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. 2017-02036

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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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. 1002.

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

Rituximab was well known before the Earliest Possible Priority Date 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 2001, Dr. Jonathan Edwards published a study involving rituximab that was so promising it "suggest[ed] that the protocol used, or a modification thereof, may be of a major benefit to subjects with RA." Clinical studies in the prior art further 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"), including TNFα inhibitors, which utilize different mechanisms of action than rituximab.

The Challenged Claims are unpatentable as obvious in light of the prior art. A person of ordinary skill in the field of rheumatology would have had a strong motivation to use an anti-CD20 therapy as an alternative therapy in patients who experienced an inadequate response to TNFα inhibitors (and other RA drugs), and a reasonable expectation of success based on, among other things, the published clinical responses to rituximab already observed in such TNFα inhibitor inadequate responders ("TNFIRs"). The claimed dosing regimen (2×1,000 mg of rituximab) adds no patentable weight because it is the obvious result of on-going routine optimization of known dosing regimens that are equivalent for therapeutic purposes to the claimed regimen. Additional limitations directed to combination therapies involving foundational RA drugs, like methotrexate and corticosteroids, do not confer patentability to the claims of the '838 patent. 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. 1003),[1] was revoked as obvious in light of one or more of the references asserted here. Ex. 1004; Ex. 1044 (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.

[1] 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 ground:

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

The cited prior art is as follows:

- Edwards JCW and Cambridge G, *Sustained Improvement in Rheumatoid Arthritis Following a Protocol Designed to Deplete B Lymphocytes,* 40 RHEUMATOLOGY 205–211 (2001) (“Edwards,” Ex. 1006). Edwards is prior art under at least 35 U.S.C. § 102(b). Edwards is a “printed publication” that published in 2001. In a previous IPR, Genentech did not dispute that Edwards was accessible to the public more than one year before 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).

- De Vita S *et al.*, *Pathogenic Role of B Lymphocytes in Rheumatoid Synovitis: B cell Selective Blocking Can Induce a Clinical Response in Patients with Refractory Rheumatoid Arthritis*, 53(3) REUMATISMO 323 (2001) (“DeVita,”

Ex. 1005). DeVita originally published in Italian. A certified translation of DeVita is attached to Exhibit 1005. DeVita is prior art under at least 35 U.S.C. § 102(b). DeVita is a "printed publication" that published in 2001. In a previous IPR, Genentech did not dispute that DeVita was accessible to the public more than one year before the Earliest Possible Priority Date. *See Boehringer*, IPR2015-00417, Paper No. 9, at 39–41.

- International Application Publication No. WO 00/67796 ("Curd," Ex. 1016) 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. 1007), William J. Jusko, Ph.D. (Ex. 1008), 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 person of ordinary skill in the art ("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. 1007 ¶ 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 how 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. 1007 ¶ 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. 1009 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. 1007 ¶ 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. 1010 at 329 (Figure 1). Remission from RA is rare and there is no cure. Ex. 1007 ¶ 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. 1010 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. 1007 ¶ 44. Patients who responded inadequately or had side-effects to such combinations were offered other therapies. Ex. 1010 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. 1011 at 735 (Table 5); Ex. 1007 ¶ 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. 1010 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. 1007 ¶ 43; *see also* Ex. 1009 at 1682 (Table 1); Ex. 1012 at 780–82. The efficacy and safety of methotrexate for treating RA was well established prior to the Earliest Possible Priority Date. *See* Ex. 1012 at 780 ("The efficacy of methotrexate in the treatment of RA is unquestioned...."); Ex. 1007 ¶¶ 43, 55. Methotrexate was the most commonly used and first prescribed DMARD by most rheumatologists in the United States for treating RA. Ex. 1012 at 779; Ex. 1007 ¶ 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. 1007 ¶¶ 44, 55–57; *see also, e.g.*, Ex. 1012 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. 1012 at 790; *see* Ex. 1013 at 1548 (stating most new biotechnology-derived therapies, including antibody therapies like some TNFα inhibitors, were combined with methotrexate); Ex. 1014 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. 1007 ¶¶ 43–44, 55–57; *see also* Ex. 1015 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. 1007 ¶ 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. 1016 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. 1007 ¶ 57; *see also* Ex. 1017 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. 1018 at 309 (comparing methotrexate, prednisolone, and sulphasalazine versus sulphasalazine alone); Ex. 1006 at 205 (combining prednisolone, rituximab, and cyclophosphamide). Common corticosteroids include "prednisone, methylprednisolone, and dexamethasone…." Ex. 1016 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. 1007 ¶ 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. 1019, 1020, 1021.

It was well understood before the Earliest Possible Priority Date that TNFα inhibitors were not effective in all RA patients. Ex. 1007 ¶ 47. Only about 60% of patients achieve a clinical response to TNFα inhibitors, with or without methotrexate. *Id.*; *see also* Ex. 1022 at 1552. And, failure of any given DMARD therapy is not predictive of whether a patient will respond to TNFα inhibitors. Ex. 1007 ¶ 47; *see also* Ex. 1022 at 1557; Ex. 1023 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. 1007 ¶ 48; *see also, e.g.*, Ex. 1025 at I129 ("alternative treatments or regimens should be considered" absent improvement in symptoms or laboratory parameters); Ex. 1010 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. 1010 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. 1019 at 16 (adalimumab and methotrexate); Ex. 1020 at 12 (etanercept and methotrexate); Ex. 1021 at 11 (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. 1007 ¶ 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. 1019 at 6, 14–15; Ex. 1020 at 12, 23–24; Ex. 1021 at 8, 16.

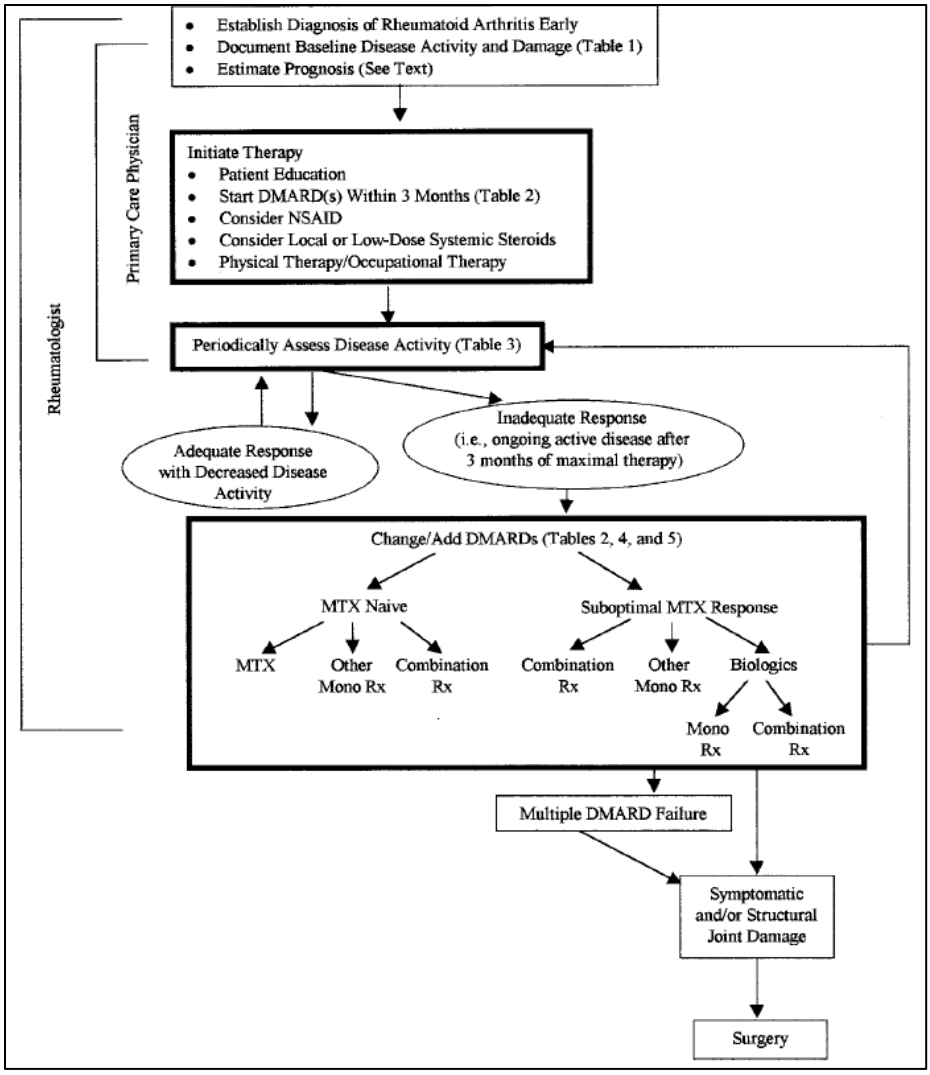

Figure 1: Outline of the management of rheumatoid arthritis.… A suboptimum response to methotrexate (MTX) is defined as intolerance, lack of satisfactory efficacy with a dosage of up to 25 mg/week, or a contraindication to the drug.… [M]ono Rx = monotherapy; combination Rx = combination therapy.

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. 1026 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. 1028 at 2460; Ex. 1007 ¶ 49; *see also* Ex. 1027 at 3268 (maximum total dose of 3,200 mg).

Rituximab was used to effectively treat RA before the Earliest Possible Priority Date. Ex. 1007 ¶¶ 50–51. By 1998, scientists realized rituximab could be useful to treat RA by causing B-cell depletion. *Id.*; *see also* Ex. 1031 at 126; Ex. 1032 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, clinical trial results were reported. *E.g.*, Ex. 1033 at Abstract.

By 2000, researchers knew rituximab remained in the blood "as long as several months after the standard 4-week [375 mg/m^2] dose regimen." Ex. 1037 at 397. "Therefore it [was] ***no surprise*** that extended numbers of doses [did not lead] to substantial increases in response rates." *Id.*;[2] *see also* Ex. 1028 at 2457, 2460 (demonstrating dose-dependent B-cell depletion); Ex. 1047 at 530 (noting rapid B-

[2] All emphasis is added unless noted otherwise.

cell depletion after initial antibody administration); Ex. 1029 at 2188, 2191 (noting B-cells were undetectable for 6 months followed by gradual recovery). As a result, research into "repetitive dosing cycles at more prolonged intervals" was under active investigation. Ex. 1037 at 397.

More than two years before the Earliest Possible Priority Date, Curd provided a virtually identical antibody dosing disclosure to the '838 patent. *Compare* Ex. 1016 at 23:14–33 *with* Ex. 1001 at 29:16–51 (containing the same description verbatim, except that the '838 patent adds: "Exemplary dosage regimens include 375 mg/m^2 weekly x 4; or 1000 mg x 2 (e.g. on days 1 and 15)."). Curd disclosed rituximab doses from 20 mg/m^2 to 1,000 mg/m^2 and four weekly 375 mg/m^2 administrations. Ex. 1016 at 23:14–33.

In 2001, Edwards reported the results of a promising study treating RA with rituximab. Ex. 1006 at 205. Edwards reports "[f]ive patients with refractory RA were treated with a monoclonal anti-CD20 antibody, cyclophosphamide and prednisolone and followed for 12–17 months." *Id.* The 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). Each patient received four intravenous infusions of rituximab: day 2 (300 mg), day 8 (600 mg), day 15 (600 mg), and day 22 (600 mg), for a total dose of 2100 mg. *Id.* The patients received "fixed" doses—*i.e.*, doses that were not adjusted based on

the patient's weight or body surface area.[3] The results showed that all patients had satisfied the ACR50 or ACR70 criteria without further therapy. Ex. 1006 at 205. Edwards concludes 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.* at 207.

Researchers were conducting routine dose optimization studies of rituximab in RA at this time, testing doses lower and higher than reported in the initial trials. *See* Ex. 1034 at 826; Ex. 1035 at 885 (Table 2) (demonstrating that virtually all patients that received total rituximab doses over 500 mg/m^2 (800 or 950 mg) achieved ACR20 or better at six months); Ex. 1036 at 3420 (administering "a total dose of 100 mg on wk #1, followed by 375 mg/m^2 [(600 or 713 mg)] on wk #2, and 500 mg/m^2 [(800 or 950 mg)] on wks 3 and 4.").

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. 1038 at S197 ("Edwards 2002"). Consistent with the routine practice of combining known therapies, patients were treated with (1) methotrexate, (2) rituximab, (3) methotrexate with rituximab, or

[3] A fixed dose is calculated by multiplying the relative dose by the patient's body surface area; about 1.6 m^2 for the average female and 1.9 m^2 for the average male. Ex. 1007 ¶ 59 n. 1; Ex. 1052 at 19; Ex. 1054 at 976; Ex. 1055 at 51–52.

(4) rituximab and cyclophosphamide. *Id.*; Ex. 1007 ¶ 53–57; Ex. 1010 at 332–333. Optimizing the dosing regimen disclosed in Edwards, patients received two intravenous 1,000 mg doses of rituximab separated by two weeks irrespective of prior response to therapy. Ex. 1038 at S197. All patients received a 17-day course of corticosteroids. *Id.* The three rituximab regimens were "well tolerated" and resulted in "substantial clinical benefit in RA," including ACR20, ACR50, and ACR70 responses. *Id.*

POSITAs were well aware by the Earliest Possible Priority Date that rituximab, an anti-CD20 antibody, operates with a different mechanism of action than TNFα inhibitors. Ex. 1007 ¶¶ 54, 147; *see also* Ex. 1039 at 4 (Fig. 1.1) (showing how B cells act upstream of TNFα during the inflammatory process); Ex. 1041 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 TNFα inhibitor would not be predictive of the result or dosing regimen necessary to produce an effective response in a patient receiving rituximab. Ex. 1007 ¶¶ 54, 136. Thus, while POSITAs were well aware of the 40% inadequate response rate for TNFα inhibitors, studies using rituximab in RA did not control for anti-TNF treatment status, and therefore treated all patients, including TNFIRs, alike. Ex. 1006 at 205; Ex. 1038 at S197; Ex. 1036 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. 1005 at 323 (treating four patients with rituximab where half "had not responded to anti-TNF alpha therapy").

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. 1001 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.

1001 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. 1001 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. The specification provides 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. 1042 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. 1043; Ex. 1044 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 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. 1042 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. 1001 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. 1046 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. 1045 at 1; Ex. 1042 at 2. Dr. Benyunes remained the only inventor for over 13 years. Ex. 1042 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 (Ex. 1036)).

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. 1001 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

Edwards describes "[a]n open study of B-lymphocyte depletion... in [RA] patients to test the hypothesis that B lymphocytes may be essential to disease perpetuation." Ex. 1006 at 205. "Five patients with refractory RA were treated with a monoclonal anti-CD20 antibody [(rituximab)], cyclophosphamide and prednisolone and followed for 12-17 months." *Id.* Irrespective of prior treatments or treatment outcomes, all patients received four intravenous infusions of rituximab on day 2 (300 mg), day 8 (600 mg), day 15 (600 mg), and day 22 (600 mg), for a

total dose of 2100 mg. *See id.* at 206. The results showed that "[a]t 26 weeks all patients satisfied the… ACR50 and patients 1–3 [satisfied] the ACR70 criteria of improvement without further therapy." *Id.* at 205. Edwards concludes 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.* at 207.

2. Overview of DeVita

DeVita reported administering rituximab to RA patients who inadequately responded to DMARDs including TNFα inhibitors. Ex. 1005. None of the patients had responded to a combination of methotrexate and cyclosporine-A. *Id.*

Two patients had experienced an inadequate response to TNFα inhibitors. *Id.*

Irrespective of prior treatments or treatment outcomes, all patients received four weekly intravenous rituximab infusions of 375 mg/m^2. *See id.* Patients could also take low doses of steroids. *Id.* One of two TNFIRs achieved an ACR20 response in month 5.[4] *Id.* DeVita concludes that "a clinical response was achieved in patients who did not respond to direct treatment against T lymphocytes [(*i.e.*, anti-TNF therapy)] and synoviocytes." *Id.*

[4] DeVita indicates that patient 4 experienced a positive result, but contains a subsequent typographical error indicating the same patient did not respond. It appears the abstract intended to refer to patient 3—*i.e.*, the other TNFIR.

3. Overview of Curd

Curd describes the intravenous administration of rituximab for treating RA. *E.g.*, Ex. 1016 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 corresponds to fixed doses of about 32 or 38 mg to about 1,600 or 1,900 mg. Ex. 1007 ¶ 59. The disclosure related to dose in Curd is nearly identical to the disclosure in the '838 patent. *Compare* Ex. 1016 at 23:14–33 *with* Ex. 1001 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. 1016 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***….").

G. Ground 1: Claims 1–14 Are Invalid Based on Edwards in View of DeVita and Curd

1. Claim 1

Edwards in view of DeVita 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"

Edwards discloses treating five patients with "severe inflammatory disease that had not been adequately controlled despite trials of at least five [DMARDs]." Ex. 1006 at 206. Although each of the patients had not responded to multiple different DMARDs, Edwards treated all patients with the same rituximab dosing regimen. *Id*. DeVita reports treating "[f]our female patients... suffering from active and erosive rheumatoid arthritis (RA)...." Ex. 1005 at 323. Two out of the four patients "had not responded to anti-TNF alpha therapy." *Id.* A patient that does not

respond to anti-TNFα therapy "experiences an inadequate response to a TNFα inhibitor" as recited in claim 1. *See* 1007 ¶ 68.

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

All three references disclose administering rituximab to patients suffering from rheumatoid arthritis. Ex. 1005 at 323 ("Four female patients... suffering from... (RA) consented to treatment with Rituximab, a chimeric anti-CD-20 monoclonal antibody."); Ex. 1006 at 206 ("Five subjects... satisfying the [ACR] criteria for classical RA"); *id.* ("All patients received... rituximab"); Ex. 1016 at 25:9–11 ("Patients with clinical diagnosis of rheumatoid arthritis (RA) are treated with rituximab (RITUXAN®)"). Rituximab is a chimeric, monoclonal antibody that binds to CD20. Ex. 1007 ¶ 49; Ex. 1005 at 323 ("… Rituximab, a chimeric anti-CD-20 monoclonal antibody").

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 administered "four i.v. infusions... on days 2, 8, 15, and 22, of 300, 600, 600 and 600 mg respectively" totaling 2,100 mg. Ex. 1006 at 206. DeVita administered "4 intravenous infusions weekly of 375 mg/m^2…." Ex. 1005 at 323. The '838 patent treats such administration as

interchangeable with two 1,000 mg doses. Ex. 1001 at 29:32–33, 31:29–31. And, in fact, the dose regimens disclosed in Edwards and DeVita are equivalent for therapeutic purposes. Ex. 1008 ¶¶ 23–28; Ex. 1030 at 299; Ex. 1044 at 976. Curd discloses a range of rituximab doses ("about 20 mg/m^2 to about 1000 mg/m^2") that includes administrations of 375 mg/m^2 and the claimed 1,000 mg dose. Ex. 1007 ¶¶ 59, 76; Ex. 1016 at 23:17–19, 25:17–23. Curd further teaches that the antibody may be administered in one or more initial doses followed by one or more subsequent doses. *See* Ex. 1016 at 23:23–25.

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

Edwards, DeVita, and Curd are all directed to using the anti-CD20 antibody rituximab to treat RA. Ex. 1007 ¶ 138.

a. The Claimed Dosing Regimen was Obvious

The claimed dose regimen, "two intravenous doses of 1000 mg," is obvious over Edwards in view of DeVita and Curd. According to Edwards, the results of the study "suggest[ed] that the protocol used, ***or a modification*** thereof, may be of major benefit to subjects with RA." Ex. 1006 at 207. A POSITA would have been motivated to modify the Edwards protocol to arrive at the claimed dose regimen with a reasonable expectation of success. In particular, a POSITA would have been

motivated to (1) move from four weekly to less frequent dosing, and (2) go from 2,100 mg of rituximab administered with four weekly doses (as disclosed in Edwards) to two doses of 1,000 mg administered over a similar timeframe with a reasonable expectation of success in treating RA, including RA in TNFIRs.

A POSITA would have been motivated to move to less frequent dosing—*i.e.*, two instead of four doses—to improve patient compliance. Ex. 1007 ¶¶ 139, 142. Rituximab is administered intravenously. Ex. 1006 at 206. Therefore, patients cannot self-administer it and, instead, travel to a facility for treatment. Ex. 1007 ¶ 142. Patients 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 requiring fewer drug administrations, and therefore reduced pain and trips to the clinic. *Id*.; *see also* Ex. 1038 at S197 (disclosing a 2002 study by Dr. Edwards treating RA patients with two 1,000 mg doses). Thus, the effort to reduce the frequency of dosing is not inventive. It is obvious because it is the product of "routine optimization of the therapy outlined in [the prior art] which would have been achievable through the use of standard clinical trial procedures." *BioMarin Pharm., Inc. v. Genzyme Therapeutic Prods., LP*, IPR2013-00537, Paper

79, at 14 (P.T.A.B. Feb. 23, 2015), *aff'd*, 825 F.3d 1360 (Fed. Cir. 2016). This is because "[t]he motivation to optimize the therapy disclosed in [the prior art] flows from the normal desire of scientists or artisans to improve upon what is already generally known"—in this case, improving patient compliance by reducing the number of trips that the patient makes to the clinic to treat his or her RA. *Id.* at 20 (internal quotation and citations omitted).

A POSITA would have preferred the fixed dosing disclosed in Edwards over dosing based on body surface area, as in DeVita and Curd. Dosing based on body surface area is most common in oncology, where rituximab's clinical use began. Ex. 1007 ¶ 140. There are significant advantages to using fixed dosing. It is cheaper and less wasteful to produce drugs for fixed dosing since the entire amount produced is administered to the patient. *Id.* Fixed dosing eliminates the possibility of operator error in calculating the appropriate dose. *Id.*; *see also* Ex. 1050 at 596–97. Moreover, fixed dosing was generally used for biologic drugs in the RA field. Ex. 1007 ¶ 140; Ex. 1019 at 16; Ex. 1020 at 3–4.

A POSITA interested in reducing the number of intravenous administrations and extending the time between treatments would have administered two 1,000 mg intravenous doses separated by several weeks as part of routine optimization during the clinical development process. In fact, that is precisely what occurred in going from the weekly fixed doses totaling 2,100 mg, as disclosed in Edwards, to

the two 1,000 mg doses separated by two weeks, as disclosed in Edwards 2002. Starting with Edwards, a POSITA understood that administering 2,100 mg in four fixed doses over four weeks produced an ACR50 or ACR70 result in every patient tested. Ex. 1006 at 205. This result suggested that "the protocol used, or a modification thereof, may be of major benefit to subjects with RA." *Id.* at 207. A POSITA would have administered roughly the same amount of antibody in two, as opposed to four, doses and expected the same result. Ex. 1007 ¶ 141. Then, the most reasonable, and obvious, treatment regimen in light of Edwards would have been to administer about 1,000 mg of antibody—or half of the total dose—on the first day followed by another 1,000 mg of antibody roughly two weeks later to yield the same total amount of antibody at four weeks. Ex. 1007 ¶¶ 143–44; *see also Boehringer*, IPR2015-00417, Paper No. 11, at 22 (instituting IPR of claim 6 of the '838 patent because the Board was "persuaded... that Petitioner is likely to establish that the selection of two intravenous doses of 1000 mg would have been a routine optimization of the therapy suggested by the combination of Curd, De Vita, and Edwards []"); *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, IPR2016-00408, Paper No. 46, at 23–25 (P.T.A.B. July 6, 2017) (discussing routine optimization of an anti-TNFα antibody from 20 mg weekly to 40 mg bi-weekly and concluding the claimed regimen was obvious over the prior art). Toxicity would not have been a significant concern for a 1,000 mg dose. Ex. 1007

¶ 143; Ex. 1028 at 2460 (administering single doses of rituximab exceeding 1,000 mg); Ex. 1027 at 3268 (disclosing a maximum total dose administered of 3,200 mg). In addition, rituximab was already commercially available as 500 mg vials. Ex. 1026 at 2. Thus, 1,000 mg doses (*i.e.*, two 500 mg vials) would have been a convenient and obvious first choice to test. Ex. 1007 ¶¶ 143, 145.

Curd further supports the obviousness of using two 1,000 mg intravenous doses of rituximab. Curd discloses one or more intravenous doses of rituximab within a broad range of 20 mg/m^2 to about 1,000 mg/m^2, and teaches that the antibody can be administered in one or more initial doses followed by one or more subsequent doses. Ex. 1016 at 23:17–19, 23:23–25. This range includes fixed doses of 1,000 mg for an average patient with a body surface area of 1.6 or 1.9 m^2; therefore creating a presumption of obviousness. Ex. 1007 ¶ 59; *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations."); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). Moreover, Curd states that the dosing amount and schedule are subject to a "great deal of therapeutic discretion" inviting POSITAs to

vary the administered dose within the range to find an optimal solution. Ex. 1016 at 23:28–29. Curd also discloses the same dosing regimen used in DeVita—four weekly administrations of 375 mg/m^2, providing a further motivation to combine.

By 2001, the most recent reports regarding the pharmacokinetics of rituximab supported extending the treatment interval to two weeks between two doses of 1,000 mg. Data demonstrated that the half-life of rituximab was on the order of weeks, not days. Ex. 1007 ¶ 141; Ex. 1008 ¶ 19; Ex. 1030 at 297, 299–300 (showing a half-life of approximately 20 days). This is consistent with the known half-life of monoclonal antibodies like rituximab generally. Ex. 1051 at 68 (reporting half-lives between 21–23 days). Also, calculations based on the known pharmacokinetics of rituximab would confirm what a POSITA already would have reasonably expected—that two 1,000 mg doses separated by two weeks produces an equivalent blood plasma profile when compared to each of (i) four 375 mg/m^2 weekly doses (*e.g.*, DeVita and Curd) and (ii) a total dose of 2,100 mg as in Edwards. Ex. 1008 ¶¶ 23–28. Because the blood plasma profiles are equivalent, a POSITA would expect the treatment outcome to be the same. *Id.*; *accord* Ex. 1001 at 29:32–33, 31:29–31. Thus, a POSITA, before the Earliest Possible Priority Date, would have been motivated to at least try two 1,000 mg doses separated by several weeks with a reasonable expectation of success because the regimen was equivalent for therapeutic purposes to the regimens taught by Edwards, DeVita,

and Curd, and would have improved patient compliance and, as a result, expected outcomes. Ex. 1007 ¶¶ 141–43; Ex. 1008 ¶ 26; *see also BioMarin*, IPR2013-00537, Paper 79, at 19 ("routine optimization of the therapy outlined in [the prior art] which would have been achievable through the use of standard clinical trial procedures"); Ex. 1001 at 29:42–43 ("these suggested amounts of antagonist ***are subject to a great deal of therapeutic discretion***").

In *Hoffmann-La Roche v. Apotex*, the Federal Circuit held that it was obvious to select once monthly dosing of a known drug by scaling up a known daily dosing regimen. 748 F.3d 1326, 1329–35 (Fed. Cir. 2014). The Court held that it was obvious to select once monthly oral dosing of ibandronate (an osteoporosis drug) at 150 mg, concluding that "it was reasonable to expect that a once monthly dose of 150 mg [(*i.e.*, 5 mg times 30 days)] would have roughly the same efficacy as a daily dose of 5 mg." *Id.* at 1332–33. Further, evidence supporting superior efficacy for that dose "[did] not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg." *Id.* at 1334. The Court concluded "it was reasonable to expect that a once monthly dose of 150 mg would have roughly the same efficacy as a daily dose of 5 mg" in light of evidence that is similar to the evidence in this case. *Id.* at 1333; *see also Cubist Pharm., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1123–25 (Fed. Cir. 2015) (holding obvious claims to a dosing regimen range given every 48 hours

where the prior art disclosed the dose range, and taught that the drug was likely to be effective in that range); *In re Copaxone Consol. Cases*, Civ. No. 14–1171–GMS, 2017 WL 401943, at *15–17, 18–19 (D. Del. Jan. 30, 2017), *appeal filed*, No. 17–1575 (Feb. 6, 2017) (holding that claims to a higher dose at a longer interval was obvious-to-try over prior art separately teaching the higher dose—even with increased side effects—and that daily injections lead to patient complications).

The specification of the ’838 patent confirms the obviousness, based on the prior art, of two 1,000 mg intravenous doses of rituximab. The specification places no significance on the recited dosing limitations. It merely characterizes the dosing regimen as one of two exemplary “therapeutically effective” regimens. Ex. 1001 at 31:29–31. The specification contains no experimental results and provides nothing more than a suggestion in its prophetic example—that is, treating patients with 1,000 mg on days one and fifteen, or 375 mg/m^2 weekly, four times—to enable a POSITA to practice the claimed methods. *Id.*; *see also Copaxone*, 2017 WL 401942, at *17 (“***It would constitute clear error*** for the court to discredit the [prior art 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)). The regimens appear twice in the specification and both times are disclosed in the same way. Ex. 1001 at 29:32–33, 31:29–31. The

specification provides no reason why a POSITA could, or should, consider the regimens as different from each other and provides no data to indicate that either regimen will produce superior—or even different—results. Ex. 1007 ¶ 27. In other words, the '838 patent equates the two bi-weekly 1,000 mg doses and the four weekly doses of 375 mg/ m^2 with respect to treating RA in TNFIRs.

For the reasons discussed above, at a minimum, two 1,000 mg doses of rituximab would have been obvious to a POSITA in light of a known problem—*i.e.*, improving patient compliance and convenience—and a finite number of possible solutions—*i.e.*, known therapeutically effective and safe dosing levels. Ex. 1007 ¶ 145.

b. It Would Have Been Obvious to Use the Claimed Dosing Regimen in TNFIRs

It also would have been obvious to use the claimed dosing regimen in TNFIRs. Against a backdrop of prior art knowledge that a high percentage of RA patients would not adequately respond to TNFα inhibitors, both Edwards and DeVita (as well as other prior art) teach that such patients may be treated with rituximab using the same dosing regimen as any other patients.[5] Ex. 1007 ¶ 136.

[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.

This demonstrates that POSITAs reasonably expected to succeed in treating TNFIRs just as they reasonably expected to succeed in treating other patients. *Id.* ¶¶ 135, 147. Clinical studies, such as DeVita, are initiated with the expectation they will succeed and not fail. *Id.* ¶ 136.

DeVita illustrates explicitly what is implicit in and suggested by Edwards—that TNFIRs were treated with the same regimen as patients that had not received TNFα inhibitors. Ex. 1005 at 323; Ex. 1006 at 206. A prior inadequate response to TNFα inhibitors was neither used as a selection criterion, nor as grounds to administer different (*e.g.*, higher) doses of rituximab in either study, even though it was well known at the time that a significant proportion of RA patients were TNFIRs. Ex. 1007 ¶¶ 47, 136; Ex. 1005 at 323; Ex. 1006 at 206; *see also* Ex. 1022 at 1557 (disclosing that about 60% of patients have an adequate response to anti-TNFα therapy); Ex. 1023 at 201; Ex. 1024 at 725–26. In fact, none of the anti-CD20 studies involving rituximab distinguished patients based on their response (or lack thereof) to prior anti-TNFα therapy when establishing a dosing regimen. Ex. 1007 ¶¶ 47, 136. DeVita then reports an ACR20 response in a TNFIR providing POSITAs a reasonable expectation that positive clinical results could be achieved in these patients. Ex. 1005 at 323; Ex. 1007 ¶ 135. Therefore, it would have been—and, indeed, it was—obvious to administer two 1,000 mg doses of rituximab to TNFIRs with a reasonable expectation of success.

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. 1001 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. 1007 ¶ 143.

Genentech has previously argued that, in view of DeVita 2002,[6] 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. 1007 ¶ 137; Ex. 1060 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 further confirms the approach of treating all

[6] DeVita 2002 (Ex. 1060) is the later publication of the results first reported in the DeVita abstract (Ex. 1005). *Compare* Ex. 1005 at 323 *with* Ex. 1060 at 2029.

refractory patients alike, including TNFIRs, without regard to their prior therapy to which they inadequately responded, including TNFα inhibitors. Ex. 1007 ¶ 63; Ex. 1006 at 206.

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. 1007 ¶¶ 136, 147. POSITAs understood as early as 1999 that attacking B-cells with rituximab exploited a different mechanism of action from TNFα inhibitors. *See* Ex. 1007 ¶¶ 54, 147; Ex. 1039 at 4 (Fig. 1.1) (showing how B cells act upstream of TNFα during the inflammatory process); Ex. 1041 at 3 (distinguishing rituximab's effect on B-cells from DMARDs that "target the immune system's T-cells or inflammatory signals"). 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. 1007 ¶ 136.

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 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).

Finally, DeVita 2002 does 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*, 737 F.3d at 738–39 (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 that criticizes, discredits, or discourages investigation into the claimed invention. To the contrary, DeVita 2002 encourages investigation into the claimed invention by demonstrating that the RA of TNFIRs could be successfully treated with rituximab. Ex. 1007 ¶ 137; Ex. 1060 at 2030–32 ("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. 1005 at 323 (concluding that "a clinical response was achieved in patients who did not respond to direct treatment against T lymphocytes and synoviocytes"). DeVita 2002's actual clinical demonstration of treating TNFIRs is 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. 1007 ¶ 47; Ex. 1023 at 201. This did not discourage POSITAs from treating RA with TNFα inhibitors. *Id.*; *see also* Ex. 1005 at 323; Ex. 1006 at 205. In the same way, rather than be discouraged, a POSITA would have been motivated to treat RA in TNFIRs in view of DeVita 2002's successful treatment of such patients. Ex. 1007 ¶ 137; *Pfizer*, 480 F.3d at 1364. 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 response like those reported in DeVita. *See* Ex. 1007 ¶ 137; Ex. 1010 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 and DeVita, taught that ***all*** RA patients should receive the same dosing regimen within the same study. Ex. 1007 ¶ 136. 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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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." Edwards discloses that "[a]t 6 months [(24 weeks)], all patients had achieved ACR50 and patients 1–3 achieved ACR70 without introduction of further therapy." Ex. 1006 at 207; *id.* (reporting three patients with a clinical impression of complete remission); *id.* (defining "Remission" as "the absence of clinical or laboratory evidence of ongoing immunological activity"); *id.* (noting that "the protocol used, or a modification thereof, may be of major benefit to subjects with RA"). Similarly, DeVita treated four patients and noted "[a] marked clinical improvement... in patients 1 and 2 as from [the] 3rd month (+3) from the start of the anti-CD20 therapy (ACR70 and ACR50 response respectively), with a response until month +10 in patient 1 (with relapse from month +11) and until month +7 in patient 2 (last follow up)." Ex. 1005 at 323 (noting that "a clinical response was achieved in patients who did not respond to direct treatment against T lymphocytes and synoviocytes").

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

Edwards in view of DeVita 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.

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 in view of DeVita 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 would have still been obvious. 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. 1001 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.

Edwards in view of DeVita and Curd renders obvious a method of treating RA in TNFIRs with two 1,000 mg doses of rituximab, and therefore also renders obvious the inevitable result of administering that dose. Edwards and DeVita both disclose ACR50 and ACR70 responses using dose regimens equivalent to or that render obvious the claimed regimen, Edwards reported a clinical impression of complete remission in three patients, and DeVita reported a clinical response in a TNFIR. Ex. 1006 at 207; Ex. 1005 at 323. Based on those results, Edwards concluded that "the protocol used, or a modification thereof, may be of major benefit to subjects with RA." Ex. 1006 at 207. A POSITA would have had a reasonable expectation of achieving similar results in TNFIRs because anti-CD20 antibodies operate on a different mechanism of action from TNFα inhibitors. Ex. 1007 ¶ 136. An inadequate response to TNFα inhibitors would not inform a POSITA about whether the patient would respond to rituximab, and therefore TNFIRs would have been considered no different than any other multiple DMARD

refractory patient. *Id.* ¶¶ 136, 147. These teachings are sufficient to render the claimed clinical outcomes obvious. *See Pfizer*, 480 F.3d at 1364.

The ’838 patent provides no clinical data to support the idea that the claimed clinical outcomes are achievable. *See* Ex. 1001 at 31:8–32:37; *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 in view of DeVita 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 DeVita, Edwards, and Curd. Ex. 1005 at 323 (“treatment with Rituximab, a chimeric anti-CD-20 monoclonal antibody”); Ex. 1006 at 206 (“All patients received... [m]onoclonal chimaeric [*sic*] anti-CD20 antibody, rituximab (Mabthera)”); Ex. 1016 at 25:9–10 (“Patients with clinical diagnosis of rheumatoid arthritis (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 in view of DeVita and Curd renders the methods of claim 2 obvious for at least the reasons discussed in Section VI.G.2.

Combination therapies involving DMARDs and biologics were well-known before the Earliest Possible Priority Date of the '838 patent. Ex. 1007 ¶¶ 55–57, 142; *see also* Ex. 1010 at 329, Figure 1. POSITAs understood that administering multiple drugs acting via different mechanisms of action would increase the probability of success in treating RA. Ex. 1007 ¶ 138; *see also* Ex. 1010 at 332–40. Virtually all new RA treatments were being tested as combination therapies with methotrexate, including most new "biotechnology-derived" therapeutic drugs like TNFα inhibitors. Ex. 1007 ¶¶ 55–57, 102; Ex. 1012 at 790; Ex. 1013 at 1548, 1550; Ex. 1014 at 592. And, as methotrexate was a known immunosuppressive agent, POSITAs understood that it could reduce the patient's reaction to the administered foreign antibodies thereby enhancing the response to rituximab. Ex. 1007 ¶ 103; Ex. 1016 at 25:9–16.

Upon this background understanding, Curd teaches that anti-CD20 therapy using rituximab may be combined with other known RA treating drugs including methotrexate. *Id.* ("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 in dosages known for such drugs or reduced dosages"). Since POSITAs understood that methotrexate was a foundational therapy, operating on a different mechanism, that could enhance the benefits of rituximab, and since Curd provides an explicit teaching that a POSITA should use such combinations, it would have been obvious to combine the method in claim 2 with the addition of methotrexate. Ex. 1007 ¶ 138.

5. Claim 5

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

Edwards in view of DeVita and Curd renders the methods of claim 4 obvious for at least the reasons discussed in Section VI.G.4. Combination therapies for treating RA were common before the Earliest Possible Priority Date. Ex. 1007 ¶¶ 55–57, 59, 103, 131, 142; Ex. 1017 at 142; Ex. 1010 at 329, Figure 1. This was so even before POSITAs understood how the drugs worked. Ex. 1007 ¶ 103; Ex. 1013 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…."). Both Edwards and DeVita allowed patients to take corticosteroids in addition to rituximab during

treatment. Ex. 1005 at 323 ("The patients could only take low doses of steroid (< or equal to 10 mg/day), NSAIDs or antimalarial drugs.); Ex. 1006 at 207 ("At 34 weeks [patient 2] was retreated with a single 500 mg dose of rituximab and started on prednisolone 10 mg daily.").

Methotrexate and corticosteroids were commonly used in combination with monoclonal antibodies to treat RA before the Earliest Possible Priority Date. Ex. 1007 ¶ 131; Ex. 1013 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. 1007 ¶ 138; Ex. 1016 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 in view of DeVita and Curd would be motivated to combine rituximab with both methotrexate and corticosteroids with a reasonable expectation of success given these express teachings and because methotrexate and corticosteroids are both immunosuppressive and anti-inflammatory agents that can

enhance the action of rituximab and relieve residual patient symptoms. *See* Ex. 1016 at 8:22–29, 25:9–16; Ex. 1007 ¶¶ 103, 131, 138; Ex. 1005 at 323; Ex. 1006 at 207.

6. Claim 6

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

Edwards in view of DeVita and Curd renders the methods of claim 5 obvious for at least the reasons discussed in Section VI.G.5. For at least the reasons discussed in Sections VI.G.4 and VI.G.5, Edwards in view of DeVita and Curd renders obvious a method of treating TNFIRs with two 1,000 mg doses of rituximab combined with methotrexate and corticosteroids. *See* Ex. 1005 at 323; Ex. 1006 at 207; Ex. 1016 at 8:22–29, 25:9–16; Ex. 1007 ¶¶ 103, 131, 138. In teaching that rituximab should be combined with immunosuppressive agents including methotrexate and corticosteroids, Curd discloses that corticosteroids include both methylprednisolone and prednisone. Ex. 1016 at 8:22–29, 25:9–16. A POSITA would have been motivated to combine rituximab with methotrexate, 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. 1016 at 8:22–29, 25:9–16; Ex. 1007 ¶¶ 103, 131, 138; Ex. 1005 at 323; Ex. 1006 at 207.

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 in view of DeVita and Curd renders the methods of claim 2 obvious for at least the reasons discussed in Section VI.G.2. Neither Edwards nor DeVita treated the disclosed RA patients with more than one B-cell surface marker antibody. Ex. 1005 at 323; Ex. 1006 at 206. The only B-cell surface marker antibody used was rituximab. Moreover, rituximab was the only such anti-CD20 antibody that had received FDA approval at the time, providing a 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 in view of DeVita 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 with DeVita 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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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. Edwards and DeVita both disclose ACR50 and ACR70 responses using dose regimens equivalent to the claimed regimen, Edwards reported a clinical impression of complete remission in

three patients, and DeVita reported a clinical response in a TNFIR. Ex. 1007 ¶¶ 105–106; Ex. 1006 at 207; Ex. 1005 at 323. A POSITA would have had a reasonable expectation of achieving similar results in TNFIRs because anti-CD20 antibodies operate on a different mechanism of action from TNFα inhibitors. Ex. 1007 ¶ 136. 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. *Id.* ¶¶ 136, 147. 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. *Id.* ¶ 107. These teachings are sufficient to render the claimed clinical outcomes obvious. *See Pfizer*, 480 F.3d at 1364.

The ’838 patent specification characterizes “erosive progression” merely as an “exploratory” endpoint. Ex. 1001 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. 1001 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. Since Edwards in view of DeVita 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 in view of DeVita 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 with DeVita

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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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.

v. 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 with

DeVita and Curd to treat TNFIRs by administering two 1,000 mg doses of rituximab and methotrexate with a reasonable expectation of success in the patient resulting in 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 in view of DeVita 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 in view of DeVita 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 in view of DeVita 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. 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 (P.T.A.B. Apr. 15, 2015). 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. 1007 ¶ 149; *see also BioMarin Pharm., Inc. v. Genzyme Therapeutic Prods., LP*, IPR2013-00534, Paper 81, at 21–22 (P.T.A.B. Feb. 23, 2015), *aff'd*, 825 F.3d 1360 (Fed. Cir. 2016) (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"); *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. 1007 ¶¶147–48 ; *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'").

I. Conclusion

For the reasons discussed above, Edwards in view of DeVita 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 13,983 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 1001 – 1061 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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