UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, 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. IPR2016-01667

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,976,838

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I. INTRODUCTION

Celltrion, Inc. ("Celltrion" or "Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 et seq. of claims 1 to 14 of U.S. Patent No. 7,976,838 ("the '838 patent," Ex. 1001).

II. PRELIMINARY STATEMENT

The '838 patent is directed to methods of treating rheumatoid arthritis ("RA") by administering two 1000 mg intravenous doses of rituximab, an anti-CD20 antibody. The use of rituximab to treat RA patients at the claimed dosages was not novel as of April 9, 2003, the earliest possible priority date for the '838 patent. The prior art disclosed that at least 92 RA patients had been administered two 1000 mg intravenous doses of rituximab prior to that date.

The purportedly novel aspect of the '838 patent claims is that the claimed dosage regimen can be used to treat a subpopulation of patients: those who experience an inadequate response to a tumor necrosis factor α ("TNFα")-inhibitor. As explained below, however, the prior art inherently disclosed the claimed method. At least 30-40% of RA patients experience an inadequate response to a TNFα-inhibitor, and at least some of the 92 RA patients who had been treated with the claimed dosage regimen would have been inadequate responders. This prior treatment thus anticipates the claimed method.

Moreover, the prior art explicitly taught that rituximab can successfully be used to treat RA patients using the claimed dosing regimen, and persons of ordinary skill in the art ("POSAs") would have understood that a significant subpopulation of RA patients experience an inadequate response to a TNFα-inhibitor. A POSA also would have understood that a patient who has failed treatment with a TNFα-inhibitor may still be successfully treated with a different agent, such as rituximab. The claimed method therefore would have been obvious to a POSA.

III. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The real party in interest is Celltrion.

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

Petitioner is not aware of any other pending judicial or administrative matters concerning the '838 patent. The '838 patent was challenged in IPR2015-00417. The PTAB instituted the IPR for claims 1-14 of the '838 patent in that proceeding on July 14, 2015. That proceeding was terminated on October 1, 2015, following a Request for Adverse Judgment by the Petitioner. Celltrion also challenged the '838 patent in IPR2015-01733, in a petition filed on August 14, 2015, which was accompanied by a motion for joinder to IPR2015-00417. After the Petitioner terminated IPR2015-00417, but before an institution decision on

Celltrion's petition, Celltrion dismissed without prejudice IPR2015-01733 and its motion for joinder.

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

Lead counsel is Elizabeth J. Holland, Reg. No. 47,657. Back up counsel are Huiya Wu, Reg. No. 44,411; Cynthia Lambert Hardman, Reg. No. 53,179; Elaine Herrmann Blais; and Robert V. Cerwinski. All counsel are with Goodwin Procter LLP. Ms. Holland, Ms. Wu, Ms. Hardman and Mr. Cerwinski, are at 620 Eighth Avenue, New York, NY 10018, tel. 212-813-8800, fax 212-355-3333. Ms. Blais is at 100 Northern Avenue, Boston, MA 02210, tel. 617-570-1000, fax 617-523-1231. Email contact for counsel is eholland@goodwinlaw.com, hwu@goodwinlaw.com, chardman@goodwinlaw.com, eblais@goodwinlaw.com, and rcerwinski@goodwinlaw.com.

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

Please direct all correspondence to counsel at the contact information above. Petitioner consents to service by electronic mail at eholland@goodwinlaw.com, hwu@goodwinlaw.com, chardman@goodwinlaw.com, eblais@goodwinlaw.com and rcerwinski@goodwinlaw.com.

IV. FEES

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

V. 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.

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

A. The Claims of the '838 Patent

The '838 patent has 14 claims, including five independent claims. Independent claim 1 states as follows:

> 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.

Independent claim 2 includes all of the limitations of claim 1 and adds that the antibody be provided "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." Independent claim 8 is identical to claim 1, but states that the antibody is rituximab. Independent claim 10 includes all of the limitations of claim 8; requires that methotrexate is also administered to the patient; and adds that the patient has no erosive progression at weeks 24 and beyond.

Independent claim 11 is directed to a method of "achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at week 24 and beyond, in a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα-inhibitor." Claim 11 requires administering to an RA patient two intravenous doses of 1000 mg rituximab and methotrexate.

The dependent claims include additional limitations such as administration of corticosteroids, and that the CD20 antibody be the only B-cell surface-marker-specific antibody administered to the patient.

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 and neutralizing its activity.” (*Id.* at 5:19-21.) The patent provides three examples of TNFα inhibitors: etanercept (ENBREL®), infliximab (REMICADE®) and adalimumab (HUMIRA®). (*Id.* at 5:21-24.)

The ’838 patent defines an “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 5:25-28.) The patent also states that the alleged invention “is not limited to a prior therapy step with such a TNFα-inhibitor” and is directed both to patients who have exhibited an inadequate response to actual treatment with a TNFα-inhibitor, and those who are predisposed to either exhibit a toxic reaction upon, or inadequately respond to, such treatment:

> [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/m^2 i.v. weeklyx4. (*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.) The patentee states, however, that the dosing amounts "are subject to a great deal of therapeutic discretion" (*id.* at 29:42-43), 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

The claims of the '606 application were initially rejected over various combinations of prior art that taught the treatment of RA with rituximab, and the possible negative side effects of TNFα-inhibitors. The applicant distinguished the cited prior art by noting that neither the claimed dosage amount nor the results of the treatment (i.e., ACR50, ACR70, and no erosive progression at 24 weeks) had been disclosed.

The applicant also submitted a declaration by Dr. Ronald F. van Vollenhoven, who had previously submitted that declaration to the European Patent Office in connection with an opposition to the foreign counterpart of the '838 patent (EP 1613350). (Ex. 1004.)[1] Dr. van Vollenhoven stated his opinion that the population of RA patients who experience an inadequate response to TNFα-inhibitor treatment is particularly "hard to treat." (Ex. 1004 ¶ 6.) He asserted that the patients who had taken TNFα-inhibitors, which were second-line therapies at that time, had already "failed at least 2-3 conventional RA therapies," and that those patients have a different "physiological and pathological status" than RA patients who do not experience an inadequate response to TNFα-inhibitor treatment. (*Id.* ¶¶ 6, 12; *see* Ex. 1002 ¶ 36.) Dr. van Vollenhoven opined that the claimed invention thus filled a long-felt need by treating this hard-to-treat sub-population. (Ex. 1004 ¶¶ 7-14; *see* Ex. 1002 ¶ 36.)

The applicant also relied on Dr. van Vollenhoven's declaration to argue that the cited prior art "taught away" from the claimed dosage amounts, which the applicant alleged were lower than those in the cited prior art, and that the resulting

[1] The European Patent Office revoked the foreign counterpart of the '838 patent because it lacked novelty. (*See* Ex. 1044 at 30-36 (concluding that the subject matter of the claims was not inventive and dismissing the patentee's appeal).)

benefits of treatment with the claimed dosages of rituximab would have been unexpected. (Ex. 1045 at 12; *see* Ex. 1002 ¶ 35.)

Following this submission, the examiner filed an "Interview Summary" explaining that the applicant had successfully argued that the cited prior art did not teach "two i.v. doses of 1000 mg of an anti-CD20 antibody," and, therefore, the examiner would reconsider the obviousness rejections. The examiner then allowed the application without further comment. (Ex. 1002 ¶ 37.)

Importantly, the examiner did not consider the arguments raised here based on Edwards 2002, a key piece of prior art that disclosed both the claimed dosage amount and regimen and disclosed the clinical benefits of the claimed treatment. (Ex. 1033.)

VII. BACKGROUND ON RA AND RITUXIMAB

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

RA is a chronic autoimmune disease that causes pain, stiffness, swelling and limited motion and function of joints. (Ex. 1002 ¶ 41.) RA can affect any joint, but the small joints in the hands and feet tend to be involved most often. (*Id*.) Two-thirds of RA patients are female. (*Id.*; *see also* Ex. 1005 at 274.)

Before the earliest possible priority date of the '838 patent (April 9, 2003), the typical practice to treat RA as outlined in the Guidelines for the Management of Rheumatoid Arthritis, 2002 Update ("ACR Guidelines," Ex. 1006), written by

the ACR Subcommittee on Rheumatoid Arthritis, was to treat symptoms by administering agents such as corticosteroids or non-steroidal anti-inflammatory drugs ("NSAIDs") along with a disease modifying anti-rheumatic drug ("DMARD") to attempt to halt or slow progression of the disease. (Ex. 1002 ¶¶ 42-43, 48; Ex. 1006 at 332-40.) The ACR Guidelines is a printed publication and is prior art under 35 U.S.C. § 102(b).

Corticosteroids, such as oral prednisone, were commonly used to treat the symptoms of RA and had been used to treat RA patients for many years prior to the earliest filing date of the '838 patent. (Ex. 1002 ¶ 43.) As of 2003, approximately 50% of RA patients, both those in regular treatment and those in clinical trials, were on a chronic low dose of oral prednisone. (Ex. 1002 ¶ 43; Ex. 1007 at 591.) Corticosteroids were used in combination with other drugs, usually DMARDs. (Ex. 1002 ¶ 43; Ex. 1006 at 332-33.) Examples of DMARDS include intravenous gold, sulfasalazine, and methotrexate. (Ex. 1002 ¶ 43; Ex. 1006 at 336-39.)

Methotrexate was, and is, a drug used in the treatment of autoimmune diseases, including RA. (Ex. 1002 ¶ 44.) Methotrexate has also been used at high doses as a treatment for certain types of cancer. (*Id.*) The efficacy and safety of methotrexate as a treatment for RA had been established long before the filing date of the '606 application. (*Id.*) 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." (Ex. 1011 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 779.) "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." (*Id*. at 790.)

The types of drugs administered to an RA patient and their dosing schedule depended on the patient's response to treatment, which was continuously monitored. (Ex. 1002 ¶ 45.) Adjustments to the type of drugs, their combinations, and their doses were made as necessary. These adjustments included combination therapy with more than one DMARD, monotherapy with a new DMARD, or therapy with a biologic agent. (*Id*. ¶¶ 45-47.) Therapy with a biologic agent was either monotherapy or combination therapy with a DMARD. (*Id*. ¶ 47; Ex. 1006 at 329.)

In the early 1990s, a committee of the ACR selected a "core set" of outcome measures for assessing patient response to RA treatments. (Ex. 1002 ¶¶ 49-50.)

The criteria assessed percentage improvement in tender joint count, swollen joint count, 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) erythrocyte 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*.; Ex. 1006 at 332.)

Another response measure was assessed by evaluating radiograph images of a patient's joints and measuring the "erosions" in the bone surface both before and after treatment. (Ex. 1002 ¶ 51; Ex. 1006 at 332.) A worsening of erosions is sometimes called "erosive progression." (Ex. 1002 ¶ 51.)

Whether ACR20, ACR50, ACR70 or some other measure is deemed to be a satisfactory response to RA treatment is a subjective decision made by an individual patient in conjunction with her physician. (*Id.* ¶ 53.) Factors that contribute to this decision include whether other treatment options are available, whether those options are appropriate for an individual patient in light of possible co-morbidities, and whether the expected side effects of such treatment outweigh any potential gain. (*Id*.)

B. TNFα Inhibitors and Inadequate Responders

Biologic agents such as TNF blocking agents were developed in the mid-1990s and represented a major advance in the treatment of RA. (Ex. 1002 ¶ 47.) Before the filing date of the '606 application, three 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 1998; and (iii) adalimumab (Humira®), approved in 2002. (*Id.*) Each of these TNFα-inhibitors is specifically mentioned in the '838 patent. (Ex. 1001 at 5:21-24.)

Like other RA treatments, TNFα-inhibitors do not produce a response in all RA patients. As of 2003, the literature reported a response in approximately 60% of patients during therapy with infliximab (Ex. 1002 ¶ 54; Ex. 1016 at 1552; Ex. 1017 at 201) and approximately 70% with etanercept. (Ex. 1002 ¶ 54; Ex. 1017 at 201.) It was estimated that a total of approximately 60% of patients initially experience a response to TNFα-inhibitor treatment. (Ex. 1002 ¶ 54.) Some patients who initially experience a response to TNFα-inhibitors eventually stop responding. (*Id.*) Approximately 50% of all patients who begin treatment with a TNFα-inhibitor stop treatment due to failure within three years. (*Id.*; Ex. 1018 at 4.) Later studies confirm this high occurrence of inadequate response to TNFα-inhibitors, and further disclose that the frequency of patients having failed one

TNFα-inhibitor who will fail other TNFα-inhibitors is closer to 60%. (Ex. 1002 ¶¶ 55-57; Ex. 1018 fig. 1.)

Patent Owner's declarant during prosecution of the '606 application, Dr. van Vollenhoven, stated that "[a]mongst the patients treated with TNF-inhibitors, about 60-70% responded, whereas about 30-40% did not." (Ex. 1004 ¶ 7; *see also* Ex. 1002 ¶¶ 58-59; Ex. 1022 at 20.) As of 2003, patients who did not respond to TNFα-inhibitor treatment were encouraged to pursue other therapeutic options, including other biologics. (Ex. 1002 ¶ 60; Ex. 1023 at I129.)

C. The Use of Rituximab To Treat RA

Rituximab was approved in the United States in 1997 with an indication to treat non-Hodgkin's lymphoma. (Ex. 1002 ¶ 62.) The Rituxan® label was printed in the 1999 Physician's Desk Reference, and is a printed publication that is prior art under 35 U.S.C. § 102(b). (Ex. 1027.) The Rituxan® label approved in 1997 stated that "Rituxan is associated with hypersensitivity reactions. . . Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, anti-histamines and corticosteroids should be available for immediate use in the event of a reaction during administration." (Ex. 1002 ¶ 63; Ex. 1027 at 1071.) These hypersensitivity reactions occur in approximately 80% of patients upon the first infusion and in approximately 40% of patients in subsequent infusions. (Ex. 1027 at 1071.) Accordingly, patients taking rituximab were typically pretreated with or co-

administered intravenous methyl-prednisolone. (Ex. 1002 ¶ 63.) Intravenous methyl-prednisolone was also often given during administration of other biologic agents to prevent or treat immediate hypersensitivity reactions. (Ex. 1002 ¶¶ 63, 126; *see also* Ex. 1040 at 16-18 (disclosing treating RA patients with methylprednisolone as an agent to combat "first dose reactions" that are sometimes experienced during infusion of a biologic agent).)

WO 00/67796 ("Curd") is an international patent application that published on November 16, 2000. (Ex. 1031.) It is a printed publication and is prior art under 35 U.S.C. § 102(b). Curd teaches "treatment of autoimmune diseases with antagonists which bind to B cell surface markers, such as CD19 or CD20." (Ex. 1031 at 1:3-4; Ex. 1002 ¶ 66.) Curd identifies rituximab (Rituxan®) as a "genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen." (Ex. 1031at 2:7-8.) Curd teaches dosing regimens of Rituxan® for the treatment of autoimmune diseases of "about 20 mg/m^2 to about 1000 mg/m^2" (*id*. at 23:17-19)[2], but also states that "these suggested amounts of antagonist are subject to a great deal of therapeutic discretion. The key factor in

[2] "mg/m^2" is a common way to recite doses that are dependent upon the body surface area ("BSA") of a patient. For the average RA patient, an adult female, the BSA is approximately 1.7 m^2. (Ex. 1002 at ¶ 72.) The doses stated in this petition are based on this average value for BSA.

selecting an appropriate dose and scheduling is the result obtained." (*Id*. at 23:28-29.) The administration is most preferably given intravenously or via subcutaneous injections. (*Id*. at 23:38-39.)

Curd includes three examples. Example 1 is directed to treating RA patients with rituximab. Rituximab is administered intravenously according to one of three schedules: (A) 50 mg/m^2 IV day 1, followed by 150 mg/m^2 IV on days 8, 15, & 22; (B) 150 mg/m^2 IV day 1, followed by 375 mg/m^2 IV on days 8, 15 & 22; (C) 375 mg/m^2 IV days 1, 8, 15 & 22. (*Id*. at 25:17-23.) The patients may also optionally be treated with one or more other agents, including methotrexate and corticosteroids. (*Id*. at 25:10-16.) Corticosteroids include prednisone and methylprednisolone. (*Id*. at 8:28-29; *see also* Ex. 1002 ¶ 66.)

De Vita, *Pathogenic Role of B Lymphocytes in Rheumatoid Synovitis: B Cell Selective Blocking Can Induce a Clinical Response in Patients with Refractory Rheumatoid Arthritis*, published in 2001 in the Italian journal "Reumatismo." ("De Vita," Ex. 1051.[3]) De Vita is a printed publication and is prior art under 35 U.S.C. § 102(b). De Vita was not before the examiner during prosecution.

[3] Exhibit 1051 includes the original Italian article along with a certified English translation and a certification of translation.

De Vita discloses that four RA patients were treated with rituximab. (*Id.* at 323; Ex. 1002 ¶ 68.) All four patients had previously not responded to combination therapy with methotrexate and cyclosporine-A. (*Id*.) Patients 3 and 4 had also not responded to previous anti-TNFα therapy. (*Id*.) The patients each received 4 intravenous infusions, one per week, of 375 mg/m^2 for a total of 2550 mg. (*Id.*) The patients concomitantly took low doses of steroids. (*Id*.)

Patients 1 and 2 enjoyed marked clinical improvement (ACR 70 and ACR 50) at three months. (*Id*.) One of the two patients who had previously failed TNFα-inhibitor therapy achieved an ACR 20 response at month 5, while the other did not respond to treatment.[4] (*Id.*) In its discussion on the success of the study, De Vita states, "[i]ndeed, by means of a selective B block, a clinical response was

[4] De Vita states that "Patient 4 obtained an ACR 20 response.… Conversely, patient 4 did not respond to the treatment." (Ex. 1051.) The article does not report the reaction of patient 3. Because the article notes that the response of these two patients "contrasted" with each other, a POSA would have understood this statement to contain a typo. A POSA would have understood that De Vita was reporting that one patient (either 3 or 4) obtained an ACR20 response while the other (either 3 or 4) did not respond to the treatment. (Ex. 1002 ¶ 69.)

obtained in non-responders to therapies directed against the lymphocytes T and synoviocytes." (*Id*.)

International Patent Application WO 00/74718 ("Goldenberg," Ex. 1038), titled "*Immunotherapy Of Autoimmune Disorders Using Antibodies Which Target B-Cells*" published on December 14, 2000. Goldenberg is a printed publication and is prior art under 35 U.S.C. § 102(b). Goldenberg teaches that an anti-CD20 antibody, designated as "IDEC-C2B8," is active against B-cell lymphomas, including non-Hodgkin's lymphoma. (*Id*. at 1:25-31; Ex. 1002 ¶ 75.) IDEC-C2B8 is an internal code referring to Rituxan® that was used early in development of that drug. Goldenberg teaches that autoimmune diseases, including RA are "a class of diseases associated with a B-cell disorder." (Ex. 1038 at 2:6-10.) One object of the invention disclosed in Goldenberg is to treat autoimmune diseases with a B-cell antigen, supplemented with "the administration of other therapeutic modalities, such as those directed against T-cells, plasma cells and macrophages." (*Id*. at 2:29-33.)

Goldenberg includes 6 examples. Example 5 describes intravenous treatment of an RA patient with 300 mg each of rituximab and "hLL2" for a period of five weeks. (*Id*. at 22.) The patient had previously failed therapy with methotrexate and obtained only minor relief with Enbrel (a TNFα-inhibitor). (*Id*.) Goldenberg describes the results as follows: "Significant improvement in measures

of disease activity is observed, which is maintained for 6 months.) The patient is again treated with the same regimen and continues to improve. Six months after the second course of therapy, additional improvement is observed." (*Id*.; *see also* Ex. 1002 ¶ 75.)

Edwards and Cambridge, *Sustained Improvement in Rheumatoid Arthritis Following a Protocol Designed to Deplete B Lymphocytes*, RHEUMATOLOGY, 40:205-211 (2001) ("Edwards 2001") (Ex.1029) is a printed publication and prior art to the '838 patent under 35 U.S.C. § 102(b). Edwards 2001 disclosed the successful treatment of five RA patients with rituximab, prednisolone (a corticosteroid), and cyclophosphamide. Each of the patients had previously failed treatment with at least five DMARDs. (*Id*. at 206.) Over the course of twenty days, the patients were each treated with four infusions of rituximab, for a total dose of 2100 mg. The patients also received daily prednisolone and two infusions of cyclophosphamide. (*Id*. at 207; Ex. 1002 ¶ 65.)

At six months, all five patients had achieved ACR50, and three of the patients had achieved ACR70. Edwards 2001 discloses that "[i]rrespective of the mechanism by which they were achived, the results obtained in this study suggest that the protocol used, or a modification thereof may be of major benefit to subjects with RA." (Ex. 1029 at 207.)

Joseph M. Tuscano, *Successful Treatment of Infliximab-Refractory Arthritis with Rituximab*, ARTHRITIS RHEUM 46:3240 LB 1 ("Tuscano") (Ex. 1034), published in December 2002, is a printed publication, and prior art to the '838 patent under 35 U.S.C. § 102(a). Tuscano was before the examiner during prosecution but was not relied upon for any rejection during the prosecution of the '606 application. Tuscano disclosed the initial results of a clinical trial that treated 7 RA patients with rituximab. (Ex. 1002 ¶ 72; Ex. 1034.) Each of these patients had previously failed treatment with infliximab, a TNFα-inhibitor. (Ex. 1034.) Rituximab was administered in an escalating dose starting at 100 mg in week 1, rising to 375 mg/m^2 in week 2, and then reaching 500 mg/m^2 in weeks 3 and 4. (*Id.*) Assuming a body surface area of 1.7 m^2, the total dose given in Tuscano was 2437.5 mg. After five months of treatment, all seven patients had improved joint scores, and three achieved an ACR20 response. (*Id.*) According to the authors, the preliminary results indicated that rituximab was a "promising agent for patients with DMARD and infliximab-refractory RA." (*Id*.)

Leandro, et al., *Clinical Outcome in 22 patients with Rheumatoid Arthritis Treated with B Lymphocyte Depletion*, ANN RHEUM DIS 2002: 61: 883-888 ("Leandro") (Ex. 1035), published in October 2002, is a printed publication, and is prior art to the '838 patent under 35 U.S.C. § 102(a). Leandro was not before the examiner during prosecution. Leandro disclosed the treatment of 22 RA patients

with various doses of rituximab. (Ex. 1002 ¶ 73; Ex. 1035 at 883.) The total doses included 510 mg, 850 mg, 960 mg, 1020 mg, 1190 mg, 2040 mg and 2380 mg. (Ex. 1002 ¶ 72.) Many of the patients also received oral prednisolone. (Ex. 1035 at 884.) Patients on all doses aside from the two lowest doses (510 mg and 850 mg) achieved a response of ACR50 or ACR70 at six months. (Ex. 1002 ¶ 72.)

D. The Prior Art Taught Combination Therapy with Methotrexate and Biologic Agents, Including Rituximab

When biologic agents were first introduced as a treatment option for RA, government agencies and practicing physicians called for the use of these agents in combination therapy with methotrexate. For example, the 1999 FDA Guidance for Industry on Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA) states that it was "inevitable that new agents [would] be used in combination with methotrexate in clinical practice unless a contraindication exists" and "data regarding use of the investigational agents in combination with methotrexate [we]re needed to evaluate the potential for immunosuppression from combination therapy." ("FDA Guidance," Ex. 1047 at 18; Ex. 1002 ¶ 47.) The FDA Guidance is a printed

publication and is prior art under 35 U.S.C. § 102(b).[5]

In practice, biologic agents were used to treat RA in combination with methotrexate. (*See, e.g*., Weinblatt et al., *A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor:Fc Fusion Protein, in Patient with Rheumatoid Arthritis Receiving Methotrexate*, 340 NEW ENGLAND JOURNAL OF MEDICINE 4, 253 (1999) (Ex. 1048); Kalden, *Rescue of DMARD Failures by Means of Monoclonal Antibodies or Biological Agents*, CLINICAL AND EXPERIMENTAL RHEUMATOLOGY (1997) (Ex. 1050); Ex. 1002 ¶ 47.)

Other prior art describes the use of methotrexate combination therapy for "refractory" or "hard-to-treat" RA patients. For example, O'Dell, "*Conventional DMARD Options for Patients with a Sub-Optimal Response to Methotrexate,* JOURNAL OF RHEUMATOLOGY ("O'Dell 2001") *(*Ex. 1049), explained that methotrexate was the first-line treatment option for RA, and, when patients exhibited only a sub-optimal response to methotrexate, other drugs were added to the methotrexate treatment. (*Id*. at 21.) O'Dell 2001 disclosed that methotrexate had been used in combination with biologic agents successfully. (*Id*. at 21; Ex.

[5] Exhibit 1052, Declaration of Sarah Fink, demonstrates that the FDA Guidance of Exhibit 1020 was originally published in February 1999, as evidenced by Exhibit 1053.

1002 ¶ 47)

Edwards et al., *Efficacy and Safety of Rituximab, a B-Cell Targeted Chimeric Monoclonal Antibody: A Randomized, Placebo-Controlled Trial in Patients with Rheumatoid Arthritis*, ABSTRACTS OF THE AMERICAN COLLEGE OF RHEUMATOLOGY 66TH ANNUAL MEETING (New Orleans, LA) ("Edwards 2002") (Ex. 1033), published in October 2002, is a printed publication and prior art to the '838 patent claims under 35 U.S.C. § 102(a). Edwards 2002 was before the examiner during prosecution but was not used in any rejection during the prosecution of the '606 application.

Edwards 2002 described a clinical trial of 161 patients with RA, all of whom were receiving methotrexate. (Ex. 1002 ¶¶ 70-71; Ex. 1033.) The patients were separated into four patient treatment groups: Group A (continuing methotrexate alone); Group B (rituximab alone); Group C (rituximab and cyclophosphamide); and Group D (rituximab plus continuing methotrexate). (Ex. 1033.) Patients receiving rituximab were given two IV doses of 1000 mg. (*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 achieving "the highest levels of ACR20, 50 and 70 responses." (*Id.*)

Edwards 2002 reported clinical responses for 122 patients at 24 weeks as follows:

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

(*Id*.)

VIII. CLAIM CONSTRUCTION

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

A. "a patient who experiences an inadequate response to a TNFα-inhibitor"

The broadest reasonable construction of "a patient who experiences an inadequate response to a TNFα-inhibitor" in light of the specification is "a patient who, due to the characteristics of the patient and her individual disease presentation, either (1) did not or would not respond to treatment with TNFα-inhibitor or (2) did or would experience a toxicity upon such treatment." (Ex. 1002 ¶ 77.) In this Petition, patients who experience an inadequate response to a TNFα-inhibitor are referred to as "inadequate responders."

This construction is in accord with the plain meaning of the words of the claim, which state that the patient is one "who experiences" an inadequate response. The claim does not limit the tense of the word "experiences" to the past "experienced" or the present "experiencing," but instead limits the term by a characteristic of the patient herself: she is one who experiences an inadequate response. (*Id*. ¶ 78.) As Dr. Boers explains, a POSA as of 2003 would have understood that whether a patient will or will not respond to TNFα-inhibitor treatment is an inherent characteristic of the patient herself. (Ex. 1002 ¶¶ 79-80.) Patent Owner's declarant, Dr. van Vollenhoven, explained as much during prosecution of the '606 application when he described patients who experience an inadequate response as having a different "physiological and pathological status" than other RA patients. (Ex. 1004 ¶ 12.)

This construction is also consistent with the patent specification, which states that "the invention is not limited to a prior treatment step," and that a patient for whom the claimed treatment is appropriate is one who is "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." (Ex. 1001 at 28:55-61.)

Indeed, Patent Owner itself has acknowledged that the trait of a patient "who experiences" an inadequate response is a trait inherent to the patient and does not

depend on whether such patient has actually been treated with a TNFα-inhibitor. During the opposition proceeding for EP 1613350, the European counterpart to the '838 patent, Patent Owner argued that "[i]t should be apparent that TNFα-inhibitor response is an inherent physiological/pathological characteristic; it is a clinical measure of response to a pharmacological agent. The response to the inhibitor is not controlled by factors external to the patient." (Ex. 1022 at 20.)

In making that statement, Patent Owner relied on an additional declaration by Dr. van Vollenhoven. In his additional EP opposition declaration, Dr. van Vollenhoven cited two papers, one of which he coauthored, and summarized their teachings as follows: "The data … demonstrate that anti-TNF inadequate responders are pathologically or physiologically distinct patients based on blood antoantibody and cytokine profiles, as well as differentially expressed gene pairs or triplets." (Ex. 1021 ¶¶ 4-7; *see also* Ex. 1002 ¶ 78.)

B. The Clause "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" Is Not Limiting (Claim 2)

Claim 2 of the '838 patent includes two separate descriptions specifying the amount of antibody administered: (1) an amount defined by a potential clinical result – "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;" and (2) "two intravenous doses of 1000 mg." The recitation of clinical results adds

nothing to a claim that also specifically recites the dosage to be administered to achieve those results. *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc*., 246 F. 3d 1368, 1375 (Fed. Cir. 2001) (holding that where the "expression of intended result essentially duplicates the dosage amounts recited in the claims that are also described in the specification as [effective]," "[t]he express dosage amounts are material claim limitations; the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim") *see also In re Montgomery*, 677 F.3d 1375, 1380-81 (Fed. Cir. 2012) (explaining that the *Ben Venue* holding is even more appropriate under the broadest reasonable interpretation claim construction standard). Because claim 2 recites a specific dosage amount, the clause setting forth the clinical response does not serve as a separate limitation in claim 2. (*See also* Ex. 1002 ¶ 83.)

C. The "Wherein" Clauses Relating to the Clinical Results of the Claimed Treatment Are Not Limiting (Claims 10, 12, 13, and 14)

Certain claims contain "wherein" 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).

These clauses are not entitled to patentable weight because they merely state the potential result of carrying out the method in the claims. According to Federal Circuit precedent, 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) (citation omitted). This precedent applies to "wherein" clauses as well. *See, e.g.*, MPEP § 2111.04 (discussing "wherein" and "whereby" clauses together as "examples of claim language . . . that may raise a question as to the limiting effect of the language in a claim"). Further, as with results recited in the preamble, "express dosage amounts are material claim limitations; the statements of the intended result of administering those amounts [in the body of the claim] does not change those amounts or otherwise limit the claim." *Ben Venue*, 246 F.3d at 1375. Therefore, the "wherein" clauses set forth the potential clinical responses to carrying out the claimed methods and do not serve as distinct limitations in claims 10, 12, 13, and 14. (*See also* Ex. 1002 ¶¶ 81-82.)

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 progression at weeks 24 and beyond" Is Not Limiting (Claim 11)

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." This 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. (*See* Ex. 1002 ¶¶ 81-82.)

Moreover, because the steps of the method ("administering to the patient rituximab, and methotrexate, wherein rituximab is administered as two intravenous doses of 1000 mg") are performed in the same way regardless of whether the intended result recited in the preamble is achieved, the preamble cannot be limiting. *See Ben-Venue*, 246 F.3d at 1375 (holding that a preamble directed to "[a] method for reducing hematologic activity" is non-limiting because the steps of the method "are performed in the same way regardless whether or not the patient experiences a reduction in hematologic toxicity").

IX. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

In Ground 1, Petitioner requests *inter partes* review and cancellation of claims 1-5 and 7-14 as anticipated by Edwards 2002.

In Ground 2, Petitioner requests *inter partes* review and cancellation of claims 1-14 as obvious over Edwards 2002 in view of Tuscano. Petitioner notes that the Board previously instituted review of claims 1-5 and 7-14 under Ground 2 in IPR2015-00417, finding that the Petitioner had shown that it was likely to prevail in proving that those claims were *prima facie* obvious under this combination of prior art. Ground 2 has not previously been presented to the Board as an argument of obviousness for claim 6.

In Ground 3, Petitioner requests *inter partes* review and cancellation of claims 1-14 as obvious over Goldenberg, Curd, and De Vita. Petitioner notes that the Board previously instituted review of claim 6, the most narrow claim of the '838 patent, under Grounds similar to Ground 3 in IPR2015-00417, finding that the Petitioner had shown that it was likely to prevail in proving that those claims were prima facie obvious under a similar combination of prior art. Ground 3 has not previously been presented to the Board as an argument of obviousness for claims 1-5 and 7-14. Ground 3 is based entirely on 102(b) prior art, in contrast to Grounds 1 and 2, which are based on 102(a) prior art. While Patent Owner may attempt to swear behind the prior art date for the art relied on in Grounds 1 and 2

(i.e., Edwards 2002 and Tuscano), Patent Owner cannot do so for the prior art relied on in Ground 3. Therefore, Ground 3 is not redundant to Grounds 1 and 2.

This petition is supported by the Expert Declaration of Maarten Boers, M.D. (Ex. 1002) and the Expert Declaration of Dr. Larentius Marais, Ph.D. (Ex. 1039). Dr. Boers is a Professor of Clinical Epidemiology and a Staff Rheumatologist in the Department of Rheumatology at the VU University Medical Center, Amsterdam, and Dr. Marais is Vice President of William E. Wecker Associates, Inc., a statistical and applied mathematics consulting firm. This petition is further supported by the Declaration of Dr. Jack Goldberg, M.D. (Ex. 1036.) Dr. Goldberg was a practicing hematologist who had experience using rituximab as of 2003. The petition and supporting declarations 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).

A. Ground I: Claims 1-5 and 7-14 Are Unpatentable as Anticipated by Edwards 2002

1. Independent Claims 1 and 8 Are Anticipated

Edwards 2002 discloses every element of claims 1 and 8.

a. A method of treating rheumatoid arthritis

This method is expressly disclosed by Edwards 2002. (*See supra* section VII.C.; Ex. 1002 ¶ 86; Ex. 1033.)

b. In a human patient who experiences an inadequate response to a TNFα-inhibitor

This element is inherent in Edwards 2002. As Dr. Boers explains and as is discussed above in the claim construction section, whether a patient is an inadequate responder to a TNFα-inhibitor depends on the inherent physiology of the patient — regardless of whether she has had prior treatment with a TNFα-inhibitor. (Ex. 1002 ¶ 87; Ex. 1001 at 28:55-61.) Edwards 2002 discloses the administration of rituximab to at least 92 patients. (Ex. 1033.) Because a high percentage of RA patients have this inherent physiology, it is certain that at least some patients in the Edwards 2002 trial are inadequate responders to a TNFα-inhibitor. (Ex. 1002 ¶¶ 88-91.)

It is well settled that at least 30-40% of RA patients experience an inadequate response to a TNFα-inhibitor. (Ex. 1002 ¶¶ 54-56.) Further, as explained by Dr. Boers, approximately 50% of patients who begin TNFα-inhibitor treatment will no longer be on that treatment within three years of starting because the treatment will eventually fail, for a variety of reasons, including the development of antibodies against the TNFα-inhibitor. (*Id*.) These patients are inadequate responders within the meaning of the patent. (Ex. 1002 ¶ 87.) Patients who have failed one TNFα-inhibitor have an even higher likelihood—up to 60% —of failing treatment on a second TNFα-inhibitor. (*Id*. ¶¶ 56, 89.)

Edwards 2002 describes a study of 161 RA patients. (Ex. 1033.) At least 92 of those patients, i.e., those in treatment groups B, C, and D, received the claimed dose of rituximab.[6] (*Id.*) As explained by Dr. Marais, assuming a random selection of 92 RA patients, and assuming an inadequate-responder rate of 30%, the most conservative rate reported, the probability that at least one RA patient who is an inadequate responder was among the 92 RA patients is "virtually 100%." (Ex. 1039 ¶ 7.) Put another way, the probability that there were no inadequate responders among the 92 is less than 1 in 10^{14} (one in a 100 thousand billion), and is less than the probability of getting all "heads" and no "tails" in 47 consecutive flips of a coin. (*Id*.) As Dr. Marais explains, there is a 95% probability that at least 20 of the 92 patients were those who experience an inadequate response to TNFα-inhibitor treatment, and there is a 99% probability that at least 18 of the 92 patients were within that sub-population. (*Id*.) The expected number of patients within the 92-patient group who were inadequate responders is 27.6. (*Id*.)

As Dr. Marais further explains, if one applies a still conservative rate of 50% for inadequate responders, the probability that there were no patients within the 92 patient group who were inadequate responders is less than 1 in a billion billion billion, approximately the same as getting all heads and no tails in 92 consecutive

[6] Edwards 2002 discloses the treatment groups and results for only 122 of the 161 patients in the trial. (Ex. 1033.)

flips of a coin. (Ex. 1039 ¶ 7, n. 6.) Further, there is a 95% probability that at least 38 of the 92 patients were inadequate responders (*id*. ¶ 7), and there is a 99% probability that at least 35 of the 92 patients were within that sub-population. (*Id*.) The expected number of patients who were inadequate responders in that 92 patient group is 46.0. (*Id*.)

Further, the patients included in the Edwards study were not randomly chosen; they were already non-responders to methotrexate.[7] (Ex. 1033.) In other words, the patients chosen for this study were in the "refractory" or "hard to treat" group of RA patients. (Ex. 1002 ¶ 89.) As Dr. van Vollenhoven explained on Patent Owner's behalf in the EP opposition proceeding, this group of patients has a higher likelihood of failing TNFα-inhibitor treatment than a random selection of RA patients. (*Id*.; Ex. 1004 ¶ 6.) This means that the patient population for the study had a higher proportion of patients who are more likely inadequate responders than patients in the general RA population. (Ex. 1002 ¶ 89.)

In sum, it is certain that at least one of the 92 patients in the Edwards 2002 study who received the claimed treatment regimen was an inadequate responder. (Ex. 1002 ¶ 91.)

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[7] Even though certain patients did not respond fully to methotrexate, they continued to be treated with it because that was standard practice at the time. (Ex. 1002 at ¶ 45.)

Inherent anticipation may be found when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F. 3d 1362, 1365 (Fed. Cir. 1999).[8] In *MEHL/Biophile Int'l. Corp.,* the Federal Circuit found that an invention directed towards hair removal via a laser procedure was inherently anticipated by a prior art publication that described the same laser procedure, but carried out on guinea pig skin to assess cell injury. *Id*. at 1366. The patentee had argued that the publication did not mention hair removal. Noting that "no one disputes that guinea pigs have hairy backs," the court found inherent anticipation because, regardless of the purpose of the procedure, the guinea pigs' hair— necessarily and inherently present—would

[8] Petitioner is aware that the Board has rejected an inherent anticipation argument for these claims in the past. (IPR2015-00417, Decision Instituting *Inter Partes* Review, Paper 11 at 15.) In that decision, the Board rejected the inherency argument in that Petition because the argument was based on "probabilities." (*Id*.) Petitioner requests that the Board consider the inherent anticipation argument anew in light of the expert declarations of Dr. Marais and Dr. Boers demonstrating the certainty that at least one RA patient was, and likely many patients were, treated according to the claimed method.

have been removed when treated by the laser. *Id*. Here too, it is indisputable that at least one patient in the Edwards 2002 trial was an inadequate responder.

In another analogous case, *In re Johannes*, 566 Fed.Appx. 923, 926 (Fed. Cir. 2014), the Federal Circuit found a claim to a method "for removing liquid from the surface of a food product" inherently anticipated. The applicant had argued that the prior art reference "did not disclose a method for blowing liquid from a food product" and that "there is no express disclosure in [the reference] that there is liquid on the surface of the sausage casing." *Id.* at 925. In upholding the finding of inherent anticipation, the court said that the Board of Patent Appeals and Interferences "reasonably conclude[d] that [the prior art's] sausage casings—which, after all, need to be dried—*necessarily include the presence of at least* some liquid on their surface." *Id*. at 926 (emphasis added). Here too, one may reasonably conclude that the Edwards 2002 patient population "*necessarily includes the presence of at least*" one patient who experiences an inadequate response to a TNFα-inhibitor.

Beyond disclosing the treatment of patients who experience an inadequate response to a TNFα-inhibitor, the Edwards 2002 reference described all of the other elements of claims 1 and 8 and thus anticipates those claims. In the trial described in Edwards 2002, the RA patients were given two doses of 1000 mg of rituximab, which is indisputably an antibody that binds to CD20. (Ex. 1033; *see*

Ex. 1002 ¶ 86.) Indeed, performance of the Edwards 2002 study today would literally infringe the '838 patent claims and it is axiomatic that "that which would literally infringe if later anticipates if earlier." *Ben Venue*, 246 F.3d at 1378.

c. **Administering to the patient an antibody that binds to CD20 /administering to the patient rituximab**

Claim 1 includes the limitation "administering to the patient an antibody that binds to CD20," while claim 8 includes the limitation "administering to the patient rituximab." Rituximab, the antibody used in the Edwards 2002 study, is an antibody that binds to CD20. (Ex. 1002 ¶ 86.) Therefore, these elements are expressly disclosed in Edwards 2002.

Claims 1 and 8 include the transition phrase "comprising" prior to describing the treatment that is given to the patient. The term "comprising" is "open-ended and does not exclude additional, unrecited elements." MPEP § 2111.03. Therefore, claims 1 and 8 allow the concomitant treatment of methotrexate, cyclophosphamide and corticosteroids, as was done in Edwards 2002.

d. **Wherein the antibody is administered as two intravenous doses of 1000 mg**

These doses are expressly disclosed in Edwards 2002. (Ex. 1033; Ex. 1002 ¶ 86.) Therefore, Edwards 2002 anticipates claims 1 and 8. (Ex. 1002 at¶ 93.)

2. Independent Claim 2 Is Anticipated

Edwards 2002 discloses every element of claim 2.

Claim 2 is directed to a method of treating RA in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody which binds to CD20 in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond, wherein the antibody is administered as two intravenous doses of 1000 mg.

Every element of claim 2 is included in claim 1, except for an "ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond." As explained above with respect to claim construction, this element merely states potential clinical results and does not further limit claim 2. The claim expressly discloses two intravenous doses of 1000 mg, which the prior art taught may produce the clinical results. Edwards 2002, which discloses the claimed intravenous doses, anticipates claim 2 for the same reasons discussed above with respect to claim 1. (Ex. 1002 ¶¶ 95-97.)

Assuming arguendo that the element "ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond" is somehow limiting, the element is expressly disclosed by Edwards 2002, which reports that for the patients in groups B, C, D, i.e., those patients on the claimed

treatment regimen, 39 patients experienced an ACR 50 response and 16 patients experienced an ACR70 response at 24 weeks. (*Id.*; Ex. 1033.)

Therefore, for the reasons discussed above with respect to claim 1, claim 2 is anticipated by Edwards 2002.

3. Independent Claim 10 Is Anticipated

Claim 10 is directed to a method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient rituximab and methotrexate, wherein the patient has no erosive progression at weeks 24 and beyond, and wherein rituximab is administered as two intravenous doses of 1000 mg.

Every element of claim 10 is included in claim 8, except for treatment with methotrexate and the clause "wherein the patient has no erosive progression at weeks 24 and beyond." Edwards 2002 disclosed the method of administering rituximab and methotrexate to an RA patient: group D received treatment with methotrexate in addition to treatment with rituximab. (Ex. 1002 ¶ 99; Ex. 1033.)

The element "in a human who experiences an inadequate response to a TNFα-inhibitor" is inherently disclosed in Edwards 2002 for the group of 30 patients who received methotrexate in addition to rituximab. (Ex. 1002 ¶ 100.) According to Dr. Marais, assuming a random selection of 30 RA patients and an inadequate responder rate of 30%, the most conservative rate reported, the

probability that at least one patient who was an inadequate responder was among the 30 patients is 99.9977%. (Ex. 1039 ¶ 7.) Put another way, the probability that there were no patients within the 30 patient group who experience an inadequate response to a TNFα-inhibitor is less than 1 in 40,000, and is less than the probability of getting all "heads" and no "tails" in 15 consecutive flips of a coin. (*Id*.) As Dr. Marais explains, there is a 95% probability that at least 5 of the 30 patients were inadequate responders (*id*.), and there is a 99% probability that at least 4 of the 30 patients were within that sub-population. The expected number of patients within the 30-patient group who were inadequate responders is 9.0. (*Id*.)

As Dr. Marais further explains, if one applies a still conservative rate of 50% for inadequate responders, the probability that there were no patients within the 30 patient group who was an inadequate responder is less than 1 in a billion, and is approximately the same as the probability of getting all "heads" and no "tails" in 30 consecutive flips of a coin. (*Id*.) Further, there is a 95% probability that at least 11 of the 30 patients would be inadequate responders (*id*.), and there is a 99% probability that at least 9 of the 30 patients are within that sub-population. The expected number of patients in the 30-patient group who were inadequate responders is 15.0. (*Id*.)

Edwards 2002 thus inherently disclosed the treatment of patients with the claimed regimen of rituximab and methotrexate who experience an inadequate response to TNFα-inhibitor treatment. (Ex. 1002 ¶¶ 100-101.)

As explained, "no erosive progression at weeks 24 and beyond" is a recitation of potential clinical results and is therefore not limiting. (Ex. 1002 ¶ 102.) Claim 10 is therefore anticipated by Edwards 2002 for the same reasons discussed above with respect to claim 8. (Ex. 1002 ¶ 103.)

Assuming arguendo that the element "no erosive progression at weeks 24 and beyond" is limiting, the element is inherently disclosed by Edwards 2002, as later references report that some patients who are treated with the regimen disclosed in Edwards 2002 had no erosive progression at week 24. (*See, e.g.*, Ex. 1041 tbl. 3 (showing that 66% of patients who received two doses of 1000 mg rituximab plus methotrexate had no worsening of erosions at week 24); *see also* Ex. 1002 ¶ 102, 122.)

Therefore, for the reasons discussed above with respect to claim 8, claim 10 is anticipated by Edwards 2002.

4. Independent Claim 11 Is Anticipated

Claim 11 is directed to a method of "achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond." The method

requires administration of two intravenous doses of 1000 mg rituximab and methotrexate. As discussed, the phrase "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 the preamble is not limiting because it merely states a potential result. Therefore, Edwards 2002 anticipates claim 11 for the reasons discussed above with respect to claim 10. (Ex. 1002 ¶¶ 104-06.)

Assuming arguendo that the element "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" is limiting, Edwards 2002 disclosed this element. Edwards 2002 reported that for the patients in Group D, i.e., those patients on the claimed treatment regimen of rituximab and methotrexate, 15 patients experienced an ACR 50 response at 24 weeks and 7 patients experienced an ACR70 response at 24 weeks. (Ex. 1033.) For these reasons and the reasons discussed above with respect to claim 10, claim 11 is anticipated by Edwards 2002. (Ex. 1002 ¶ 105.)

5. Claim 3 Is Anticipated

Claim 3 depends on claim 2 and specifies that the antibody is rituximab. The antibody used in Edwards 2002 is rituximab. Accordingly, and for the reasons

described above with respect to claim 2, Edwards 2002 anticipates claim 3. (*See id*. ¶¶ 107-09.)

6. Claims 4 and 9 Are Anticipated

Claims 4 and 9 depend on claims 2 and 8, respectively, and further require that the patient be treated with methotrexate. Patients in Group D of the Edwards 2002 trial received methotrexate in addition to rituximab. (Ex. 1033.) Therefore, for the reasons discussed above with respect to claims 2, 8, and 10, Edwards 2002 anticipates claims 4 and 9. (*See* Ex. 1002 ¶¶ 110-12.)

7. Claim 5 Is Anticipated

Claim 5 depends on claim 4 and further requires that the patient is treated with a corticosteroid. (Ex. 1033.) Edwards 2002 disclosed that all patients received a 17-day course of corticosteroids. Thus, for the reasons discussed above with respect to claim 4, Edwards 2002 anticipates claim 5. (*See* Ex. 1002 ¶¶ 113-15.)

8. Claim 7 Is Anticipated

Claim 7 depends on claim 2 and further requires that the CD20 antibody is the only B-cell surface marker antibody administered to the patient. Rituximab was the only antibody administered to the patients in the Edwards study. Thus, for the reasons discussed above with respect to claim 2, Edwards 2002 anticipates claim 7. (*See id*. ¶¶ 116-18.)

9. Claims 12 and 13 Are Anticipated

Claims 12 and 13 depend on claim 11 and further specify that the clinical response be ACR50 at week 24 and ACR70 at week 24, respectively. As discussed above, these "wherein" clauses have no patentable weight because they merely state the potential outcome of practicing the claimed method. Therefore, claims 12 and 13 are identical in scope to claim 11 and are anticipated for the reasons discussed above with respect to claim 11. (*See id*. ¶ 119.)

Assuming arguendo that the "wherein" clauses do have patentable weight, Edwards 2002 disclosed that 15 of the patients who received rituximab and methotrexate achieved ACR50 at 24 weeks and 7 of those patients achieved ACR70 at 24 weeks. For these reasons and the reasons discussed above with respect to claim 11, Edwards 2002 anticipates claims 12 and 13. (*See id*. ¶¶ 119-20.)

10. Claim 14 Is Anticipated

Claim 14 depends on claim 11 and further specifies that the clinical response is no erosive progression at week 24. As discussed above, the "wherein" clause in this claim has no patentable weight because it merely states a potential outcome of the claimed method. Therefore, claim 14 is identical in scope to claim 11, and is anticipated for the reasons discussed above with respect to claim 11. (*See id*. ¶ 121.)

Assuming arguendo that the "wherein" clause does have patentable weight, this claim is anticipated by Edwards 2002 for the same reasons as discussed above with respect to claim 10. (*See id*. ¶¶ 121-23; Ex. 1041 at 2800.)

B. Ground 2: Claims 1-14 Are Obvious over Edwards 2002 in View of Tuscano

Unlike Ground 1, which is based on anticipation, Ground 2 is based on an obviousness analysis.

1. Level of Ordinary Skill in the Art

RA is a chronic inflammatory disorder that affects tens of millions of people worldwide. (Ex. 1002 ¶ 39.) 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.*)

In light of the specification, the references of record, and other available evidence, a POSA at the time of the alleged invention would have been a practicing rheumatologist with a medical degree (M.D. or equivalent) and: (i) at least 5 years of experience treating RA patients; (ii) an understanding of the pathophysiology of RA and other auto-immune disorders, including those in which

B-cells are thought to play a role; and (iii) an understanding of all of the available and proposed methods of treating RA and other auto-immune disorders, including those in which B-cells are thought to play a role, and how they work to treat such disorders. A POSA would also have an understanding of clinical trials for RA treatments, including how the trials are designed and how to interpret results. (*Id.* ¶ 40.)

2. Scope and Content of the Prior Art

The scope and content of the prior art is described above, in section VII.

3. Differences between the Claims and Prior Art

As explained above in the anticipation section, Edwards 2002 expressly disclosed every limitation of the claims except for "a patient who experiences an inadequate response to a TNFα-inhibitor," which is inherently disclosed by Edwards 2002. This element, however, is expressly disclosed by Tuscano, which concluded that rituximab is a promising treatment for RA patients who experience an inadequate response to a TNFα-inhibitor. (*See Ex*. 1002 ¶ 125.)

4. Conclusion of Obviousness

A POSA would have been motivated to administer rituximab according to the regimen disclosed in Edwards 2002, with a reasonable expectation of success, because Edwards 2002 disclosed that the regimen is an effective therapy for RA. (Ex. 1002 ¶ 126.) "Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."

Hoffmann-La Roche Inc. v. Apotex Inc., 748 F.3d 1326, 1331 (Fed. Cir. 2014) (citations omitted).

A POSA would have been motivated to use the regimen with patients who had a prior failure to TNFα-inhibitor treatment because Tuscano explicitly suggested that rituximab could successfully be used in this patient sub-population. (Ex. 1002 ¶ 126; *see also* Ex. 1032 at 2030-31 (disclosing improvement in the condition of patient 4, who had previously experienced an inadequate response to a TNFα-inhibitor, upon treatment with rituximab); Goldenberg, Ex. 1038 at 22 (disclosing "significant improvement" upon treatment with rituximab for a patient who had previously only partially responded to treatment with ENBREL®, a TNFα-inhibitor).)

The Edwards 2002 regimen disclosed two doses of 1000 mg rituximab and concomitant administration of methotrexate and corticosteroids. To the extent that the ACR50 and ACR70 responses of claims 11, 12, and 13 are limitations, they are explicitly disclosed in Edwards 2002. To the extent that the "no erosive progression at weeks 24 and beyond" of claims 10 and 14 is a limitation, a POSA would have understood from the ACR50 and ACR 70 responses disclosed in

Edwards 2002 that there would be no erosive progression at week 24 and beyond.[9] (Ex. 1002 ¶ 122, 126.) Therefore, claims 1-5 and 7-14 are obvious over Edwards 2002 in view of Tuscano. (*Id.*) Edwards 2002 taught two doses of 1000 mg rituximab and a POSA would have been motivated to use this dose to treat RA in an inadequate responder with a reasonable expectation of success.

Although Tuscano disclosed a higher total dose of rituximab than the claimed 2000 mg total dose, the claimed doses are obvious, as the lower doses were successfully used in Edwards 2002. (Ex. 1002 ¶ 128; Ex. 1033.) Other studies, which report using about 2000 mg total dose of rituximab to treat RA successfully, would also have provided a POSA motivation to use a 2000 mg total dose of rituximab to treat RA with a reasonable expectation of success. (*See* Ex. 1035 (using doses of 600, 700, and 1200 mg/m^2 (960, 1120, and 1920 mg) of rituximab on patients some of whom achieved ACR20, ACR50, or ACR70 at 6 months); *see also* Ex. 1002 ¶ 128.)

Moreover, there is nothing critical about the claimed total dose of 2000 mg. The patent specification makes this clear, because it includes both the claimed dose (two doses of 1000 mg) and four doses of 375 mg/m^2 as "a therapeutically

[9] Moreover, that limitation is inherently met by the method disclosed in Edwards 2002. (Ex. 1041 at 2800 (disclosing 60% of patients in a study that had no erosive progression after treatment with the claimed method.)

effective dose" in the single disclosed example. (Ex. 1001 at 31:28-31.) In view of the prior art, it would have been a matter of routine optimization for a POSA as of 2003 to adjust the doses of rituximab to achieve the desired clinical outcome. (Ex. 1002 ¶ 128.)

Claim 6 depends on claim 5 and further requires that the corticosteroid treatment consists of methylprednisolone and prednisone. As discussed above, approximately 50% of all RA patients are treated with oral prednisone, and this practice was in place as of 2003. (Ex. 1007 at 591.) Further, intravenous methylprednisolone was often given during administration of biologic agents, including administration of rituximab to treat lymphoma and administration of other biologic agents to treat RA, in order to mitigate immediate hypersensitivity reactions that sometimes occur when biologic drugs are infused. (Ex. 1002 ¶ 129.) The Rituxan® label indicates that corticosteroids should be available to treat immediate hypersensitivity reactions that occur with the first infusion of rituximab in the majority of patients (approximately 80%), and during subsequent infusions in some patients (approximately 40%). (Ex. 1027 at 1071; s*ee also* Ex. 1025 at 928 ("Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids, and/or epinephrine) should be available for immediate use in the event of a reaction."); Ex. 1040 at 16-18 (disclosing treatment of RA patients with methylprednisolone as an agent to

combat "first dose reactions" that are sometimes experienced during infusion of biologic agents).)

It would have been obvious to treat RA patients, including inadequate responders, with rituximab, methotrexate, and oral prednisone particularly because oral prednisone was already included in most RA treatment regimens. (Ex. 1002 ¶¶ 129-30.) It also would have been obvious to include intravenous administration of methylprednisolone to combat possible immediate hypersensitivity reactions during the administration of rituximab. (*Id*.) Claim 6 is therefore obvious over Edwards 2002 in view of Tuscano and the knowledge of one of ordinary skill in the art. (*Id*.)

Alternatively, Curd disclosed treatment with corticosteroids and rituximab to treat RA, and identified both prednisone and methylprednisolone as corticosteroids. (Ex. 1031 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."); *see id*. at 8:28- 29 (referring to "steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone"); *see also* Ex. 1002 ¶ 127.) Thus, claim 6 is also obvious over Edwards 2002 in view of Tuscano and Curd. (Ex. 1002 ¶ 130.)

C. Ground 3: Claims 1-14 are Obvious Over Goldenberg, Curd, and De Vita

As discussed above, Ground 3 is based on section 102(b) art, not section 102(a) art, as in Grounds 1 and 2.

1. The Level of Ordinary Skill in the Art

The level of ordinary skill in the art is described above in section IX.B.1.

2. Scope and Content of the Prior Art

The scope and content of the prior art is described above in section VII.

3. Differences between the Claims and the Prior Art

The prior art discloses the successful treatment of RA patients with rituximab, administered intravenously, with a total dose ranging from 1500 mg (Goldenberg) to 2100 (Edwards 2001) to 2550 mg (De Vita). Curd discloses concomitant treatment with other agents, including methotrexate and corticosteroids, which are defined to include both prednisone and methylprednisolone. (Ex. 1031 at 8:28-29, 25:17-23.) Goldenberg also teaches concomitant treatment with other agents, including the "particularly preferred" methotrexate (Ex. 1038 at 2:29-32; 16:31-17:8), and De Vita discloses concomitant treatment with steroids (Ex. 1051). (*See* Ex. 1002 ¶ 134: *see also*, Edwards 2001, Ex. 1029 at 206 (disclosing the successful use of corticosteroids with rituximab to treat RA).)

The prior art does not teach the exact claimed dose of rituximab. However, it does teach a range of total doses reported to treat RA successfully, and the claimed dose falls within this range. The prior art further teaches that the dose of rituximab should be decided with "therapeutic discretion" based on the results achieved in the patients. (Ex. 1031 at 23:28-29.) The prior art therefore teaches that a POSA may arrive at the claimed dose of rituximab by routine optimization.

4. Conclusion of Obviousness

A POSA would have been motivated to treat RA patients who had previously failed TNFα-inhibitor treatment with rituximab with a reasonable expectation of success because the prior art, e.g. Goldenberg and De Vita, taught that such patients may be successfully treated with rituximab. Ex. 1002 ¶ 135. A POSA would have further been motivated to include concomitant treatment with methotrexate because the prior art, e.g. Curd and Goldenberg, taught exactly that combination of agents. (Ex. 1031 at 25:9-23; Ex. 1038 at 2:29-32; 16:31-17:8; Ex. 1002 ¶ 137.) Further, the prior art as a whole taught that combination therapy including methotrexate is commonly used to treat patients with "refractory" or "hard-to-treat" RA. (*See, e.g.*, Ex. 1049 at 21; Ex. 1002 ¶ 137.) The prior art as a whole also taught that new biologic treatments should be used in combination with methotrexate (*see, e.g.*, Ex. 1047 at 18), and that new biologics were, in fact, being used in combination with methotrexate (*see, e.g.*, Ex. 1050 at 206). In view of this

prior art, a POSA would have had a reasonable expectation of success in treating inadequate responders with combination therapy including rituximab and methotrexate. (Ex. 1002 ¶ 137.)

A POSA would have been motivated to optimize the dose of rituximab used to treat RA. (Ex. 1002 ¶ 136.) Goldenberg discloses successful treatment of RA with a total dose of 1500 mg (Ex. 1038 at 22) and De Vita discloses successful treatment of RA with a total dose of 2550 mg. (Ex. 1051). The claimed dose, 2000 mg, falls squarely between these two successful doses. Further, while Goldenberg discloses a total of five intravenous administrations of rituximab and De Vita discloses a total of four, a POSA would have been motivated to administer rituximab in as few doses as possible to increase patient compliance and convenience because rituximab is administered intravenously in a doctor's office or infusion center. (Ex. 1002 ¶ 136.) Curd would also have motivated a POSA to optimize the selection of an appropriate dose and scheduling. (Ex. 1031 at 23:28-29 ("[T]hese suggested amounts of antagonist are subject to a great deal of therapeutic discretion.").) Via routine optimization, a POSA would have arrived at the claimed dose of rituximab, as evidenced by Edwards 2002. (*See* Ex. 1033 (arriving at a dose 2 x 1000 mg); Ex. 1002 ¶ 135.)

Further, the claimed dose produced only predictable results (see *infra*, in the section on secondary considerations). "Reached by means of routine procedures,

and producing only predictable results, the recited dosages" do not distinguish the claims from the prior art. *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989).

A POSA would have had a reasonable expectation of success because the prior art teaches the successful treatment of RA with rituximab for patients who had previously failed TNFα-inhibitor treatment with rituximab, and the prior art also teaches that refractory patients are often successfully treated with combination therapy that includes methotrexate. (Ex. 1002 ¶ 135.)

1. Independent Claims 1 and 8 Are Obvious

Claim 1 of the '838 patent is directed to a method of treating an RA patient who experiences an inadequate response to a TNFα-inhibitor with two intravenous doses of 1000 mg of an antibody that binds to CD20, and methotrexate. Claim 8 is identical to claim 1, but replaces the term "an antibody that binds to CD20" with "rituximab," which was known to be "an antibody that binds to CD20."

As explained above, a POSA would have been motivated to treat an inadequate responder with rituximab because both Goldenberg and De Vita taught that these patients may be successfully treated with rituximab. As further explained above, a POSA would have arrived at the claimed dose via routine optimization of the amount and schedule of doses disclosed in the prior art, e.g. Goldenberg, Curd and De Vita. (Ex. 1002 ¶¶ 138-39.)

Claims 1 and 8 are therefore obvious over Goldenberg, Curd, and De Vita.

2. Independent Claim 2 Is Obvious

Claim 2 is directed to a method of treating RA in an inadequate responder, comprising administering an antibody that binds to CD20 in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond, wherein the antibody is administered as two intravenous doses of 1000 mg.

Every element of claim 2 is included in claim 1, except for an "ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond." As explained above with respect to claim construction, this element merely states potential clinical results and does not further limit claim 2. Goldenberg, Curd, and De Vita therefore render claim 2 obvious. (Ex. 1002 ¶¶ 138-39, 143.)

Assuming, arguendo, that this limitation is somehow limiting, a POSA would have understood that treatment with rituximab would results in clinical improvement of RA symptoms, as was disclosed in De Vita and Goldenberg. Therefore, a POSA motivated to treat inadequate responders with rituximab would have reasonably expected the recited clinical improvements. (Ex. 1002 ¶ 143.)

3. Independent Claim 10 Is Obvious

Claim 10 is directed to a method of treating an inadequate responder comprising administering rituximab and methotrexate, wherein the patient has no erosive progression at weeks 24 and beyond, and wherein rituximab is administered as two intravenous doses of 1000 mg.

Every element of claim 10 is included in claim 8, except for treatment with methotrexate and the clause "wherein the patient has no erosive progression at weeks 24 and beyond." As explained, a POSA would have been motivated to treat inadequate responders with methotrexate because Goldenberg and Curd each taught co-administration of methotrexate, and the prior art as a whole taught that refractory RA patients should be treated with combination therapy that includes methotrexate. "No erosive progression at weeks 24 and beyond" is a recitation of potential clinical results and is therefore not limiting. Claim 10 is therefore rendered obvious by Goldenberg, Curd, and De Vita for the same reasons discussed above with respect to claim 8. (Ex. 1002 ¶¶ 138-40, 143.)

Assuming, arguendo, that the stated results are limiting, claim 10 would have been obvious for the same reasons discussed above with respect to claim 2. (Ex. 1002 ¶ 143.)

4. Independent Claim 11 Is Obvious

Claim 11 is directed to a method of "achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond." The method requires administration of two intravenous doses of 1000 mg rituximab and methotrexate. As discussed, the phrase "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 the preamble is not limiting because it merely states a potential result. Therefore, claim 11 is obvious over Goldenberg, Curd, and De Vita for the reasons discussed above with respect to claims 1, 8, and 10. (Ex. 1002 ¶¶ 138-40, 143.)

Assuming, arguendo, that the claimed results are limiting, claim 11 would have been obvious for the same reasons discussed above with respect to claim 2.

5. Claim 3 Is Obvious

Claim 3 depends on claim 2 and specifies that the antibody is rituximab. For the reasons described above with respect to claim 2, claim 3 is obvious over Goldenberg, Curd, and De Vita. (*See id*. ¶¶ 138-39, 143.)

6. Claims 4 and 9 Are Obvious

Claims 4 and 9 depend on claims 2 and 8, respectively, and further require that the patient be treated with methotrexate. For the reasons discussed above with

respect to claims 2,8 and 10, claims 4 and 9 are obvious over Goldenberg, Curd, and De Vita. (Ex. 1002 ¶¶ 138-40, 143.)

7. Claim 5 Is Obvious

Claim 5 depends on claim 4 and further requires that the patient is treated with a corticosteroid. Goldenberg, Curd, and De Vita all disclose concomitant treatment with a steroid, and Curd discloses that the steroid should be a corticosteroid. (Ex.1031 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."); *see also* Ex. 1007 at 591 (disclosing that over 50% of RA patients are on concomitant corticosteroid therapy).) Thus, for the reasons discussed above with respect to claim 4, claim 5 is obvious over Goldenberg, Curd, and De Vita. (*See* Ex. 1002 ¶¶ 138-41, 143.)

8. Claim 6 Is Obvious

Claim 6 depends on claim 5 and further requires that the corticosteroid treatment consists of methylprednisolone and prednisone. As discussed above, approximately 50% of RA patients are treated with corticosteroids, including methylprednisolone and prednisone, and this was true as of 2003. (Ex. 1007 at 591; *see also* Ex. 1031 at 8:28- 29 (referring to "steroids such as glucocorticosteroids, e.g., prednisone, methylprednisolone, and dexamethasone").)

Claim 6 is therefore obvious over Goldenberg, Curd, and De Vita, for this reason and the reasons discussed above with respect to claim 5. (Ex. 1002 ¶¶ 138-41, 143.)

9. Claim 7 Is Obvious

Claim 7 depends on claim 2 and further requires that the CD20 antibody is the only B-cell surface marker antibody administered to the patient. Rituximab was the only antibody administered to the patients in De Vita. Thus, for the reasons discussed above with respect to claim 2, claim 7 is obvious over Goldenberg, Curd, and De Vita. (*See id*. ¶¶ 138-39, 142-43.)

10. Claims 12, 13, and 14 Are Obvious

Claims 12, 13, and 14 depend on claim 11 and further specify that the clinical response be ACR50 at week 24, ACR70 at week 24, and no erosive progression at week 24, respectively. As discussed above, these "wherein" clauses have no patentable weight because they merely state the potential outcome of practicing the claimed method. Therefore, claims 12, 13, and 14 are each identical in scope to claim 11 and are obvious over Goldenberg, Curd, and De Vita for the reasons discussed above with respect to claim 11. (Ex. 1002 ¶¶ 138-40, 143.)

Assuming, arguendo, that the claimed results are limiting, claims 12, 13, and 14 would have been obvious for the reasons discussed above with respect to claim 2. (Ex. 1002 ¶ 143.)

D. Secondary Considerations

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness, under either Ground 2 or Ground 3.

1. No Unexpected Results

With respect to Ground 2, all results that are achieved with the claimed regimen were also achieved by Edwards 2002, which disclosed the identical regimen. (Ex. 1002 ¶ 145.) Results that are achieved by a known method cannot be "unexpected." Further, the identification of a sub-population that was previously treated with the claimed dosage regimen cannot give rise to unexpected results. *See, e.g.*, *Abbvie v. Mathilda & Terence Kennedy Institute*, 764 F.3d 1366, 1369, 1380-81 (Fed. Cir. 2014) (using the results in the prior art, which taught treatment of RA patients with a TNFα-inhibitor and methotrexate, to show that the results of the claimed method, treatment of RA patients with "active disease" with a TNFα-inhibitor and methotrexate, were not unexpected). The results have been achieved regardless of whether the sub-population is specifically identified. Moreover, the results achieved with the claimed dosage regimen were also achieved by some patients who were inadequate responders in Edwards 2002 because it is "virtually 100%" certain that at least one of the patients in the Edwards 2002 trial was within the claimed sub-population of inadequate responders. (Ex. 1039 ¶ 7.)

It would not be unexpected that a patient who has failed a TNFα-inhibitor treatment would subsequently be successful on rituximab. In practice, rheumatologists often tried a new therapy for RA when a previous one fails, and failure of one, while an indication that a patient may be "hard-to-treat," did not mean that any subsequent successful treatment is an unexpected result. (Ex. 1002 ¶ 145; Ex. 1023 at I129.)

With respect to Ground 3, the prior art specifically taught that rituximab at doses both above and below the claimed doses successfully treated inadequate responders. Therefore, the results achieved with the claimed regimen are not unexpected. (Ex. 1002 ¶ 146.)

2. No Teaching Away

During prosecution, Patent Owner relied on Dr. van Vollenhoven's declaration stating that the prior art taught away from the claimed range, because the prior art, such as De Vita, taught higher dosages, and a POSA would have used higher doses for a hard-to-treat population. (Ex. 1045 at 12.) As discussed above, however, the prior art taught that a wide range of doses of rituximab, from 960 to 2550 mg, treated RA successfully. (Ex. 1035.) The claimed dose falls squarely within the prior art dose range and is identical to the dose used successfully in Edwards 2002. Moreover, it was within the skill of, and would have been routine for, a POSA to adjust and optimize the dose of rituximab to achieve the desired

claimed result as was done in Edwards 2002. (Ex. 1002 ¶ 147.) Thus, far from teaching away, the prior art taught the utility of the claimed dose. (*Id*.)

3. No Long-Felt But Unmet Need

During prosecution of the '606 application, Patent Owner, supported by a declaration by Dr. van Vollenhoven, argued that because the population of RA patients who are inadequate responders to TNFα-inhibitor treatment are so difficult to treat, there was a long-felt and unmet need for a new treatment for such patients, and that the regimen claimed in the patent met that need. (Ex. 1004 ¶¶ 7-8, 14.)

To the extent that there was any need, that need was met in 1997 when rituximab was first approved for use to treat non-Hodgkin's lymphoma. (Ex. 1002 ¶¶ 148-49.) The literature taught that an antibody that binds to CD20 cells such as rituximab would successfully treat many disease states in addition to non-Hodgkin's lymphoma, and disclosed significant off-label use of rituximab to treat those diseases. For example, Dr. Jeffery Gryn used rituximab off-label to treat a patient with myelofibrosis who was unable to receive red blood cell transfusion due to the presence of alloantibodies. (Ex. 1043.) Further, other physicians privately used rituximab off-label: Dr. van Vollenhoven used rituximab to treat lupus nephritis (Ex. 1004 ¶ 31); Dr. Gryn also suggested the use of rituximab to treat RA (Ex. 1009); Dr. John Looney suggested the use of rituximab to treat autoimmune diseases (Ex. 1020); and Dr. Jack Goldberg used rituximab to treat

patients with RA complicated by Felty's disease (Ex. 1036 ¶¶ 15-16). And, of course, Edwards 2002 reported on the use of rituximab to treat patients with RA. (Ex. 1033.) Therefore any need was met when rituximab was first approved. (Ex. 1002 ¶ 148.)

Further, even assuming arguendo that there was a need to treat patients who experience an inadequate response to TNFα-inhibitors, this need was not long-felt: the first TNFα-inhibitor was approved to treat RA in 1998, the second in 1999, and the third in 2002. Thus, any need could not have been "long-felt." *See, e.g.*, *In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d 367, 428 (S.D.N.Y. 2014), *aff'd sub nom. Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345 (Fed. Cir. 2016) ("The Court finds that the two-and-a-half-year period in between did not give rise to a *long-felt* need.").

4. Simultaneous Invention

As discussed above, many independent groups of physicians and researchers had treated RA with rituximab (and methotrexate) prior to 2003, including treating patients who had failed TNFα-inhibitor therapy. (Ex. 1002 ¶ 150.) This evidence supports a finding that the claimed method is obvious: "Independently made, simultaneous inventions, made within a comparatively short space of time, are persuasive evidence that the claimed apparatus was the product only of ordinary

mechanical or engineering skill." *George M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (quotations omitted).

5. No Skepticism by Persons of Ordinary Skill in the Art

Petitioner is not aware of any skepticism regarding the claimed method by persons of ordinary skill in the art. To the contrary, the evidence suggests that many people simultaneously treated (or suggested treatment of) RA with rituximab (and methotrexate), indicating that skilled persons would not have been skeptical that the claimed method would work, but rather would have had a reasonable expectation that such treatment would be successful. (Ex. 1002 ¶ 151.)

X. 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.

Respectfully submitted,

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List of Exhibits for U.S. Patent No. 7,976,838 Petition for *Inter Partes* Review

Exhibit No.	Description
1001	U.S. Patent 7,976,838
1002	Declaration of Maarten M. Boers, M.D.
1003	Curriculum Vitae of Maarten M. Boers, M.D.
1004	First Declaration of Ronald F. van Vollenhoven, dated October 6, 2010, submitted during prosecution of '838 patent on October 12, 2010
1005	Gabriel, *The Epidemiology of Rheumatoid Arthritis*, Rheumatoid Arthritis, 27(2) (2001)
1006	American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, *Guidelines for the Management of Rheumatoid Arthritis 2002 Update*, Arthritis & Rheumatism, 46(2):328-346 (February 2002)
1007	T. Pincus & C.M. Stein, *"No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?*, 15 Clinical & Experimental Rheumatology 591 (1997)
1008	Bijlsma et al., *Glucocorticoids in the treatment of early and late RA*, Ann Rheum Dis 2003;62:1033-7
1009	Gryn letter to Parker, dated May 6, 1998
1010	Kremer, *Methotrexate for Rheumatoid Arthritis*, Arthritis & Rheumatism, 37(3):316-328 (1994)
1011	O'Dell, *Methotrexate Use in Arthritis*, Rheumatic Disease Clinics of North America, 23(4) (1997)

1012	Boers et al., *Randomised Comparison of Combined Step-down Prednisolone, Methotrexate and Sulphasalazine with Sulphasalazine Alone in Early Rheumatoid Arthritis*, The Lancet, 350:309-18 (1997)
1013	Boers M, Tugwell P, Felson DT, van Riel PL, Kirwan JR, Edmonds JP, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. J Rheumatol Suppl 1994;41:86-9.
1014	Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35
1015	Genant et al., *Assessment of Rheumatoid Arthritis Using a Modified Scoring Method on Digitized and Original Radiographs*, Arthritis & Rheumatism, 41(9):1583-1590 (1998)
1016	Maini 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, 41(9):1552-1563 (1998)
1017	Seymour et al., *Anti-TNF agents for Rheumatoid Arthritis*, J. Clin. Pharmacol. 51, 201-08 (2001)
1018	Rubbert-Roth et al., *Treatment Options in Patients with Rheumatoid Arthritis Failing Initial TNF Inhibitor Therapy: A Critical Review*, Arthritis Research & Therapy 11(Suppl. 1):S1 (2009)
1019	Ismail Simsek, *Predictors of Response to TNF Inhibitors in Rheumatoid Arthritis,* BULLETIN OF THE NYU HOSPITAL FOR JOINT DISEASES 2012:70(3): 187-90
1020	Looney letter to Dutcher, dated January 15, 1999
1021	Third Declaration of Ronald F. van Vollenhoven, dated May 10, 2012

1022	EP1613350 – Patent Owner's Statement of Grounds for Appeal, dated May 10th, 2012
1023	Furst et al., *Access to disease modifying treatments for rheumatoid arthritis patients*, Ann. Rheum. Dis. 58: (Suppl I) I129-I130 (1999)
1024	Edwards et al., Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody is also Antigen, British Society for Rheumatology, 37:126-130 (1998)
1025	Physicians' Desk Reference for Remicade, 927-930 (2000)
1026	Maloney et al., *IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma*, Blood, 90(5):2188-2195 (1997)
1027	Rituxan® Drug Label 1997
1028	Maloney et al., Phase 1 Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients With Recurrent B··Cell Lymphoma, Blood, 84(8):2457-2466 (1994)
1029	Edwards et al., *Sustained Improvement in Rheumatoid arthritis following a protocol designed to deplete B lymphocytes*, Rheumatology, 40:205-211 (2001)
1030	The University College London Hospitals, The Joint UCL/UCLH Committees on the Ethics of Human Research, Treatment of subjects with rheumatoid arthritis with a monoclonal anti-CD20 antibody, October 23, 1998, Letter
1031	Curd et al., WO 00/67796 "*Treatment of Autoimmune Diseases with Antagonists which Bind to B Cell Surface Markers*," filed on May 4, 2000, published on Nov. 16, 2000
1032	De Vita et al., *Efficacy of Selective B Cell Blockade in the Treatment of Rheumatoid Arthritis*, Arthirtis & Rheumatism, 46(8):2029-2033 (2002)

1033	Edwards, Efficacy and Safety of Rituximab, a B-Cell Targeted Chimeric Monoclonal Antibody: A Randomized, Placebo-Controlled Trial in Patients with Rheumatoid Arthritis, Arth. & Rheum. 46(9):S197 (2002) ("Edwards 2002")
1034	Tuscano, *Successful Treatment of Infliximab-Refractory Arthritis with Rituximab*, Annual Scientific Meeting of the American College of Rheumatology, 3420 (2002) ("Tuscano")
1035	Leandro et al., *Clinical Outcome in 22 Patients with Rheuamtoid Arthritis Treated with B Lymphocyte Depletion*, Ann. Rhem. Dis., 61:883-888 (2002) ("Leandro")
1036	Declaration of Jack Goldberg, MD, FACP
1037	Curriculum Vitae of Jack Goldberg, M.D., F.A.C.P.
1038	Goldenberg WO 00/74718
1039	Declaration of M. Laurentius Marais, Ph.D.
1040	Can. Patent No. 2,461,714 (filed Sept. 26, 2002)
1041	Stanley B. Cohen et al., *Rituximab for Rheumatoid Arthritis Refractory to Anti-Tumor Necrosis Factor Therapy*, 54 Arthritis & Rheumatism 2793 (2006)
1042	Curriculum Vitae of M. Laurentius Marais, Ph.D.
1043	Gryn et al., *Clearance of erythrocyte allo-antibodies using Rituximab*, Bone Marrow Transplantation, 29:631–632 (2002)
1044	Decision of the Boards of Appeal of the European Patent Office relating to EP1613350, dated May 17, 2013

1045	Amendment filed in U.S. Patent Application 12/052,606, dated December 17, 2010
1046	William Schwieterman, *Immunosuppression in Combination with Monoclonal Antibodies*, Biologic Agents in Autoimmune Disease (March 2-4, 1995) ("FDA Conversation")
1047	Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA) (1999)
1048	Weinblatt et al., *A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate*, New England Journal of Medicine, 340(4):253-9 (1999)
1049	O'Dell, *Conventional DMARD Options for Patients with a Suboptimal Response to Methotrexate*, The Journal of Rheumatology, 62:21-26 (2001)
1050	Kalden et al., *Biologic Agents in the treatment of inflammatory rheumatic diseases*, 9:206-212 (1997)
1051	De Vita et al., *Pathogenetic Role of B Lymphocytes In Synovitis Arthritis: Selective B Cell Block Can Induce A Clinical Response In Patients With Refractory Rheumatoid Arthritis*, Reumatismo, 53:323 (2001)
1052	Declaration by Sarah Fink
1053	FDA, 64 Fed. Reg. 7898 (1999)
1054	Boers, *Demonstration of response in rheumatoid arthritis patients who are nonresponders according to the American College of Rheumatology 20% criteria: the paradox of beneficial treatment effects in nonresponders in the ATTRACT trial*, ARTHRITIS & RHEUMATISM, 44(11):2703-2704 (2001)

CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for Inter Partes Review of U.S. Patent No. 7,976,838 B2 contains 13,937 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: August 24, 2016

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that on August 24, 2016, I caused a true and correct copy of the foregoing materials:

- Petition for *Inter Partes Review* of U.S. Patent No. 7,976,838 B2, Claims 1-14 under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 et seq.;
- Exhibits 1001-1054; and
- List of Exhibits for Petition for *Inter Partes Review* of U.S. Patent No. (Ex.1001-1054)

To be served by Federal Express Next Business Day Delivery on the patent owner at the correspondence address of record for the subject patent as listed on PAIR:

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