman v. Rutter*, 243 F.3d 1345, 1358–59 (Fed. Cir. 2001).

In order for Genentech to try to antedate Edwards 2002 based on a prior joint conception of any claim of the '838 patent by Dr. Stevens and Dr. Benyunes, Dr. Stevens and Dr. Benyunes must have actually collaborated in conceiving of the claimed subject matter. *Kimberly-Clark Corp. v. Procter & Gamble Distrib. Co.*, 973 F.2d 911, 917 (Fed. Cir. 1992) (holding "that joint inventorship under Section 116 requires at least some quantum of collaboration or connection"). "[A] long line of decisions in [the Federal Circuit] holds that a person is a joint inventor only if he contributes to the conception of the claimed invention." *Eli Lilly and Co. v. Aradigm Corp*, 376 F.3d 1352, 1358–59 (Fed. Cir. 2004). Dr. Stevens and Dr. Benyunes must each have contributed in a manner "that is not insignificant in quality, when that contribution is measured against the dimension of the full invention." *Nartron Corp. v. Schukra U.S.A. Inc.*, 558 F.3d 1352, 1356–57 (Fed. Cir. 2009) (citation omitted). And, each collaborator's contribution must, itself, have been inventive. *Scott v. Zimmer, Inc.*, 889 F. Supp. 2d 657, 662–63 (D. Del. 2012) (citing *Eli Lilly*, 376 F.3d at 1362; *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997)). That is, each of their contributions must have been "something more than what is in the prior art" and cannot have been obvious in

view of the prior art. *Id.*; *see also Garrett Corp. v. United States*, 422 F.2d 874, 881 (Cl. Ct. 1970) (holding that "suggesting [a] broad idea" that was "held [] to be obvious in view of the prior art" was insufficient to show co-inventorship). It is not enough for them to "simply provide[]…well-known principles or explain[] the state of the art without ever having a firm and definite idea of the claimed combination as a whole…." *Nartron*, 558 F.3d at 1356 (citation and quotation omitted).

As discussed above in Section VI.C.4, it appears that the addition of Dr. Stevens as an inventor of the '838 patent more than 13 years after the '838 patent issued, and a year after the PTAB had instituted an IPR based on Edwards 2002, was part of a legal strategy to attempt to antedate Edwards 2002. Accordingly, to the extent Genentech attempts to rely on any alleged inventive contribution from Dr. Stevens to antedate Edwards 2002, that attempt is likely to fail, particularly in view of Genentech's heavy burden.

I. Secondary Considerations of Nonobviousness Do Not Support a Finding of Nonobviousness

In response to Boehringer Ingelheim's ("BI") petition, Genentech cited alleged evidence of commercial success, unexpected results, and long-felt but unmet need. *Boehringer*, IPR2015-00417, Paper No. 9, at 53–59. The PTAB rejected this evidence. *Boehringer*, IPR2015-00417, Paper No. 11, at 24–25.

Having failed to demonstrate secondary considerations against BI, Genentech did not advance any arguments regarding secondary considerations in response to Celltrion's petition. *See Celltrion*, IPR2016-01667, Paper No. 13, at 1–61.

Any alleged evidence of commercial success lacks a nexus to the recited claims. Rituximab sales are attributable to the use of rituximab in oncology and immunology and are attributable to the merits of the antibody itself, as opposed to dosing or administration to a specific subset of patients. Ex. 1107 ¶ 149; *see also BioMarin Pharm. Inc. v. Genzyme Therapeutic Prods.*, IPR2013-00534, Paper 81, at 21–22 (P.T.A.B. Feb. 23, 2015) (holding that Patent Owner failed to demonstrate a nexus between the claimed "biweekly dosing schedule" and cited secondary considerations, instead finding that "the discussion of secondary considerations relate[d] to the merits of the therapeutic compositions of GAA brought to market by Patent Owner" that "were known in the art"), *aff'd*, 825 F.3d 1360; *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010) ("[i]t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.") (quoting *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990)); *id.* at 1281 (affirming district court's holding that patentee failed to show a nexus between the claimed method and the cited commercial success). Any alleged evidence of unexpected results and/or long-felt need would also fail. TNFIRs had been successfully treated in the art, and the

recited dosing amounts were likewise known. Ex. 1107 ¶ 147; *see also Abbvie*, 764 F.3d at 1380 (rejecting argument based on "the unexpected result of improving the health of the 'hardest-to-treat [RA] patients'").

J. Conclusion

For the reasons discussed above, Edwards 2002 in view of Patel or Tuscano and Curd renders claims 1–14 of the '838 patent obvious. Petitioner respectfully requests that the Board grant its IPR petition for all claims.

CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Petition contains 13,961 words as counted by the word processing program used for its preparation (Microsoft Word 2010).

The undersigned further certifies that this brief complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

Dated: 8/31/2017

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Sandoz Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 7,976,838 and Exhibits 1101 – 1165 were served on August 31, 2017 via Federal Express to the correspondence address for the attorney of record for Genentech Inc., the assignee of the '838 patent.

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