Paper No.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Boehringer Ingelheim International GmbH and
Boehringer Ingelheim Pharmaceuticals, Inc.
Petitioner,

v.

Genentech, Inc.
Patent Owner

Patent No. 7,976,838 B2
Issued: July 12, 2011
Filed: March 20, 2008
Inventor: Mark C. Benyunes

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

Inter Partes Review No. TBD

PETITION FOR *INTER PARTES* REVIEW

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I. PRELIMINARY STATEMENT

The challenged claims of U.S. Patent No. 7,976,838 ("the '838 patent") relate to methods of treating rheumatoid arthritis ("RA") by administering two 1000 mg intravenous doses of an anti-CD20 antibody—namely, rituximab.[1] The claims are directed to methods of treating patients who experience an "inadequate response" to well-known RA drugs, known as TNFα-inhibitors.[2] Non-responders to TNFα-inhibitors account for approximately 40% of the patient population.[3] In the context of the '838 patent, however, the percentage of non-responders is even higher, given that, according to the patent, individuals can experience an "inadequate response" if they are merely prone to experience a toxicity or deemed unlikely to respond to treatment. In other words, the '838 patent states that

[1] Rituximab is also known by the brand name RITUXAN®.

[2] The body produces tumor necrosis factor alpha (TNFα) as a result of RA, and TNFα inhibitors are used as a therapy for treating the disease. (*See, e.g.*, Ex. 1001 at 4:25-27.)

[3] *See* Ex. 1002 at ¶ 50 (stating the patient response rate to TNFα-inhibitors is about 60%); Ex. 1029 at 1557 (reporting a response rate to TNFα-inhibitors of approximately 60%); Ex. 1011 at 207 (estimating between 50 and 70% of patients will respond to TNFα-inhibitors).

patients can experience an "inadequate response" to a TNFα-inhibitor even if they have never been given the drug.

The preamble phrase referring to patients "who experience[] an inadequate response to a TNFα-inhibitor" appears in each of the challenged claims. This preamble phrase is not a claim limitation under the broadest reasonable construction because it does not recite essential structure and the phrase is not necessary to give life, meaning, and vitality to the claims. The actual elements of the claims describe structurally complete methods of treating RA by administering two 1000 mg doses of an anti-CD20 antibody (*e.g.*, rituximab) and in some cases other therapeutic agents, including methotrexate and corticosteroids. The methods of treatment are the same regardless of who receives them.

Under the broadest reasonable construction, the challenged claims are anticipated by at least two separate prior art references. These prior art references summarize the results of a clinical study designed by a British researcher named Jonathan Edwards, M.D. (and others), in which 161 RA patients were separated into four groups and given some combination of the following: (i) two 1000 mg IV doses of rituximab; (ii) methotrexate; and (iii) a 17-day course of corticosteroids. The results of the study were described as "positive" and summarized in a press release announcing that "[t]hese data suggest that targeting B-cells with

[rituximab] may represent a completely new approach to treating patients with rheumatoid arthritis."

Even if the preamble phrase "who experiences an inadequate response to a TNFα-inhibitor" were a limitation, it would be inherently disclosed by the administration of the required dosing regimen to any sizeable patient population. This is due to the high percentage of non-responders to TNFα-inhibitors, which constitutes at least 40% of all RA patients. In a study involving 160 patients, such as the prior art study designed by Dr. Edwards, for example, about 60 non-responders to TNFα-inhibitors would be necessarily present and the "limiting" preamble phrase would be met.

Other prior art also renders the challenged claims unpatentable. The prior art discloses a wide range of dosing regimens for treating RA with rituximab (including ranges that encompass the doses required by the '838 patent), as well as numerous combination therapies involving methotrexate and corticosteroids. The prior art explicitly discloses the administration of rituximab to RA patients who did not respond to TNFα-inhibitors. In light of the known RA therapies available as of the earliest priority date of the '838 patent, a person of ordinary skill would have had a reasonable expectation of success using the claimed methods of treating RA. At minimum, the claimed methods of treatment would have been obvious, given

the known problem of treating TNF non-responders and the finite number of identified predictable solutions for effectively treating RA.

For these reasons, and those set forth in detail below, the challenged claims should be found unpatentable.

II. MANDATORY NOTICES

A. Real Parties-in-Interest or Privies

The real parties in interest are: (i) Boehringer Ingelheim Pharmaceuticals, Inc., located at 900 Ridgebury Road, Ridgefield, CT 06877; and (ii) Boehringer Ingelheim International GmbH, located at Binger Strasse 173, Ingelheim am Rhein, Germany 55216 (collectively, "Boehringer" or "Petitioner").

B. Related Matters

Simultaneously with this Petition, Petitioner has filed Petitions for Inter Partes Review against United States Patent Nos. 7,820,161 and 8,329,172. The following patent may claim the benefit of the priority of the filing date of U.S. Patent No. 7,976,838: USPN 7,708,994(USSN 11/439906).

C. Lead and Back-Up Counsel

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III. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

Petitioner challenges claims 1-14 of the ’838 patent (Ex. 1001) as unpatentable under 35 U.S.C. §§ 102 and 103 on the specific grounds set forth in Section IX below. This petition is supported by the Declaration of Joachim R. Kalden, M.D. (Ex. 1002). The petition and supporting declaration show that there is at least a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. *See* 35 U.S.C. § 314(a).

V. SUMMARY OF THE ’838 PATENT AND PROSECUTION HISTORY

The ’838 patent issued on July 12, 2011, from application no. 12/052,606 (“the ’606 application”), which was filed on March 20, 2008. The ’606 application

claimed priority to a provisional application filed on April 9, 2003. Therefore, any publication prior to April 9, 2003 will qualify as prior art under 35 U.S.C. §102(a), and any publication prior to April 9, 2002 will qualify as prior art under 35 U.S.C. §102(b).

A. The Claims of the '838 Patent

1. Independent Claims 1, 2, 8, 10, and 11

Claims 1, 2, 8, and 10 share the same preamble: "[a] method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor." The preamble of claim 11 is somewhat different: "[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." As explained below, the preamble phrase "who experiences an inadequate response to a TNFα-inhibitor," which appears in all of the challenged claims, is not a limitation. *See* Section VI.A *infra*. Nor is the preamble of claim 11 a limitation on claim scope. *See* Section VI.D *infra*.

All challenged claims require two 1000 mg intravenous doses of rituximab or, more generally, an antibody that binds to CD20. Claims 10 and 11 also require the co-administration of methotrexate.

Some independent claims of the ’838 patent purport to require a specific clinical response to the claimed methods of administration. For example, claim 2 further requires any one of three clinical responses: (i) “an ACR50 response at week 24;” (ii) an “ACR70 response at week 24;” or (iii) “no erosive progression at week 24 and beyond.” Similarly, claim 10 includes a “wherein” clause that purports to require “no erosive progression at week 24 and beyond.” Such “wherein” clauses that merely characterize the result of the administration steps are not entitled to patentable weight. *See* Section VI.C *infra*.

2. Dependent Claims 3-7, 9, and 12-14

The ’838 patent also contains nine dependent claims. The dependent claims include additional limitations that, for example, require: (i) that the administered antibody is rituximab (claim 3); (ii) co-administration of methotrexate and/or corticosteroids (claims 4-6 and 9); (iii) that the CD20 antibody is the only B-cell surface marker antibody administered to the patient (claim 7); or (iv) specific clinical responses (claims 12-14).

B. Specification of the ’838 Patent

The ’838 patent states that “[t]he present invention concerns therapy with antagonists which bind to B cell surface markers, such as CD20.” (Ex. 1001 at 1:14-15.) According to the patent, “the invention concerns the use of such

antagonists to treat autoimmune disease in a mammal who experiences an inadequate response to a TNFα-inhibitor." (*Id*. at 1:15-18.)

The '838 patent defines a "TNFα inhibitor" as "an agent that inhibits to some extent, a biological function of TNFα, generally through binding to TNFα-inhibitor and neutralizing its activity." (*Id*. at 5:19-21) The patent provides several examples of TNFα inhibitors, including Etanercept (ENBREL®), infliximab (REMICADE®) and Adalimumab (HUMIRA™). (*Id.* at 5:21-24.)

According to the '838 patent, an "inadequate response to a TNFα-inhibitor" refers to "an inadequate response to previous or current treatment with a TNFα-inhibitor because of toxicity and/or inadequate efficacy." (*Id*. at 5:25-28.) Further, the patent explains that patients who experience "an inadequate response" are not necessarily limited to patients who have actually been treated with a TNFα-inhibitor:

> [T]he 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.)

The ’838 patent includes only one example. The example states: “A patient with active rheumatoid arthritis who has an inadequate response to one or more TNFα-inhibitor therapies is treated with an antibody that binds the B-cell surface antigen, CD20.” (*Id*. at 31:8-11.) Specifically, “[t]he CD20 antibody used for therapy may be Rituximab (commercially available from Genentech, Inc.) or humanized 2H7 v16.” (*Id*. at 31:26-28.)

The lone example in the ’838 patent refers to two “therapeutically effective” doses of CD20 antibody: (i) “1000 mg i.v. on Days 1 and 15,” and (ii) “375 mg/m2 i.v. weekly x 4.” (*Id*. at 31:29-31.) Elsewhere, the ’838 patent also refers to these same doses of CD20 antibody, stating that “[e]xemplary dosage regimens include 375 mg/m2 weeklyx4; or 1000 mgx2 (e.g. on days 1 and 15).” (*Id*. at 29:32-33.) However, the patent states that the dosing amounts “are subject to a great deal of therapeutic discretion” (*id*. at 29:42-45), and indicates that the specific dosing regimen is not critical because “[t]he key factor in selecting an appropriate dose and scheduling is the result obtained” in the patient (*id*. at 29:44-45).

C. Prosecution History of the ’838 Patent

During the prosecution, the assignee of the ’838 patent, Genentech, Inc. (“Genentech”), relied on a declaration by Dr. van Vollenhoven that Genentech had originally submitted to the European Patent Office in connection with an

opposition to the foreign counterpart of the '838 patent (EP 1613350).[4] (*See* Ex. 1016.) According to Genentech, Dr. van Vollenhoven's declaration "discusses anti-TNF inadequate responder patients . . . and explains how they were considered the most therapy-resistant and difficult to treat rheumatoid arthritis patients in April 2003 when the above application was filed." (Ex. 1036 at 11.)[5] The applicant argued during the prosecution of the '838 patent that the 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 . . . ." (*Id.* at 11-12.) The applicant also argued that the declaration explains how the alleged invention produces unexpected results. (*Id.* at 12.)

VI. CLAIM CONSTRUCTION

Because the '838 patent has not yet expired, the challenged claims should be given their broadest reasonable construction in light of the specification of the patent. 37 C.F.R. § 42.100(b).

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[4] Despite the submission of Dr. van Vollenhoven's declaration, the European Patent Office revoked the foreign counterpart of the '838 patent because it lacked novelty. (*See* Ex. 1019 at 1; Ex. 1018 at 30-36 (concluding that the subject matter of the claims was not inventive and dismissing the patentee's appeal).)

[5] Citations to the exhibits refer to the pagination of the original documents.

A. The Preamble Phrase "who experiences an inadequate response to a TNFα-inhibitor" Is Not Limiting

The preamble of each independent claim of the '838 patent includes the following phrase: "who experiences an inadequate response to a TNFα-inhibitor." The preamble of claim 1, for example, reads: "[a] method of treating rheumatoid arthritis in a human patient ***who experiences an inadequate response to a TNFα-inhibitor***." (emphasis added). The broadest reasonable construction of the phrase "who experiences an inadequate response to a TNFα-inhibitor" is one where the preamble is not a limitation on the scope of the challenged claims.

Whether a preamble should be treated as a claim limitation is "determined on the facts of each case in light of the claim as a whole and the invention described in the patent." *Storage Tech. Corp. v. Cisco Sys., Inc.*, 329 F.3d 823, 831 (Fed. Cir. 2003). While there is no simple test to determine when a preamble limits claim scope, "[g]enerally, the preamble does not limit the claims." *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). A preamble may be limiting if it "recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (internal quotation marks omitted). "A preamble is not regarded as limiting, however, 'when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed

invention.'" *Am. Med. Sys. v. Biolitec, Inc.*, 618 F.3d 1354, 1359 (Fed. Cir. 2010) (quoting *Catalina*, 289 F.3d at 809).

Deleting the preamble phrase "who experiences an inadequate response to a TNFα-inhibitor" would not affect the structure or steps of the alleged invention, which is a method for treating RA by administering an anti-CD20 antibody (*e.g.*, rituximab) in two IV doses of 1000 mg.[6] The methods of treatment are the same regardless of who receives them.

The preamble phrase merely refers to a subgroup of the patient population that constitutes nearly half of all RA patients. (*See* Section VIII.C *infra*.) Moreover, the specification of the '838 patent explains that an "inadequate response" can be experienced due to toxicity and/or a lack of efficacy, even if the patient has never been treated with TNFα-inhibitors:

> [T]he 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.

[6] Some claims also require co-administration of methotrexate and/or corticosteroids in undisclosed amounts. *See* Ex. 1001 ('838 patent) at claims 4-6, 10, and 11.

(Ex. 1001 at 28:45-61.)

In sum, the broadest reasonable construction of the claims is that the preamble phrase "who experiences an inadequate response to a TNFα-inhibitor" is not a limitation. To the extent the preamble phrase is deemed to be a limitation, however, it must be construed in light of the statements in the specification indicating that an "inadequate response" may be due to toxicity and/or inadequate efficacy (Ex. 1001 at 5:25-28) and may be experienced in patients who have never been treated with TNFα-inhibitors (*id*. at 28:45-61).

B. Two 1000 mg Doses of the CD20 Antibody Must Necessarily Be "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"

Claim 2 of the '838 patent includes two separate limitations specifying the amount of antibody administered. First, the claim calls for "administering to the patient an antibody which binds to CD20 in an amount that is effective to provide an ACR50 response at week 24, an ACR70 response at week 24 or no erosive progression at weeks 24 and beyond." Second, the claim goes on to specify the actual amount to be administered—that is, "two intravenous doses of 1000 mg." Therefore, claim 2 tells us that two intravenous doses of 1000 mg ***must be*** effective for providing one or more of the clinical responses recited in the claim—*i.e.*, an ACR50 response at week 24, an ACR70 response at week 24, and/or no erosive progression at weeks 24 and beyond.

C. The "Wherein" Clauses Relating to the Clinical Results of the Claimed Treatment Have No Patentable Weight

Certain dependent claims contain "whereby" clauses that state the intended clinical result of administering methotrexate and two 1000 mg doses of rituximab:

- "wherein the patient has no erosive progression at weeks 24 and beyond" (claim 10);
- "wherein the clinical response is ACR50 response at week 24" (claim 12);
- "wherein the clinical response is ACR70 response at week 24" (claim 13); and
- "wherein the clinical response is no erosive progression at weeks 24 and beyond" (claim 14).[7]

"A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim." *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d. 1165, 1172 (Fed. Cir. 1993). The same is also true for "wherein" clauses. *See, e.g.*, MPEP § 2111.04 (discussing "wherein" and "whereby" clauses together as "examples of claim

[7] *See* Section VIII.A *infra* for a discussion of clinical responses to RA treatments and the criteria set forth by the American College of Rheumatology (*e.g.*, ACR50 and ACR70).

language . . . that may raise a question as to the limiting effect of the language in a claim").

The "wherein" clauses at issue here are not entitled to patentable weight and should not be given any limiting effect because they merely identify the clinical responses that are the intended result of the administration steps recited elsewhere in the claims. The patients receive the same treatment—that is, two IV doses of 1000 mg of an anti-CD20 antibody (*e.g.*, rituximab) and co-administration of methotrexate. The alleged invention is the same regardless of the physical response experienced by the patient, which will inevitably vary in each individual who receives the treatment. (Ex. 1002 at ¶ 89.)

The Board of Patent Appeals and Interferences ("BPAI") was faced with the same issue in *Ex Parte Berzofsky*, Appeal No. 1010-011270, 2011 WL 891756 (BPAI Mar. 10, 2011), where the claims incorporated certain "wherein" clauses providing that the administration of a monoclonal antibody results in "inhibiting recurrence of the tumor in the subject." *Id.* at *5. The BPAI found that:

> 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. Therefore, the wherein clause is not entitled to weight in construing the claims.

Id.

The BPAI's reasoning in *Ex parte Berzofsky* applies here. The intended result of the claimed administration, as reflected in the "wherein" clauses of claims 10, 12, 13 and 14, should carry no weight in construing the claims.

D. The 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 procession at weeks 24 and beyond" Is Not Limiting

The preamble of claim 11 reads: "[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." The preamble merely states the purpose or intended use of the invention, which is set forth fully in the body of the claim. The broadest reasonable construction of claim 11 is that the preamble is not a limitation on the scope of the claim.

"If . . . the body of the claim fully and intrinsically sets forth the complete invention, including all of its limitations, and the preamble offers no distinct definition of any of the claimed invention's limitations, but rather merely states, for example, the purpose or intended use of the invention, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). Indeed, "where a patentee defines a structurally complete

invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation." *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997).

The body of claim 11 defines the structure of the alleged invention—that is, "administering to the patient rituximab, and methotrexate, wherein rituximab is administered as two intravenous doses of 1000 mg." The preamble is not a limitation here because it merely states the purpose or intended use of the claimed treatment (*i.e.*, "achieving a clinical response").

VII. LEVEL OF ORDINARY SKILL

Rheumatoid arthritis is a chronic inflammatory disorder that affects tens of millions of people worldwide. (Ex. 1002 at ¶ 37.) The disorder has been the subject of substantial research and published literature concerning the treatment of patients and new RA therapies. (*Id.*) Many practicing rheumatologists are involved with clinical trials involving new drugs and methods of treatment. For this reason, doctors in the field of rheumatology tend to be well informed about current trends and developing therapies for treating rheumatoid arthritis. (*Id.*) This was true at the time of the alleged invention and remains true today. (*Id.*)

A person of ordinary skill as of the priority date would have been a practicing rheumatologist with at least 2-3 years of experience treating RA

patients, knowledge about the available methods of treating RA, and an understanding of the pathophysiology of RA. (*See* Ex. 1002 at ¶ 38.)

VIII. THE STATE OF THE PRIOR ART

A. RA Treatments and the American College of Rheumatology (ACR) Criteria

Rheumatoid arthritis is a chronic autoimmune disease that causes pain, stiffness, swelling and limited motion and function of joints. (Ex. 1002 at ¶ 39.) RA can affect any joint, but the small joints in the hands and feet tend to be involved most often. (*Id.*) While effective therapeutic regimens have been available for many years before the earliest priority date of the '838 patent, patients often fail to respond to these treatments, fail to sustain an initial response, or suffer from significant toxicity necessitating withdrawal of treatment. (*Id.* at ¶ 40.) Moreover, remission is rare and a curative treatment is not known. (*Id*.)

Before the earliest priority date of the '838 patent (April 9, 2003), typical practice involved treating RA first with a single agent. (Ex. 1002 at ¶ 42.) If a satisfactory response was not achieved after 3-6 months, then combination treatments were given, which usually involved the administration of methotrexate. (*Id*.) Patients who then failed to respond to such combination therapies were offered other therapeutic options. (*Id*.)

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

RA treatments. (Ex. 1002 at ¶ 43.) The criteria measure percentage improvement in tender joint count, swollen joint counts, and three out of five core set items, including: (i) MD global assessment; (ii) patient global assessment; (iii) patient pain; (iv) disability (self-reported using validated instrument); and (v) erythrocyle sedimentation rate/C-reactive protein. (*Id.*) "ACR20" means that a patient achieved a 20 percent improvement in tender joint count, swollen joint count, and three of the five core set items. (*Id.*) "ACR50" and "ACR70" means that a patient achieved 50 percent and 70 percent improvements, respectively. (*Id.*)

B. Treating RA with Anti-CD20 Antibody Rituximab

Rituximab (a/k/a Rituxan, Mabthera, and IDEC-C2B8) is an antibody that targets and kills B-cells in humans. (Ex. 1002 at ¶ 51.) More specifically, the product label for rituximab states that it is "a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes." (Ex. 1012 at 1.)

By 1998, scientists had realized that rituximab could be used to treat RA by selectively targeting and killing mature B-cells. (Ex. 1002 at ¶¶ 52-53.) In November 1997, rituximab received FDA approval for treating B-cell non-Hodgkin's lymphoma (NHL). (Ex. 1002 at ¶ 51.) The product label states that rituximab is "a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration." (Ex. 1012 at 1.) The administration of rituximab

to human patients causes a sustained and rapid depletion of B-cells. (Ex. 1027 at 2457 ("CD20 B cells were rapidly and specifically depleted in the peripheral blood at 24 to 72 hours and remained depleted for at least 2 to 3 months in most patients."); Ex. 1020 at 2188 ("Rapid binding to and depletion of CD20 normal B cells and tumor cells in the peripheral blood and bone marrow was observed . . .").)

1. The Work of Dr. Edwards

In 1998, Dr. Edwards published a paper titled, "Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody is also Antigen" ("Edwards I"). (Ex. 1021.) The paper published in the *British Journal of Rheumatology* in March 1998. (*Id.*) The publication is prior art under 35 U.S.C. §102(b).

Edwards I proposed using CD20 antibodies to treat RA by selectively depleting B-cells. In the paper, Dr. Edwards explained his hypothesis that the destruction of RF-producing B-cells using anti-CD20 antibodies (or other agents) is a strategy that would logically lead to a possible cure for RA. Dr. Edwards wrote that "the logical thing to do is destroy all mature B cells." (Ex. 1021 at 128-9.) The paper states: "Recent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects…." (*Id.* at 129.) Here, Dr. Edwards cited to a 1994 publication by

Maloney *et al*. describing the intravenous use of anti-CD20 antibody rituximab to selectively deplete B cells (Ex. 1027).

In May 1998, Dr. Edwards gave a presentation to the Australian Rheumatology Association, titled "The Case for Killing B Cells with Anti-CD20 in RA" ("Edwards II"). (Ex. 1035.) The abstract summarizes the case made by Dr. Edwards for killing B-cells in RA patients using an anti-CD20 antibody. The abstract states: "[T]he broad prediction is that at least in early disease anti-CD20 might be curative in RA . . . . The treatment would appear to be very safe, and a clinical trial is proposed." (*Id.* at 53.) The published abstract is prior art under 35 U.S.C. §102(b).

On April 22, 1999, Dr. Edwards gave a presentation at the Fourth International Synovitis Workshop in Dallas, Texas. The abstract of that presentation ("Edwards III"), which was submitted to the Dallas workshop and distributed to attending delegates, summarized the elements of Dr. Edwards's hypothesis regarding the pathogenesis of RA. (Ex. 1037.) Edwards III states that "deletion of IgG RF-committed B cells should produce long-term remission" and that "[i]nitial results from a phase I therapeutic trial of B cell depletion will be presented." (*Id.*) The published abstract is prior art under 35 U.S.C. §102(b).

In 2001, Dr. Edwards reported the "initial results" referred to above in an article published in the journal *Rheumatology* that was titled, "Sustained

Improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes" ("Edwards IV"). (Ex. 1022.) The paper is prior art under 35 U.S.C. §102(b).

According to Edwards IV, "[a]n open study of B-lymphocyte depletion was undertaken in rheumatoid arthritis (RA) patients to test the hypothesis that B lymphocytes may be essential to disease perpetuation." (Ex. 1022 at 205.) The paper reports that "[f]ive patients with refractory RA were treated with a monoclonal anti-CD20 antibody, cyclophosphamide and prednisolone and followed for 12-17 months." (*Id.*) All patients received four IV 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. (*Id.* at 206.) Patients also received oral administrations of prednisolone. (*Id.*) The results of the study showed that "[a]t 26 weeks all patients satisfied the American College of Rheumatology ACR50 and patients 1-3 the ACR70 criteria of improvement without further therapy." (*Id.*) The paper concludes that "[t]hese finding are consistent with the concept that RA is critically dependent on B lymphocytes and suggest that B-lympocyte depletion may be a safe and effective therapy." (*Id.*)

In August 2002, Dr. Edwards published an article, titled "B-lymphocyte depletion therapy in rheumatoid arthritis and other autoimmune disorders," in *Biochemical Society Transactions* ("Edwards V"). (Ex. 1038.) The article notes

that "[t]he main agent in use at present for B-lymphocyte depletion is the anti-CD20 antibody rituximab." (*Id.* at 825.) The article further notes that "[r]ituximab was licensed for use against lymphoma in 1997-1998 and has therefore been available for off-label use." (*Id.* at 826.) Dr. Edwards pointed out that while the recommended dose for treating lymphoma—*i.e.*, "four infusions of 375 mg/m^2 of body surface area at 1-week intervals"—has been used in many protocols, "both lower and higher doses have been tried." (*Id.*) In addition, the article states that "[r]ituximab has often been used alone, but it has also been used in combination with cyclophosphamide and/or glucocorticoid." (*Id.*) This article is prior art under 35 U.S.C. §102(a).

Dr. Edwards also collaborated with Roche to design a new trial for treating RA with rituximab. Dr. Edwards presented the initial results of the Roche study at the Annual American College of Rheumatology meeting in October 2002. The abstract that accompanied the presentation, dated October 26, 2002, was titled, "Efficacy and Safety of Rituximab, a B-Cell Targeted Chimeric Monoclonal Antibody: A Randomized, Placebo-Controlled Trial in Patients with Rheumatoid Arthritis" ("Edwards VI"). (Ex. 1003.) On October 28, 2002, Genentech also issued a press release (the "Genentech Press Release") that announced the interim results of the same clinical study. (Ex. 1004.) Both references are prior art under at least 35 U.S.C. §102(a).

According to Edwards VI, the Edwards-Roche study consisted of 161 patients with RA, all of whom were rheumatoid factor positive and receiving methotrexate. (Ex. 1003.) The patients were separated into four patient groups: Group A (continuing methotrexate alone); Group B (rituximab alone); Group C (rituximab and cyclophosphamide); and Group D (rituximab plus continuing methotrexate). (*Id.*) Patients receiving rituximab were given two IV doses of 1000mg. (*Id.*) In addition, all groups received a 17-day course of corticosteroids. (*Id.*) All three rituximab regimens were "well tolerated" and produced "substantial clinical benefit in RA," with the combination therapies the highest levels of ACR20, 50, and 70 responses. (*Id.*)

Similarly, the Genentech Press Release stated: "Rituxan [*i.e.*, rituximab] was administered as two intravenous infusions, with doses (1g) [1000 mg] given two weeks apart." (Ex. 1004 at 2.) The Genentech Press Release also reports that patients participating in the study received intravenous and oral corticosteroids. (*Id.*) According to the Genentech Press Release, the resulting data "suggest that targeting B-cells with Rituxan may represent a completely new approach to treating patients with rheumatoid arthritis." (*Id.* at 1.) The Genentech Press Release summarized the results of the study as follows:

- Patients receiving Rituxan alone (n=31): 18 patients (58%) experienced ACR20 responses, 10 patients (32%) experienced ACR50 responses and 4 patients (13%) experienced ACR70 responses.

- Patients receiving Rituxan plus methotrexate (n=30): 24 patients (80%) experienced ACR20 responses, 15 patients (50%) experienced ACR50 responses, and 7 patients (23%) experienced ACR70 responses.

(*Id.* at 2.) The final results of this clinical study were eventually published by Dr. Edwards in the New England Journal of Medicine in 2004. (*See* Ex. 1023.)

2. Genentech's 2000 PCT Application (Curd et al.)

In 1999, two researchers from Genentech (Drs. Curd and Kunkel) and one from IDEC Pharmaceuticals (Dr. Grillo-López) filed a PCT patent application (the "Curd PCT Publication") that published in November 2000. (Ex. 1005.) The publication of that PCT application is prior art under 35 U.S.C. §102(b).

The Curd PCT Publication described the intravenous administration of more than one dose of rituximab for treating RA. (*See, e.g., id.* 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].").) The Curd PCT Publication also allowed for multiple doses in a broad range: "Suitable dosages for [RITUXAN®] are, for example, in the range from about 20mg/m^2 to about 1000mg/m^2." (*Id.* at 23:18-19.) Those relative doses

correspond to absolute doses of about 32mg to about 1600mg for an average patient.[8] (Ex. 1002 at ¶¶ 54 & 84 n.3.)

The Curd PCT Publication also discussed combination therapies involving methotrexate and corticosteroids. (*See* Ex. 1005 at 25:10-16 ("[T]he patient is optionally further treated with any one or more agents employed for treating RA such as . . . immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages."); *id.* at 8:28-29 (referring to "steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone").) In fact, Genentech obtained claims in the United States for combination therapies involving rituximab, methotrexate, and glucocorticosteroids based on the same disclosure. (*See* Ex. 1015 at 30:4-5.)

3. The De Vita Study

In 2001, Italian researchers published an abstract, titled "Selective B Cell Block Can Lead Clinical Response in Patients with Refractory Rheumatoid Arthritis" ("De Vita 2001"). (Ex. 1006.)[9] The abstract is prior art under 35 U.S.C. §102(b).

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[8] On average, patients have a surface area of about 1.6m^2. (*See* Ex. 1002 at 22 n.3 & 36 n.4.)

[9]A certified translation of the Italian language abstract is attached to Ex. 1006. The abstract, which describes the positive result for Patient 4, contains a subsequent

De Vita 2001 reported the administration of rituximab to RA patients who were non-responsive to other DMARDs and TNFα-inhibitors. (*Id.*) The rituximab treatment involved "4 intravenous infusions per week of 375 mg/m^2 each." (*Id.*)

The results of the study were published in *Arthritis & Rheumatism*, a prestigious peer-reviewed journal, in 2002. (Ex. 1007.) Specifically, "[f]ive female patients with active, evolving erosive RA were treated with rituximab, an anti-CD20 chimeric monoclonal antibody." (*Id.* at 2029.) The anti-CD20 therapy "consisted of 4 weekly intravenous infusions of 375 mg/m^2, as in treatment of B cell lymphoma." (*Id.* at 2030.) The study showed that rituximab therapy was "clinically beneficial in 4 of 5 patients with aggressive, refractory RA," including in one non-responder to a TNF-α inhibitor, who achieved an ACR20 response. (*Id.* at 2030-32.)

4. The Tuscano Abstract

In 2002, the initial results of a clinical trial established rituximab as a "promising agent for patients with DMARD and infliximab-refractory RA" ("Tuscano"). (Ex. 1008.) The results were presented at the Annual Scientific Meeting of the American College of Rheumatology. *Id*. The presentation was accompanied by a published abstract, titled "Successful Treatment of Infliximab-

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typographical error indicating that the same patient did not respond. It appears that the abstract intended to refer Patient 3—*i.e.*, the other infliximab-refractory patient.

Refractory Rheumatoid Arthritis with Rituximab." (*See id.*) Tuscano is prior art under 35 U.S.C. §102(b).

Tuscano states: "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." (*Id.*) Rituximab was administered in an escalating dose starting at 100 mg/m^2 in week one, rising to 375 mg/m^2 in week 2, and then reaching 500 mg/m^2 in weeks 3 and 4. (*Id.*) After 5 months of treatment, all 7 patients had improved joint scores, and 3 achieved an ACR20 response. (*Id.*) The abstract concluded: "While the current patient numbers are small, and enrollment is ongoing, this data supports the hypothesis that B lymphocytes mediate pathology in RA, and that rituximab is a promising agent for patients with DMARD and infliximab-refractory RA." (*Id.*)

C. TNFα-Inhibitors and Non-Responders

Tumor necrosis factor alpha (TNFα) blocking agents were developed in the mid-1990s and represented a major advance in the treatment of RA. (Ex. 1002 at ¶ 44.) Before the filing date of the '838 patent, at least three blockbuster TNFα-inhibitors had been developed and approved by the U.S. Food and Drug Administration (FDA) for treating RA: (i) etanercept (Enbrel®) approved in 1998; (ii) infliximab (Remicade®) approved in 1999; and (iii) adalimumab (Humira®)

approved in 2002. (*Id*.). Each of these TNFα inhibitors is specifically mentioned in the '838 patent. (*See*, *e.g.*, Ex. 1001 at 5:21-24.)

It was well-known that TNFα-inhibitors did not produce a response in all RA patients. (Ex. 1002 at ¶ 45.) In 1999, for example, Dr. Kalden co-authored a publication recognizing that "a certain percentage of patients given a TNF blocking agent do not respond to that treatment . . . ." (Ex. 1034 at 725-726.) In a separate paper also published in 1999, Dr. Kalden and his co-authors suggested that non-responders to TNF blocking agents seek alternative treatments. (Ex. 1009 at I129 ("If such improvement has not occurred within this time frame [8 to 12 weeks], alternative treatments or regimens should be considered.").) Finally, Dr. Kalden participated in a study to test the therapeutic efficacy of TNFα-inhibitors combined with low-dose weekly methotrexate. (Ex. 1029.) Dr. Kalden and his colleagues reported clinical response rates of approximately 60% during active therapy with a TNFα-inhibitor (infliximab), with or without methotrexate. (*See* Ex. 1002 at ¶ 46; Ex. 1029 at 1557.)

In 2001, a separate publication by Seymour et al. reported similar response rates for TNFα-inhibitors etanercept and infliximab. (Ex. 1011 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 [Enbrel®] patients; 21% to 42% of infliximab [Remicade®] patients).").) The paper estimated that

between 50 and 70% of patients would respond to anti-TNF therapy. (*Id.* at 207 ("If between 50 and 70% of patients treated with anti-TNF drugs respond then the annual cost to the NHS could be between £48 M and £129 M.").)

In sum, a person of ordinary skill would have known that the clinical response rate to TNF-α inhibitors among RA patients was approximately 60%. (Ex. 1002 at ¶ 50.)

D. Combination Therapies Involving Methotrexate and Corticosteroids

1. Methotrexate

Methotrexate is a drug used in the treatment of autoimmune diseases, including rheumatoid arthritis. (Ex. 1002 at ¶ 60.) Methotrexate has also been used at high doses as a treatment for certain types of cancer. (*Id.*) Methotrexate is an example of a DMARD, which slows the progression of RA by reducing the rate of damage to bone and cartilage. (*Id.*)

The efficacy and safety of methotrexate as a treatment for RA had been clearly established long before the filing date of the '838 patent. (*Id.*) "The efficacy of methotrexate in the treatment of RA [was] unquestioned . . . ." (Ex. 1010 at 780.) In fact, methotrexate was "not only the most commonly used but also the first prescribed DMARD by most rheumatologists in the United States for the treatment of RA." (*Id.* at 779.) The "ability of patients to tolerate [methotrexate] safely with long-term use" distinguished methotrexate from other

DMARDs used to treat RA. (*Id.* at 788.) Indeed, methotrexate "simultaneously revolutionized and revitalized the treatment of patients with RA." (*Id.* at 789).

2. Corticosteroids

Corticosteroids had been used in treating RA patients for many years prior to the earliest filing date of the '838 patent. (*See, e.g.*, Ex. 1034 at 142 ("Oral glucocorticoids are widely used to treat patients with rheumatoid arthritis . . . .").) Corticosteroids (*e.g.*, prednisolone) had also been combined with rituximab and methotrexate for the purposes of treating rheumatoid arthritis long before the filing date of the '838 patent. For example, the Curd PCT Publication discussed combination therapies involving rituximab, methotrexate, and corticosteroids. (*See* Ex. 1005 at 25:10-16 ("[T]he patient is optionally further treated with any one or more agents employed for treating RA such as . . . immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages."); *id.* at 8:28-29 (referring to "steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone").) Similarly, Dr. Edwards combined anti-CD20 antibody rituximab with a corticosteroid (prednisolone) in his early work with rituximab. (*See* Ex. 1022 at 205 ("Five patients with refractory RA were treated with a monoclonal anti-CD20 antibody, cyclophosphamide, and prednisolone and followed for 12-17 months.").)

Numerous other publications discussed treating RA with corticosteroids before the earliest filing date of the '838 patent. (*See*, *e.g.*, Ex. 1028 at 309 ("In a multicentre, double-blind, randomised trial (COBRA), we compared the combination of sulphasalazine (2 g/day), methotrexate (7·5 mg/week), and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7·5 mg/day) with sulphasalazine alone."); Ex. 1033 at 803 (studying the results of methotrexate therapy in juvenile RA, noting that 10 of the 12 responders were receiving corticosteroids when methotrexate treatment began); Ex. 1032 at 613 ("The studies with a stepdown strategy (four in total) all used steroids [i.m. methylprednisone pulses or predniso(lo)ne orally]. Steroids were added to i.m. gold (in two studies) or sylphasalazine (also in two studies; in one study prednisolone was added together with methotrexate).").)

3. Combination Therapies Involving Methotrexate and Corticosteroids

Combination therapies for treating RA with methotrexate and corticosteroids were well known in the prior art. (Ex. 1002 at ¶¶ 63-64.) Because methotrexate was the most popular and effective DMARD by the late 1990s, any new RA treatment under development would generally be added to ongoing treatment with methotrexate. (*See* Ex. 1010 at 790 ("Because methotrexate is the single most effective DMARD and because most patients with RA who receive methotrexate obtain a response, albeit sometimes an incomplete response, it follows that the

combination therapies most commonly used in clinical practice include methotrexate."); *see also* Ex. 1014 at 1548 ("Most of the new biotechnology-derived therapeutic interventions are being studied as both monotherapy and combination therapy with MTX.").) In fact, at that time, "most [physicians] would agree, that methotrexate should be the cornerstone of most combinations; it is also the standard against which combinations should be measured." (Ex. 1010 at 790; *see also* Ex. 1013 at 593 (stating that new drugs and biotechnology products, in particular, "should be tested in combination with methotrexate for approval in marketing, particularly as this is how they are likely to be used.").)

In general, combination therapies were targeted to partial responders to methotrexate—that is, patients who received some benefit in terms of reduced RA symptoms but who still experienced symptoms of active disease and were therefore in need of additional relief. (Ex. 1002 at ¶¶ 61-62.) For example, Dr. Kalden co-authored a publication in 1997 that stated the following: "Combining methotrexate and repeated application of an anti-TNF-α monoclonal antibody . . . demonstrated that this type of therapy was especially effective in RA patients in whom disease control with methotrexate alone is incomplete." (Ex. 1031 at 209.)

The results of a study published in 1996 showed that combining methotrexate with the repeated application of an anti-TNF-α monoclonal antibody was especially effective in RA patients for whom disease control with

methotrexate alone was incomplete. (*See* Ex. 1026.) According to the study, "adjunctive therapy with an anti-TNF-α mAb may be an important therapeutic approach for RA patients whose disease is incompletely controlled by MTX [methotrexate]." (*Id.*) Patients in the study also received doses of prednisone, a corticosteroid. (*Id.* ("Patients continued treatment with MTX 10 mg/week throughout the trial and were allowed stable doses of NSAID and prednisone (≤ 7.5 mg/d).").)

Similarly, the Curd PCT Publication discussed combination therapies involving rituximab, methotrexate, and corticosteroids. (*See* Ex. 1005 at 25:10-16 ("[T]he patient is optionally further treated with any one or more agents employed for treating RA such as . . . immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages."); *id.* at 8:28-29 (referring to "steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone").)

Finally, the study that Dr. Edwards designed in conjunction with Roche treated RA patients with rituximab, methotrexate, and corticosteroids. (Ex. 1003.) The initial results of this study were also summarized in the Genentech Press Release. (Ex. 1004 ("[A] fourth group received [rituximab] in combination with methotrexate (at least 10 mg weekly). [Rituximab] was administered as two

intravenous infusions, with doses (1g) given two weeks apart. Each group also received a course of intravenous and oral corticosteroids.").)

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. No Differences Exist Between the Challenged Claims and the Prior Art

1. "A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor" (claims 1, 2, 8, and 10)

The broadest reasonable construction of the preamble phrase "in a human patient who experiences an inadequate response to a TNFα-inhibitor" is that it is not a limitation of claims 1, 2, 8, and 10. *See* Section VI.A *supra*. There is no suggestion in the prosecution history that the patentee added this preamble phrase to distinguish the alleged invention from the prior art. In fact, the preamble phrase was included in the original set of claims submitted to the Patent Office. (*See* Ex. 1039 at 51 (showing the preamble phrase in claims 1 and 12 submitted with the provisional application).) Moreover, the preamble phrase does not embody any essential component of the invention. The structure of the alleged invention here includes steps for treating RA by administering an anti-CD20 antibody (*e.g.*, rituximab) in two IV doses of 1000 mg (sometimes with co-administration of methotrexate and/or corticosteroids). The remainder of the claims contains all of the steps necessary to practice the alleged invention, which is the same regardless of who receives the treatment. *See Am. Med. Sys.*, 618 F.3d at 1360 (concluding

that the preamble phrase "photoselective vaporization" is not a claim limitation, noting that "the bodies of the asserted method claims contain all the steps necessary to practice the invention").

Even if the entire preamble were limiting, it would be inherently and necessarily disclosed in the prior art. It was well known years before the priority date of the '838 patent that TNFα-inhibitors do not produce a response in all RA patients. (Ex. 1002 at ¶¶ 50, 65.) Approximately 40% of patients do not respond to TNFα-inhibitors. (Ex. 1002 at ¶ 50 (stating the patient response rate to TNFα-inhibitors is about 60%); Ex. 1029 at 1557 (reporting a response rate to TNFα-inhibitors of approximately 60%); Ex. 1011 at 207 (estimating between 50 and 70% of patients will respond to TNFα-inhibitors).) In addition, given that the '838 patent states that an "inadequate response" can be experienced by individuals who have never been treated with a TNFα-inhibitor (Ex. 1001 at 28:45-61), the percentage of non-responders in the context of the '838 patent would be even higher. (Ex. 1002 at ¶¶ 60, 66.) Given the high percentage of non-responders, it would only take a few RA patients to participate in a clinical study before a non-responder to TNFα-inhibitors would necessarily be present. (*See id.* at ¶ 67.) For example, the treatment of non-responders to TNFα-inhibitors was inherently disclosed in the study designed by Dr. Edwards and Roche—summarized in Exs. 1003 and 1004—which involved 161 patients with RA, a significant number of

which would have been non-responders to TNFα-inhibitors. (Ex 1002 at ¶¶ 65-67.)

In any event, treating RA patients who do not respond to TNFα-inhibitors was expressly disclosed in the prior art. (Ex. 1002 at ¶¶ 65-68.) De Vita 2001 discussed the administration of rituximab to four RA patients, two of which "had not responded to anti-TNF alpha therapy." (Ex. 1006.) Similarly, the entire focus of the Tuscano abstract was the treatment of infliximab-refractory RA patients with rituximab.[10] (Ex. 1008.) In fact, the title of the abstract is "Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis with Rituximab." (*Id.*) The results of the Tuscano study showed that "rituximab is a promising agent for patients with DMARD and infliximab-refractory RA." (*Id.*)

Moreover, it would have also been obvious to a person of ordinary skill to treat RA patients who do not respond to TNFα-inhibitors with alternative therapies. (Ex. 1002 at ¶¶ 68-72.) A person of ordinary skill treating RA patients would have tried alternative methods of treatment for patients who did not adequately respond to TNFα-inhibitors like infliximab and etanercept. (*Id.* at ¶ 70.) Specifically, a person of ordinary skill would have tried other known RA therapies using drugs with different modes of action, as well as combination therapies, until the patient exhibited an improvement in signs and symptoms. (*Id.*) For example, Dr. Kalden

[10] Infliximab is a well-known TNFα-inhibitor. (Ex. 1002 at ¶ 69.)

co-authored a consensus statement concerning RA treatments that addressed alternative treatments for non-responders to TNFα-inhibitors:

> TNF blocking agents, when given in adequate doses and sufficiently frequent dosing regimens, should lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 8 to 12 weeks. ***If such improvement has not occurred within this time frame, alternative treatments or regimens should be considered.***

(Ex. 1009 (emphasis added).)

At a minimum, it would have been obvious to try alternative RA therapies when dealing with patients who did not adequately respond to TNFα-inhibitors. (Ex. 1002 at ¶ 71.) The Supreme Court has explained the obvious-to-try rationale as follows:

> When 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.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). With only a finite number of safe and effective treatments for RA patients, persons of ordinary skill in the art

would have had a reasonable expectation of success when treating non-responders to TNFα-inhibitors with alternative therapies involving different modes of action. (Ex. 1002 at ¶ 72.) If patients do not respond adequately to a commonly prescribed method of treatment (*e.g.*, anti-TNF drugs), common sense dictates that the treating physician would try a different method of treatment also known to be effective in reducing RA symptoms. (*Id.* at ¶ 71.) *See Hoffman La Roche, Inc. v. Apotex, Inc.* 748 F.3d 1326, 1332-33 (Fed. Cir. 2014) (affirming district court's judgment of obviousness, finding that the claimed method of treatment was "obvious to try" given a reasonable expectation of success and a finite number of identified, predictable solutions).

2. "administering to the patient an antibody that binds to CD20," "wherein the antibody comprises rituximab," and "administering to the patient rituximab" (claims 1, 2, 3, 8)

Treating RA patients with an antibody that binds to CD20 (*e.g.*, rituximab) was well known in the prior art years before the earliest filing date of the '838 patent.

Dr. Edwards began publishing work on RA therapies using anti-CD20 antibodies, including rituximab, as early as 1998. *See* Section VIII.B.1 *supra*. Dr. Edwards published an article in the *British Journal of Rheumatology* in March 1998 that proposed treating RA with rituximab, which is by definition an antibody that binds to CD20. (*See* Ex. 1021; *see also* Ex. 1002 at ¶¶ 73, 89 (explaining that

rituximab binds to CD20).) In May 1998, Dr. Edwards gave a presentation to the Australian Rheumatology Association, titled "The Case for Killing B Cells with Anti-CD20 in RA." The abstract that accompanied the presentation stated: "[T]he broad prediction is that at least in early disease anti-CD20 might be curative in RA . . . The treatment would appear to be very safe, and a clinical trial is proposed." (Ex. 1035 at 53.) In 1999, Dr. Edwards again discussed his theory for treating RA with anti-CD20 antibodies during a presentation at the Fourth International Synovitis Workshop in Dallas, Texas. (*See* Ex. 1030.) He then published the results of a promising rituximab study in the journal *Rheumatology* in a 2001 paper titled, "Sustained Improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes." (Ex. 1022.)

Dr. Edwards collaborated with Roche to conduct a clinical trial treating 161 patients with rituximab. Dr. Edwards presented the initial results of the Roche study at the Annual American College of Rheumatology meeting in October 2002. The abstract that accompanied the presentation, dated October 26, 2002, was titled, "Efficacy and Safety of Rituximab, a B-Cell Targeted Chimeric Monoclonal Antibody: A Randomized, Placebo-Controlled Trial in Patients with Rheumatoid Arthritis." (Ex. 1003.) The results of the study were also summarized in the Genentech Press Release. (Ex. 1004.)

In 2000, the published Curd PCT Publication described the intravenous administration of more than one dose of rituximab for the purpose of treating RA. *See* Section VIII.B.2 *supra*. The Curd PCT Publication described the intravenous administration of more than one dose of rituximab for treating RA. (*See, e.g.*, Ex. 1005 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].").)

In 2001, Italian researchers published an abstract that reported on the administration of rituximab to RA patients who were not responsive to other treatments. *See* Section VIII.B.3 *supra*. The rituximab treatment involved "4 intravenous infusions per week of 375 mg/m^2 each." (Ex. 1006.)

In 2002, Tuscano published an abstract titled, "Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis with Rituximab." *See* Section VIII.B.4 *supra*. The abstract "describe[d] 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. 1008.)

3. "wherein the antibody is administered as two intravenous doses of 1000 mg" and "wherein rituximab is administered as two intravenous doses of 1000 mg" (all claims)

The study designed by Dr. Edwards and Roche administered rituximab in two IV doses of 1000 mg. The abstract accompanying Dr. Edwards's presentation

stated that these patient groups received "Rituximab (2 x 1g i.v. infusions)." (Ex. 1003.) Similarly, the Genentech Press Release summarizing the same Roche study reported that "Rituxan [*i.e.*, rituximab] was administered as two intravenous infusions, with doses (1g) [1000 mg] given two weeks apart." (Ex. 1004 at 2.)

The Curd PCT Publication disclosed multiple IV doses of rituximab in a range that includes 1000 mg. The reference states, in pertinent part, "[O]ne may administer . . . one or more subsequent dose(s) . . . and the subsequent dose may be in the range from about 250mg/m^2 to about 1000mg/m^2." (Ex. 1005 at 23:23-27.) This dosing range corresponds to absolute doses of about 32 mg to about 1600 mg for an average patient, assuming an average body surface area of 1.6 m^2. (*See* Ex. 1002 at ¶ 84.) The Curd PCT Publication creates a presumption of obviousness because the range of possible rituximab doses disclosed in the prior art includes the claimed 1000 mg amount. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1332 (Fed. Cir. 2004) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness"); *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").

Other known dosing schemes for treating RA with rituximab included: (i) "4 intravenous infusions per week of 375 mg/m^2 each" (Ex. 1006); (ii) "four i.v. infusions (over 3 h) on days 2, 8, 15, 22, of 300, 600, 600 and 600 mg respectively" (Ex. 1022 at 206); and (iii) "100 mg/m^2 in week one, rising to 375 mg/m^2 in week 2, and then reaching 500 mg/m^2 in weeks 3 and 4" (Ex. 1008).

In light of the known dosing schedules for rituximab, a person of ordinary skill would have had a reasonable expectation of success for two IV doses of 1000 mg based on the fact that less frequent doses (*e.g.*, biweekly) would increase patient compliance. (Ex. 1002 at ¶ 88.) Moreover, a person of ordinary skill would optimize dosing of rituximab when treating RA in clinical practice. (*Id.*) Such dosage optimization is a routine step in the development of any treatment regimen. (*Id.*) This is precisely what Dr. Edwards did when he went from using four weekly doses in Edwards IV (totaling 2100 mg) to two bi-weekly doses of 1000 mg in the subsequent Roche study (Edwards VI).

In *Hoffmann La Roche v. Apotex*, the Federal Circuit Court of Appeals 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 at 1329-35. Specifically, the Court held that it was obvious to select once monthly oral dosing of ibandronate (a drug for

treating osteoporosis) at 150 mg, concluding that "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." *Id.* at 1332-33. Further, evidence supporting superior efficacy for that dose "does 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. Here, the prior art established at least a reasonable expectation of success using two intravenous doses of rituximab to treat RA. (Ex. 1002 at ¶ 88.)

The prior art also provided substantial guidance as to the total dose that would produce effective results. (Ex. 1002 at ¶ 87.) The results of Edwards IV demonstrated the efficacy of four weekly doses of rituximab totaling 2100 mg. (Ex. 1022 at 206, 207 ("A simple binomial analysis indicates that further, similar cases treated in the same way can be expected with 95% confidence to have a minimum chance of 47.8% of achieving ACR50 6 months after B-lymphocyte depletion . . . the same percentage figures can be applied to ACR70 at 18 months.").) In light of similar evidence, the Federal Circuit 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." *Hoffmann-La Roche*, 748 F.3d at 1333.

At minimum, two 1000 mg doses of rituximab would have been obvious for a person of ordinary skill in light of a known problem—*i.e.*, improving patient

compliance—and a finite number of possible solutions—*i.e.*, known therapeutically effective and safe dosing levels. (Ex. 1002 at ¶ 88.)

4. "administering to the patient an 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 or beyond" (claim 2)

Claim 2 includes two separate elements regarding the amount of antibody administered to the patient. First, the claim requires the administration of an antibody in an amount effective to provide certain clinical responses in patient (*e.g.*, ACR50 at week 24). Second, the claim requires the administration of two 1000 mg doses of the antibody. In order to reconcile these two elements, two 1000 mg doses of the antibody must be an amount sufficient to provide the required clinical responses. *See* Section VI.B *supra*. This is confirmed by the patent's specification. The lone example in the '838 patent identifies two "therapeutically effective" dosing regimens of CD20 antibody: (1) two bi-weekly 1000 mg doses; and (2) four weekly doses of 375 mg/m^2. (*See* Ex. 1001 at 31:29-31 ("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 x 4.").) The specification identifies "potential secondary endpoints" for these treatments, including "[p]roportion of patients with ACR50 and 70 responses at Week 24." (*Id.* at 32:3-6.)

The prior art also discloses therapeutically effective doses of CD20 antibody capable of achieving at least one of the clinical responses recited in claim 2. For example, the abstract of Dr. Edwards's presentation of the Roche study to the Annual American College of Rheumatology Meeting showed ACR50 and ACR70 responses after 24 weeks with in patient groups receiving two 1000 mg IV doses of rituximab alone and in combination with other drugs, including methotrexate. (*See* Ex. 1003.) The Genentech Press Release also reported ACR50 and ACR70 responses after 24 weeks in patients receiving two 1000 mg IV doses of rituximab. (Ex. 1004 at 2.) In Edwards IV, patients achieved ACR50 and ACR70 responses where the total dose was 2100 mg. (Ex. 1022 at 206, 207 ("A simple binomial analysis indicates that further, similar cases treated in the same way can be expected with 95% confidence to have a minimum chance of 47.8% of achieving ACR 50 6 months after B-lymphocyte depletion . . . the same percentage figures can be applied to ACR70 at 18 months.").) Further, De Vita 2001 also reported ACR50 and ACR70 responses in RA patients receiving four weekly doses of 375 mg/m2 of rituximab. (Ex. 1006.)

5. "wherein the patient has no erosive progression at weeks 24 and beyond," "wherein the clinical response is ACR50 at week 24," "wherein the clinical response is ACR70 at week 24," wherein the clinical response is no erosive progression at weeks 24 and beyond" (claims 10, 12-14)

The "wherein" clauses in claims 10 and 12-14 are not entitled to weight in construing the claims and should not be given any limiting effect because they merely identify the clinical responses that are the intended result of the administration steps recited elsewhere in the claims. *See* at Section VI.C *supra*.

The same treatment is "administered" to patients in all these claims: rituximab (in two intravenous doses of 1000 mg) and methotrexate. The "wherein" clauses do not inform the mechanics of how the "administering" step is performed; they merely recite clinical results of that step. Such intended results carry no weight and have no limiting effect. *See Ex Parte Berzofsky*, 2011 WL 891756 at *5 (finding that "wherein" clauses that "merely characterize the result" of an "administering" step without informing the mechanics of that step are "not entitled to weight in construing the claims").

Even if these "wherein" clauses were deemed to be limiting, the recited clinical responses are nothing more than the natural result of the "administering" step. Claims 10 and 12-14 require the administration of two 1000 mg doses of rituximab and an unspecified amount of methotrexate for the purpose of treating RA. This treatment will produce a clinical response in some but not all patients.

(Ex. 1002 at ¶ 89.) Any clinical response that occurs would be the natural result of receiving rituximab and methotrexate. (*Id*.) Put another way, there is nothing inventive about the patient's natural response to an established treatment regimen.

The lone example in the specification of the '838 patent confirms that the co-administration of rituximab and methotrexate produces the required clinical responses. The example identifies the dosing levels for rituximab and methotrexate (MTX). (*See* Ex. 1001 at 31:29-33 ("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. weeklyx4. Patients may also receive concomitant MTX (10-25 mg/week per oral (p.o.) or parenteral) . . . .").) The example then identifies "potential secondary endpoints" for these treatments, including a "[p]roportion of patients with ACR50 and 70 responses at Week 24." (*Id*. at 32:3-6.)

The prior art also discloses that the required clinical responses are achieved from the co-administration of rituximab and methotrexate. For example, the abstract of Dr. Edwards's presentation of the Roche study to the Annual American College of Rheumatology Meeting showed ACR50 and ACR70 responses after 24 weeks with in patient groups receiving two 1000 mg i.v. doses of rituximab alone and in combination with methotrexate. (*See* Ex. 1003.) The Genentech Press Release also reported ACR50 and ACR70 responses after 24 weeks in patients

receiving rituximab in combination with methotrexate. (Ex. 1004 at 2.) In addition, prior art studies involving rituximab alone also achieved the required clinical responses. (*See* Ex. 1022 at 206, 207 (discussing ACR50 and ACR70 responses where the total dose of rituximab was 2100 mg); Ex. 1006 (reporting ACR50 and ACR70 responses in RA patients receiving four weekly doses of 375 mg/m2 of rituximab).) It would also be common for patients responding well to the treatment—*e.g.*, those obtaining ACR50 and ACR70 responses—to experience no erosive progression during the course of their treatment. (Ex. 1002 at ¶ 89.)

While there may have been no way for a skilled clinician to accurately predict exactly which individual patients will achieve the required clinical response prior to treatment, a person of ordinary skill would have had a reasonable expectation of success—that is, achieving the same clinical responses required by the claims—when treating RA patients with rituximab based on the data available at the time of the invention. (*Id*.)

6. "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" (claim 11)

The broadest reasonable construction of claim 11 is that the preamble is not a limitation on the scope of the claim. *See* Section VI.D *supra*. The body of claim 11 defines the structure of the alleged invention: "administering to the patient

rituximab, and methotrexate, wherein rituximab is administered as two intravenous doses of 1000 mg." The preamble merely states the purpose or intended use of the treatment method (*i.e.*, "achieving a clinical response"). Because the body of the claim sets forth the complete invention and the preamble only states the purpose or intended use of the invention, the preamble is not a claim limitation. *See Rowe*, 112 F.3d at 478 ("[W]here a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation.").

In any event, both the specification of the '838 patent and the prior art confirm that the clinical responses included in the preamble (*e.g.*, ACR50 or ACR70 at week 24) will be obtained in RA patients treated with rituximab and methotrexate. (*See* Ex. 1002 at ¶ 94.)

Further, while there is no way for a skilled clinician to accurately predict which patients will achieve the required clinical response prior to treatment, a person of ordinary skill would have had a reasonable expectation of success when treating RA patients with rituximab based on the data available at the time of the invention. (Ex. 1002 at ¶ 89.)

7. "wherein the patient is further treated with concomitant methotrexate (MTX)," "administering methotrexate to the patient," and "administering to the patient rituximab, and methotrexate" (claims 4, 9, 10, and 11)

The co-administration of rituximab and methotrexate was well known in the prior art before the earliest filing date of the ’838 patent. The abstract of Dr. Edwards’s presentation of the Roche clinical study to the Annual American College of Rheumatology Meeting reported that one patient group (Group D) received two intravenous 1000 mg doses of rituximab in combination with continuing methotrexate treatments of greater than 10 mg/wk. (Ex. 1003.) The same co-administration of rituximab and methotrexate was reported in the October 28, 2002 Genentech Press Release. (*See* Ex. 1004 at 2 (“Patients were randomized into one of four treatment groups . . . a fourth group received [rituximab] in combination with methotrexate (at least 10 mg weekly).”).)

The Curd PCT Publication also discussed combining rituximab and methotrexate for the treatment of rheumatoid arthritis. Example 1 of the Curd PCT Publication discussed the treatment of RA patients with rituximab in combination with other “optional” agents, including methotrexate. (*See* Ex. 1005 at 25:9-16.)

It was well known in the prior art that methotrexate was the “cornerstone” and “foundation” of combination therapies for RA. (Ex. 1010 at 790, 792; Ex. 1002 at ¶ 97.) In fact, prior to the filing date for the ’838 Patent, combination therapies involving methotrexate had received “widespread attention because of positive results.” (Ex. 1010 at 790.) Indeed, “virtually all” of the new RA treatments were being tested with methotrexate, and most of new “biotechnology-

derived therapeutic interventions" were studied as both monotherapies and in combination with methotrexate. (Ex. 1014 at 1548.)

A person of ordinary skill would have also been aware of the immunosuppressive effects of methotrexate and its ability to reduce the immune response to antibodies like rituximab, thereby improving their ability to treat RA. (Ex. 1002 at ¶ 100.)

8. "wherein the patient is further treated with a corticosteroid regimen" and "wherein the corticosteroid regimen consists of methylprednisolone and prednisone" (claims 5 and 6)

The co-administration of rituximab and a corticosteroid regimen was well known in the prior art before the earliest filing date of the '838 patent. The abstract of Dr. Edwards's presentation of the Roche clinical study to the Annual American College of Rheumatology Meeting stated that, in addition to rituximab and methotrexate, "[a]ll [patient] groups also received a 17 day course of corticosteroids (total dose of 960mg)." (Ex. 1003.) Similarly, the Genentech Press Release mentioned that "[e]ach [patient] group also received a course of intravenous and oral corticosteroids." (Ex. 1004 at 2.)

The Curd PCT Publication also discussed combination therapies involving rituximab, methotrexate, and corticosteroids. (Ex. 1005 at 25:10-16 ("[T]he patient is optionally further treated with any one or more agents employed for treating RA such as . . . immunosuppressive agents such as methotrexate or

corticosteroids in dosages known for such drugs or reduced dosages."); *id.* at 8:28-29 (referring to "steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone").)

Corticosteroids had been used to treat RA for many years before the earliest filing date of the '838 patent. (Ex. 1002 at ¶ 103; *see also, e.g.*, Ex. 1025 at 142 ("Oral glucocorticoids are widely used to treat patients with rheumatoid arthritis . . . .").) Combinations therapies for treating RA with methotrexate and corticosteroids were also well known in the prior art. (Ex. 1002 at ¶¶ 101-103.) For example, in his initial study, Dr. Edwards gave the participants intravenous infusions of anti-CD20 antibody rituximab, oral prednisolone (a corticosteroid (Ex. 1002 at ¶ 101)), and cyclophosphamide. (Ex. 1022; *see also* Ex. 1033 at 803 (studying the results of methotrexate therapy in juvenile RA, noting that 10 of the 12 responders were receiving corticosteroids when methotrexate treatment began); Ex. 1032 at 613 ("The studies with a stepdown strategy (four in total) all used steroids [i.m. methylprednisone pulses or predniso(lo)ne orally]. Steroids were added to i.m. gold (in two studies) or sylphasalazine (also in two studies; in one study prednisolone was added together with methotrexate)."); Ex. 1028 at 309 ("In a multicentre, double-blind, randomised trial (COBRA), we compared the combination of sulphasalazine (2 g/day), methotrexate (7·5 mg/week), and

prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7·5 mg/day) with sulphasalazine alone.").)

9. "wherein the CD20 antibody is the only B-cell surface marker antibody administered to the patient" (claim 7)

In virtually every prior art reference discussed above, rituximab is the only B-cell surface marker antibody administered to the patient. (Ex. 1002 at ¶ 104.) This is true not only of Dr. Edwards's work (*see*, *e.g.*, Exs. 1003, 1004, 1021 and 1022), but also of the Curd PCT Publication (*see* Ex. 1005). The same is also true of the prior art proposal submitted by Dr. Gryn (Ex. 1024), the work of De Vita et al. (Ex. 1006) and the clinical trial proposed and presented by Tuscano (Ex. 1008).

B. Proposed Combinations of Prior Art

1. Edwards VI (Ex. 1003) and Genentech Press Release (Ex. 1004) Anticipate Claims 1-5 and 7-14

Edwards VI (Ex. 1003) and the Genentech Press Release (Ex. 1004) expressly disclose: (i) treating RA by administering two 1000 mg doses of anti-CD20 antibody rituximab alone and in conjunction with methotrexate and corticosteroids; and (ii) ACR50 and ACR70 clinical responses. These references also inherently disclose the treatment of non-responders to TNFα-inhibitors, even if one assumes that the preamble phrase "who experiences an inadequate response to a TNFα-inhibitor" is limiting. Accordingly, Edwards VI (Ex. 1003) and the Genentech Press Release (Ex. 1004) anticipate claims 1-5, 7-9, and 11-13. Moreover, if the "wherein" clauses requiring "no erosive progression at weeks 24

and beyond" receive no patentable weight, Edwards VI (Ex. 1003) and the Genentech Press Release (Ex. 1004) also anticipate claims 10 and 14 of the '838 patent.

2. All Challenged Claims Are Rendered Obvious by the Prior Art

The challenged claims are also obvious in light of the following prior art, as set forth below:

Claims	Prior Art and Proposed Combinations
1-5 7-14	• Ex. 1003 (Edwards VI) • Ex. 1003 (Edwards VI) in view of Ex. 1006 (De Vita 2001) • Ex. 1003 (Edwards VI) in view of Ex. 1008 (Tuscano) • Ex. 1004 (Genentech Press Release) • Ex. 1004 (Genentech Press Release) in view of Ex. 1006 (De Vita 2001) • Ex. 1004 (Genentech Press Release) in view of Ex. 1008 (Tuscano) • Ex. 1005 (Curd PCT Publication) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1006 (De Vita 2001) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1022 (Edwards

Claims	Prior Art and Proposed Combinations
	IV) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1008 (Tuscano) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1006 (De Vita 2001) and Ex. 1022 (Edwards IV) • Ex. 1006 (De Vita 2001) and Ex. 1005 (Curd PCT Publication) • Ex. 1006 (De Vita 2001) and Ex. 1005 (Curd PCT Publication) and Ex. 1022 (Edwards IV) • Ex. 1006 (De Vita 2001) and Ex. 1005 (Curd) PCT Publication and Ex. 1008 (Tuscano)
6	• Ex. 1003 (Edwards VI) in view of Ex. 1005 (Curd PCT Publication) • Ex. 1004 (Genentech Press Release) in view of Ex. 1005 (Curd PCT Publication) • Ex. 1005 (Curd PCT Publication) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1006 (De Vita 2001) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1022 (Edwards

Claims	Prior Art and Proposed Combinations
	IV) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1008 (Tuscano) • Ex. 1005 (Curd PCT Publication) in view of Ex. 1006 (De Vita 2001) and Ex. 1022 (Edwards IV)

A person of ordinary skill would have reason to combine the teachings of the above references with a reasonable expectation of success. (Ex. 1002 at ¶ 115.) Each of the references is directed to the treatment of RA with rituximab. Rituximab was a well-known anti-CD20 antibody used for the treatment of RA alone and in combination with other drugs, such as methotrexate and corticosteroids, before the earliest filing date of the '838 patent. (*Id*.) Persons of ordinary skill in the art had a clear incentive to improve treatments by optimizing dosing levels and regimens to reduce RA symptoms in refractory patients. (*Id*.) There was a clear reason to combine known elements to improve treatment for all RA patients, including those who did not experience an adequate response to TNFα inhibitors. (*Id*.)

X. SECONDARY CONSIDERATIONS

As an initial matter, "where a claimed invention represents no more than the predictable use of prior art elements according to established functions . . .

evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness." *Ohio Willow Wood Co. v. Alps South, LLC,* 735 F.3d 1333, 1344 (Fed. Cir. 2013). "For objective evidence [of non-obviousness] to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). Indeed, "weak secondary considerations generally do not overcome a strong prima facie case of obviousness." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010); *Hoffmann-La Roche,* 748 F.3d at 1334-35 (finding that evidence of secondary considerations did not rebut *prima facie* showing of obviousness).

During the prosecution of the '838 patent, the applicant relied on a declaration submitted by Dr. van Vollenhoven, dated October 6, 2010. (*See* Ex. 1016.) However, Dr. van Vollenhoven did not prepare or submit his declaration for U.S. prosecution of the '838 patent; rather, the declaration was submitted to the European Patent Office during opposition proceedings relating to EP 1613350, a foreign counterpart of the '838 patent.[11] (*See* Ex. 1036 at 11.) The applicant

[11] Notably, the European Patent Office revoked the foreign counterpart of the '838 patent despite the submission of Dr. van Vollenhoven's declaration. (*See* Ex. 1019 at 1 (stating that proceedings were terminated because "[t]he patent was revoked").)

argued that the van Vollenhoven declaration established that the invention of the '838 patent addressed an "unmet medical need in April 2003, by providing an effective treatment regimen for particularly hard to treat and drug-refractory anti-TNF inadequate responders." (*Id.* at 11-12.) Notably, van Vollenhoven did not characterize the alleged "unmet need" as long-felt. In addition, the applicant argued that the declaration explained "how the invention produces results that would have not have been expected from the prior art." (*Id.* at 12.)

As discussed in detail in Dr. Kalden's supporting declaration, the alleged invention did not meet a long-felt need. (Ex. 1002 at ¶¶ 107-109.) Rituximab therapies involving two IV doses of 1000 mg were known in the prior art. (*See* Exs. 1003 and 1004.) Further, according to the '838 patent, the standard dosing regimen (375 mg/m^2 i.v. weekly x 4) was "therapeutically effective" for treating RA in non-responders to TNFα inhibitors. (Ex. 1001 at 31:29-31.) Many early publications discuss treating RA with this standard dosing regimen of rituximab. (*E.g.*, Exs. 1005, 1006, and 1024.) Accordingly, there was no long-felt need for an effective treatment regimen for anti-TNF inadequate responders.

Dr. Kalden also rebuts the applicants' claim that the '838 patent somehow produced unexpected results. (Ex. 1002 at ¶¶ 110-113.) During the prosecution of the '838 patent, the applicants argued that Dr. van Vollenhoven's declaration "explains how the invention produces results that would not have been expected

from the prior art." (Ex. 1036 at 12.) But this is simply not accurate. While Dr. van Vollenhoven states that achieving ACR50, ACR70, and radiographic responses would have been "considered important advances in April 2003," he never argued these results were unexpected. In fact, Dr. van Vollenhoven limits his claim of unexpected results only to what was specifically discussed in the references at issue during the European opposition. (Ex. 1016 at ¶ 30.)

XI. CONCLUSION

For the reasons set forth above, Petitioner respectfully submits that it has established a reasonable likelihood of success with respect to the challenged claims and requests that this petition be granted.

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 50-3081.

Dated: December 15, 2014

Respectfully submitted,
Proskauer Rose LLP

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Attachment A: Certificate of Service

CERTIFICATE OF SERVICE

I hereby certify that on this 15th day of December 2014, a copy of this PETITION FOR INTER PARTES REVIEW and copies of all supporting materials and exhibits have been served by Express Mail on the following addresses for patent owner(s):

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Attachment B: List of Evidence and Exhibits Cited in the Petition

Exhibit	Reference
1001	U.S. Patent No. 7,976,838
1002	Declaration of Joachim Kalden, M.D.
1003	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*, Abstracts of the American College of Rheumatology 66th Annual Meeting, Oct. 24-29, 2002 (New Orleans, LA)
1004	Genentech Press Release: *Preliminary Positive Data from Investigational Randomized Phase II Trial Demonstrates Rituxan as a Potential Treatment for Rheumatoid Arthritis,* (Oct. 28, 2002)
1005	PCT Application WO 00/67796 (Curd et al.)

Exhibit	Reference
1006	De Vita S. et al., *Ruolo Patogentico Dei Linfociti B Nella Sinovite Reumatoide: Il Blocco Selettivo B Cellulare Puo Indurre Risposta Clinica In Pazienti con Artrite Reumatoid Refrattaria*, Official Journal of the Italian Society of Rheumatology, Vol. 53, No. 3 (Suppl. No. 4) (2001) [ENGLISH TRANSLATION]
1007	De Vita S. et al., *Efficacy of Selective B Cell Blockade in the Treatment of Rheumatoid Arthritis*, Arthritis & Rheumatism, Vol. 46, No 8, pp 2029-2033 (Aug. 2002)
1008	Tuscano JM, *Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis with Rituximab*, Arthritis Rheum 46: 3420, LB 11 (2002)
1009	Furst D E et al., *Access to disease modifying treatments for rheumatoid arthritis patients*, Ann Rheum Dis, 58 (Suppl I), I129-130 (1999)
1010	O'Dell J, *Methotrexate Use in Rheumatoid Arthritis*, Rheumatic Disease Clinics of North America, Vol. 23, No. 4, pp 779-796 (1997)

Exhibit	Reference
1011	Seymour H E et al., *Anti-TNF agents for rheumatoid arthritis*, Br J Clin Pharmacol, 51, 201-208 (2001)
1012	1997 Product Label for RITUXAN®
1013	Pincus T et al., *"No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?*, Clinical and Experimental Rheumatology, 15: 591-596 (1997)
1014	Kremer J, *Combination Therapy with Biologic Agents in Rheumatoid Arthritis: Perils and Promise*, Arthritis & Rheumatism, Vol. 41, No. 9, pp 1548-1551 (1998)
1015	U.S. Patent No. 7, 820,161
1016	Declaration of Ronald van Vollenhoven (Oct. 6, 2010)
1017	Intentionally Omitted
1018	5-17-2013 European Board of Appeal Decision on EP1613350

Exhibit	Reference
1019	8-22-2013 Termination of European Opposition Proceedings related to EP1613350
1020	Maloney D et al., *IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma*, Blood, Vol. 90, No. 6, pp. 2188-2195 (1997)
1021	Edwards JCW et al., *Rheumatoid Arthritis: the Predictable Effect of Small Immune Complexes in which Antibody Is Also Antigen*, British Journal of Rheumatology, 37: 126-130 (1998)
1022	Edwards JCW et al., *Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes*, Rheumatology 40:205-211 (2001)
1023	Edwards JCW et al., *Efficacy of B-Cell-Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis*, N Engl J Med, Vol. 350, No. 25, pp 2572-2581 (2004)

Exhibit	Reference
1024	Letter from Dr. Jeffrey Gryn to Cooper Cancer Institute, dated May 6, 1998
1025	Kirwan J, *The Effect of Glucocorticoids on Joint Destruction in Rheumatoid Arthritis*, N Engl J Med, Vol. 333, No. 3, pp 142-146 (1995)
1026	Kavanaugh AF et al., *Anti-TNF-α Monoclonal Antibody (mAb) Treatment of Rheumatoid Arthritis (RA) Patients with Active Disease on Methotrexate (MTX); Results of a Double-Blind, Placebo Controlled Multicenter Trial*, Arthritis Rheum.; Vol. 39, No. 9 (suppl) (1996)
1027	Maloney DG et al., *Phase I Clinical Trial Using Escalating Single Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma*, Blood, Vol. 84, No. 8, pp 2457-2466 (1994)

Exhibit	Reference
1028	Boers M et al., *Randomised Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine with Sulphasalazine Alone in Early Rheumatoid Arthritis*, The Lancet, 350: 309-318 (1997)
1029	Maini R et al., *Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis*, Arthritis & Rheumatism, Vol. 41, No. 9, pp 1552-1563 (1998)
1030	Dr. Edwards' presentation at the Fourth International Synovitis Workshop in Dallas, Texas (April, 1999)
1031	Kalden JR et al., *Biologic agents in the treatment of inflammatory rheumatic diseases*, Current Opinion in Rheumatology, 9:206-212 (1997)
1032	Verhoeven AC et al., *Combination Therapy in Rheumatoid Arthritis: Updated Systematic Review*, British Journal of Rheumatology, 37: 612-619 (1998)

Exhibit	Reference
1033	Truckenbrodt et al., *Methotrexate Therapy in Juvenile Rheumatoid Arthritis: A Retrospective Study*, Arthritis and Rheumatism, Vol. 29, No. 6, pp. 801-807 (June 1986)
1034	Furst DE et al., *Building towards a consensus for the use of tumour necrosis factor blocking agents*, Ann Rheum Dis, 58:725-726 (1999)
1035	Edwards JCW, *The Case for Killing B Cells with Anti-CD20 in RA*, Australian Rheumatology Association, 41st Ann. Sci. Conf., R21, 53 (May 24-27, 1998)
1036	Applicant's Amendment, dated December 17, 2010
1037	Edwards JCW, *Can IgG Rheumatoid Factors explain everything?*, Arthritis Research, Vol. 1 Suppl. 1, Abstracts ("Edwards III")
1038	Edwards JCW, *B-lymphocyte depletion therapy in rheumatoid arthritis and other autoimmune disorders*, Biochemical Society Transactions (2002), Vol. 30, Part 4, pp. 824-828 ("Edwards V")
1039	U.S. Provisional App. 60/461,481