

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Genentech, Inc. and
Biogen IDEC, Inc.
Patent Owner

Patent No. 7,820,161 B1

Issued: October 26, 2010

Filed: May 4, 2000

Inventors: John G. Curd, Lori A. Kunkel, and Antonio J. Grillo-López

Title: TREATMENT OF AUTOIMMUNE DISEASES

Inter Partes Review No. TBD

PETITION FOR INTER PARTES REVIEW

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I. PRELIMINARY STATEMENT

The challenged claims of U.S. Patent No. 7,820,161 (“the ’161 patent”) (Ex. 1001) relate to methods of treating rheumatoid arthritis (“RA”) with two known therapeutic agents—rituximab and methotrexate. During prosecution, the patentees tried and failed to obtain a patent directed to treating RA with rituximab alone. After seven years, the patentees cancelled the pending claims directed to rituximab as a lone therapeutic agent and amended the remaining claims to require the co-administration of methotrexate—*i.e.*, the most popular and effective drug for treating RA known in the prior art. Such combination therapies had demonstrated so much promise in the prior art that, before the earliest priority date of the ’161 patent, the United States Food and Drug Administration (“FDA”) told the drug development industry that “it is inevitable that new agents [for RA] will be used in combination with methotrexate in clinical practice unless a contraindication exists,” and that “data regarding use of the [new] investigational agent in combination with methotrexate [were] needed to evaluate the potential for immunosuppression from combination therapy.” (Ex. 1011 at 18; Ex. 1012 at 18.)¹ The challenged claims are unpatentable as obvious in light of the prior art.

Treating RA with rituximab was well known before the earliest priority date of the ’161 patent. This is why the patentees could not obtain a patent directed to

¹ All page numbers cited herein refer to the original pagination of the exhibits.

treating RA with rituximab alone. In fact, two separate doctors proposed treating RA with rituximab. In March 1998, Dr. Jonathan C.W. Edwards published a paper linking the treatment of RA with the killing of mature B-cells. (Ex. 1025.) Dr. Edwards noted that the destruction of mature B-cells can be achieved with an anti-CD20 antibody, and rituximab specifically, with minimal unwanted effects. (*Id.* at 129-30.) Separately, in a letter dated May 6, 1998, an oncologist named Dr. Jeffrey Gryn wrote to IDEC Pharmaceuticals² and proposed a pilot study on the effect of rituximab in patients suffering from autoimmune diseases, including RA. (Ex. 1026.) The patentees submitted Dr. Gryn's letter in an IDS during prosecution of the '161 patent. (Ex. 1007.) The Gryn letter confirms that those with no more than an ordinary level of skill recognized before the priority date of the '161 patent that rituximab was useful for treating RA.

Treating RA with methotrexate was also well known in the prior art. Methotrexate was not only the most commonly-used RA drug, but also the first drug prescribed by rheumatologists in the United States for treating RA patients. (*See* Ex. 1003 at 779 (“To overstate the importance of methotrexate in the contemporary management of rheumatoid arthritis (RA) would be difficult.”).) Indeed, methotrexate had achieved a position of “therapeutic dominance” before

² IDEC was a predecessor to Biogen Idec, one of the two assignees of the '161 patent.

the earliest priority date of the '161 patent due to its demonstrated efficacy and long-term tolerability. (Ex. 1017 at 847.)

A person of ordinary skill had compelling reasons to combine rituximab with methotrexate and other therapeutic agents to treat RA. By 1997, the use of combination therapies to treat RA had “increased dramatically” and “over 90% of rheumatologists used combinations” to treat RA. (Ex. 1003 at 789.) The prior art established that “most would agree . . . that methotrexate should be the cornerstone of most combinations,” and that “it is also the standard against which combinations should be measured.” (*Id.* at 790.) Indeed, it was “advantageous from both a clinical and a business standpoint to develop most drugs in RA at [that] time for use in combination with methotrexate.” (Ex. 1008 at 592.) The consensus among persons of ordinary skill was that the combination of biological agents with methotrexate was of “special value” when treating RA. (Ex. 1020 at S-96.)

All elements of the challenged claims were well known to a person of ordinary skill, who had a strong reason to combine the elements as claimed. The available clinical and experimental data associated with combination therapies provided a person of ordinary skill with a reasonable expectation of success when combining rituximab and methotrexate. Moreover, the dependent claims of the '161 patent relate to specific dosing amounts and other established RA treatments (*e.g.*, glucocorticosteroids)—all of which had been known for years in the prior art.

This petition will show that the challenged claims would have been obvious to a person of ordinary skill at the time of the alleged invention. For the reasons set forth below, the challenged claims should be found unpatentable.

II. MANDATORY NOTICES

A. Real Parties-in-Interest or Privies

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

B. Related Matters

Simultaneously with this petition, Petitioner has filed petitions for Inter Partes Review against United States Patent Nos. 7,976,838 and 8,329,172. The following patents and patent applications may claim the benefit of the priority of the filing date of U.S. Patent No. 7,820,161: U.S. Patent No. 8,545,843 (USSN 12/886171), and USSN 13/969276.

C. Lead and Back-Up Counsel

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III. CERTIFICATION OF GROUNDS FOR STANDING

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

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

Petitioner challenges claims 1-12 of the '161 patent (Ex. 1001) as unpatentable under 35 U.S.C. § 103 on the specific grounds set forth in Section IX below. This petition is supported by the Declaration of Joachim R. Kalden, M.D., submitted herewith (Ex. 1002). The petition and supporting declaration show that there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. *See* 35 U.S.C. § 314(a).

V. SUMMARY OF THE '161 PATENT AND PROSECUTION HISTORY

The '161 patent (Ex. 1001) issued on October 26, 2010, from Application Ser. No. 09/564,288 ("the '288 application") (Ex. 1027), which was filed on May

4, 2000. The '288 application claimed priority to two provisional applications filed on May 7, 1999 and June 17, 1999, respectfully. The earliest priority date associated with the '161 patent is May 7, 1999. Therefore, any publication prior to May 7, 1998 will qualify as prior art under 35 U.S.C. §102(b).

A. The Claims of the '161 Patent

1. Independent Claims 1, 5, and 9

Claims 1, 5, and 9 of the '161 patent are shown in the table below. The three claims are identical in substance. Claims 5 and 9 simply replace the term “rituximab” in claim 1 with the following language: “an antibody that binds to the CD20 antigen on human B lymphocytes.” Claims 5 and 9 then add a “wherein” clause that: (i) repeats the requirement from step (a) that administration must be intravenous; and (ii) defines the “CD20 antibody” as “rituximab.” Because rituximab is, by definition, “an antibody that binds to the CD20 antigen on human B lymphocytes” (Ex. 1002 at ¶ 84), independent claims 1, 5, and 9 are identical in scope.

| Claim 1 | Claim 5 | Claim 9 |
|--|--|--|
| 1. A method of treating rheumatoid arthritis in a human comprising: (a) administering to the human more than one intravenous dose of a therapeutically effective amount of <u>rituximab</u> ; | 5. A method of treating rheumatoid arthritis in a human comprising: (a) administering to the human more than one intravenous dose of a therapeutically effective amount of <u>an antibody</u> | 9. A method of treating rheumatoid arthritis in a human comprising: (a) administering to the human more than one intravenous dose of a therapeutically effective amount of <u>an antibody</u> |

| Claim 1 | Claim 5 | Claim 9 |
|--|--|---|
| <p>and</p> <p>(b) administering to the human methotrexate.</p> | <p><u>that binds to the CD20 antigen on human B lymphocytes; and</u></p> <p>(b) administering to the human methotrexate;</p> <p><u>wherein the CD20 antibody administration consists of intravenous administration of the CD20 antibody, and the CD20 antibody is rituximab.</u></p> | <p><u>that binds to the CD20 antigen on human B lymphocytes; and</u></p> <p>(b) administering to the human methotrexate;</p> <p><u>wherein the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab.</u></p> |

2. Dependent Claims 2-4, 6-8, and 10-12

The '161 patent contains three sets of dependent claims. The first set of dependent claims (claims 2, 6, and 10) require a dose of the antibody (*i.e.*, rituximab) in the range “from about 250 mg/m² to about 1000 mg/m².” The only difference between these dependent claims is that claims 6 and 10 replace the term “rituximab” that appears in claim 2 with the word “antibody.” But again, the underlying independent claims define the claimed “antibody” as “rituximab.” In fact, claims 2, 6 and 10 are identical in scope because the claims from which they depend are also identical in scope. The full text of claims 2, 6, and 10 are shown in the table below.

| Claim 2 | Claim 6 | Claim 10 |
|---|--|---|
| 2. The method of claim 1, wherein each administration of the <u>rituximab</u> is a dose in the range from about 250 mg/m ² to about 1000 mg/m ² . | 6. The method of claim 5, wherein each administration of the <u>antibody</u> is a dose in the range from about 250 mg/m ² to about 1000 mg/m ² . | 10. The method of claim 9, wherein each administration of the <u>antibody</u> is a dose in the range from about 250 mg/m ² to about 1000 mg/m ² . |

The second set of dependent claims in the '161 patent (claims 3, 7, 11) require the administration of a “glucocorticosteroid” to the human mentioned in the independent claims. Dependent claims 3, 7, and 11 are identical in scope given that the claims from which they depend are also identical in scope.

| Claim 3 | Claim 7 | Claim 11 |
|--|--|---|
| 3. The method of claim 1, comprising administering to the human a glucocorticosteroid. | 7. The method of claim 5, comprising administering to the human a glucocorticosteroid. | 11. The method of claim 9, comprising administering to the human a glucocorticosteroid. |

The third set of dependent claims (claims 4, 8, and 12) are also identical in scope. They each require a subsequent dose of antibody (*i.e.*, rituximab) that exceeds the initial dose. The only difference between these dependent claims is that claims 8 and 12 replace the term “rituximab” that appears in claim 4 with the word “antibody.” Here again, the underlying independent claims define the claimed “antibody” as “rituximab.” The full text of claims 4, 8, and 12 are shown in the table below.

| Claim 4 | Claim 8 | Claim 12 |
|---|--|---|
| 4. The method of claim 1, comprising administering an initial dose of the rituximab followed by a subsequent dose, where the mg/m ² dose of the <u>rituximab</u> in the subsequent dose exceeds the mg/m ² dose of the rituximab in the initial dose. | 8. The method of claim 5, comprising administering an initial dose of the antibody followed by a subsequent dose, where the mg/m ² dose of the <u>antibody</u> in the subsequent dose exceeds the mg/m ² dose of the antibody in the initial dose. | 12. The method of claim 9, comprising administering an initial dose of the antibody followed by a subsequent dose, where the mg/m ² dose of the <u>antibody</u> in the subsequent dose exceeds the mg/m ² dose of the antibody in the initial dose. |

B. Specification of the '161 Patent

The '161 patent characterizes the alleged invention as follows: “[t]he present invention concerns treatment of autoimmune diseases with antagonists which bind to B cell surface markers, such as CD19 or CD20.” (Ex. 1001 at 1:13-15.)

The specification provides three examples of treating autoimmune diseases with rituximab (*i.e.*, RITUXAN®).³ Example 1 relates to patients with RA. (*Id.* at 27:35-67.) Example 2 relates to patients with autoimmune hemolytic anemia (AIHA). (*Id.* at 28:1-31.) Example 3 relates to patients with adult immune thrombocytopenic purpura (ITP). (*Id.* at 28:33-29:41.) All of these examples recommend three specific dosing schedules, including “375 mg/m² IV days 1, 8, 15

³ See Ex. 1001 at 8:61-64 (“The terms ‘rituximab’ or ‘RITUXAN®’ herein refer to the genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen and designated ‘C2B8’ in U.S. Pat. No. 5,736,137 . . .”).

& 22.” (*Id.* at 27:59, 28:15, 29:9.) This is the same dosing and administration recommended for treating non-Hodgkin’s lymphomas, as provided in the FDA-approved product insert for rituximab, dated November 1997. (*See* Ex. 1006 at 2 (“The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22).”))

C. Prosecution History of the ’161 Patent

1. The Patentees Were Not Successful in Their Attempt to Patent the Treatment of RA with Rituximab Alone

The ’288 application, filed on May 4, 2000, included 26 claims, including claims that covered the use of a single antagonist or antibody (*e.g.*, rituximab) for treating autoimmune diseases. (*See* Ex. 1027 at 46-49.) The patentees maintained claims directed to the use of a single antagonist or antibody through a series of Office Actions and rejections over the course of seven years. Ultimately, however, none of these original claims issued.

In a Request for Continued Examination, dated June 20, 2006, the patentees proposed a new claim that, for the first time, included a limitation directed to the administration of “at least one other therapeutic agent” to treat RA. (Ex. 1028 at 10.) That new claim (claim 185) was subsequently amended and issued as claim 1 of the ’161 patent.

2. The Patentees Canceled the Original Claims Directed to Treating RA with Rituximab Alone in the Face of Edwards 1998 and Other Art

On February 7, 2007, the Examiner issued an Office Action that rejected certain pending claims as anticipated by a 1998 publication by Dr. Edwards (Ex. 1025). (*See* Ex. 1029 at ¶ 13.)

The patentees responded on December 5, 2007, by: (i) cancelling the rejected claims directed to treating RA with rituximab as a lone therapeutic agent; and (ii) amending other claims (including claim 185) to include a limitation requiring the administration of methotrexate in combination with an anti-CD20 antibody. (*See* Ex. 1030 at 3-4.)

Following another Office Action, dated June 29, 2009 (Ex. 1031), the patentees canceled then-pending independent claim 172 and further limited claim 185 to a method comprising the combination of methotrexate and rituximab. (*See* Ex. 1032 at 2, 4.) The pending claims were later allowed on the basis of arguments and two declarations submitted by Dr. van Vollenhoven. (*See* Ex. 1014; Ex. 1015.) Dr. van Vollenhoven's declarations regarding alleged unexpected results are addressed below in Section X.

3. The Patentees' Rule 131 Declaration Alleging Prior Invention Related Only to Cancelled Claims Directed to a Single Therapeutic Agent

In 2003, before the pending claims had limitations directed to methotrexate, the applicants submitted a declaration pursuant to 37 C.F.R. § 1.131 (“Rule 131”) alleging conception of treating autoimmune diseases with rituximab “prior to May 6, 1998.” (Ex. 1010 at ¶ 5.) As evidence of conception, the declaration pointed to “a presentation that Dr. Antonio Grillo-Lopez prepared and delivered [in August 1997] that disclosed, among other things, the use of Rituxan [rituximab] . . . to treat . . . autoimmune diseases.” (*Id.* at ¶ 6.) Notably, however, the declaration and accompanying presentation do not reference several key elements of the challenged claims, including: (i) treating RA with rituximab; (ii) administering methotrexate; (iii) any details regarding the frequency or amount of rituximab dosing; and (iv) administering a glucocorticosteroid. (*See generally id.* at 6-19.)

The Rule 131 declaration and the attached presentation submitted by the applicants are not probative evidence of conception of the challenged claims because they do not establish that the applicants had a definite and permanent idea of the “complete and operative invention.” *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986) (“Conception is the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention”) (internal quotation marks omitted).

Indeed, the materials provided by the applicants fail to address the vast majority of limitations in the claims that ultimately issued in the '161 patent. *See Singh v. Brake*, 317 F.3d 1334, 1340 (Fed. Cir. 2002) (“A conception must encompass all limitations of the claimed invention . . .”).

VI. CLAIM CONSTRUCTION

Because the '161 patent has not yet expired, the challenged claims should be given their broadest reasonable construction in light of the specification of the patent. 37 C.F.R. § 42.100(b).

The broadest reasonable construction of independent claims 1, 5, and 9 includes the administration to a human of: (a) two or more intravenous doses of a therapeutically effective amount of rituximab, an anti-CD20 monoclonal antibody; and (b) at least one dose of methotrexate. The independent claims do not specify the amount or the timing of the doses of either rituximab or methotrexate. The independent claims also do not specify an order for the required doses, meaning that the doses could be given in any order or concurrently. Further, the independent claims do not identify the method of administration for methotrexate. Nor do they require a therapeutically-effective dose of methotrexate.

Dependent claims 2, 6, and 10 include a wide range of rituximab doses “from about 250 mg/m² to about 1000 mg/m².” The broadest reasonable

interpretation of these claims would include doses ranging from some amount less than 250 mg/m² to some amount greater than 1000 mg/m².

Dependent claims 3, 7, and 11 require the administration of a glucocorticosteroid to a human. These claims do not specify a dose amount, order of dosing, or method of administration. Nor do these claims require multiple doses of the glucocorticosteroid or a therapeutically-effective dose.

Finally, dependent claims 4, 8 and 12 recite that the amount of rituximab in a subsequent dose exceeds the amount of rituximab in the initial dose. The broadest reasonable interpretation of these claims would include, at minimum, two doses, where the second dose is larger than the first by some incremental amount, however small.

VII. LEVEL OF ORDINARY SKILL

RA is a chronic inflammatory disorder that affects tens of millions of people worldwide, causing pain, stiffness and swelling of joints, most often in the hands and feet. (Ex. 1002 at ¶ 37.) RA is an autoimmune disease, the cause of which is not known. (*Id.* at ¶ 38.) There is no known cure for RA. (*Id.* at ¶ 38.) The disorder has been the subject of substantial research and published literature concerning the treatment of patients and new RA therapies. (*Id.* at ¶¶ 35, 38.) Many practicing rheumatologists are involved with clinical trials involving new drugs and methods of treatment. (*Id.* at ¶ 35.) For this reason, doctors in the field

of rheumatology tend to be well informed about current trends and developing therapies for treating RA. (*Id.*)

In light of the specification, the references of record, and other available evidence, a person of ordinary skill at the time of the invention would have been a practicing rheumatologist with a medical degree and: (i) at least 2-3 years of experience treating RA patients; (ii) an understanding of the pathophysiology of RA; and (iii) knowledge about the available methods of treating RA. (*Id.* at ¶ 36.)

VIII. THE STATE OF THE PRIOR ART

A. Rituximab and the Depletion of B-Cells

Rituximab is a monoclonal antibody created by IDEC Pharmaceuticals (now Biogen IDEC) in the early 1990s and developed in conjunction with Genentech since 1995. Rituximab is sold under the brand name Rituxan® and Mabthera® in the United States and Europe, respectively. Early in its development, rituximab was also known as “IDEC-C2B8.” (Ex. 1002 at ¶ 40.) Rituximab’s efficacy in treating RA is derived from its well-publicized ability to destroy mature B-cells without being toxic to patients. (*Id.*)

1. 1997 FDA-Approved RITUXAN® Product Insert

In 1997, the FDA approved the use of rituximab for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin’s lymphoma. The FDA-approved product insert for rituximab, dated November

1997 (“FDA label”), constitutes prior art under 35 U.S.C. § 102(b). (*See* Ex. 1006.)

The FDA label states: “The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.” (Ex. 1006 at 1.) The FDA label also described rituximab as “a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration.” (*Id.*)

The FDA label provided that the recommended dosage for rituximab was “375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15 and 22).” (*Id.* at 2.) The label also discussed the pharmacokinetics of rituximab in patients given single doses at 10, 50, 250, and 500 mg/m² as an IV infusion. (*Id.* at 1.)

Finally, the FDA label notes that “[a]dministration of RITUXAN resulted in a rapid and sustained depletion of circulating and issue-based B cells.” (*Id.* at 2.) In fact, “[a]mong the 166 patients in the pivotal study, circulating B-cells . . . were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients.” (*Id.*)

2. 1994 Maloney et al. Publication

In 1994, Maloney et al. published a paper titled, “Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma” (“Maloney 1994”). (*See* Ex. 1023.) The publication is prior art under 35 U.S.C. §102(b).

The Maloney 1994 reference described “the first phase I clinical trial of single-dose infusion with the chimeric anti-CD20 antibody (IDEC-C2B8) [*i.e.*, rituximab] in patients with relapsed B-cell NHL [non-Hodgkin’s lymphoma].” (Ex. 1023 at 2457.) The paper began by noting that “[t]he B-cell antigen CD20 is expressed on normal B cells and by nearly all B-cell lymphomas.” (*Id.* at 2457.) The paper observed that “[t]here was a dose-dependent, rapid and specific depletion of the B cells in all patients especially those receiving [rituximab] doses of more than 100 mg.” (*Id.* at 2460.) All patients completed the planned antibody infusion with minimal infusional-related toxicity. (*See id.* at 2460, 2436; *see also* Ex. 1002 at ¶ 40.) The paper concluded: “Ultimately, extension of these studies to patients with minimal residual disease, using antibody alone or in combination with conventional therapies, may provide the greatest benefit.” (Ex. 1023 at 2465.)

3. 1997 Maloney et al. Publication

In 1997, Maloney et al. published another paper titled, “IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed

Low-Grade non-Hodgkin's Lymphoma" ("Maloney 1997"). (See Ex. 1024.) The publication is prior art under 35 U.S.C. §102(b).

The Maloney 1997 reference reported the results of a phase II evaluation for rituximab on "the clinical results obtained in the treatment of 37 patients with relapsed low-grade or follicular lymphoma." (Ex. 1024 at 2189.) The paper noted: "IDEC-C2B8 [rituximab] is a chimeric monoclonal antibody (MoAb) directed against the B-cell-specific antigen CD20 expressed on non-Hodgkin's lymphomas (NHL)." (*Id.* at 2188.) Patients received dose levels of rituximab at 375 mg/m² for four weeks. (*Id.* at 2189-90.) The paper observed: "As expected, normal B cells were rapidly deleted from the peripheral blood of nearly all patients and remained depleted until nearly 6 months posttreatment, followed by a slow recovery." (*Id.* at 2193.) Finally, the publication concluded that rituximab "presents the opportunity to obtain meaningful tumor reductions with minimal toxicity in patients with relapsed low-grade NHL." (*Id.* at 2194.)

B. Treating RA with Rituximab By Destroying Mature B-Cells

1. 1995 Edwards Publication

In 1995, Dr. Edwards co-authored a publication titled, "Is rheumatoid arthritis a failure of B cell death in synovium?" ("Edwards 1995"). (See Ex. 1035.) The publication is prior art under 35 U.S.C. §102(b).

The Edwards 1995 paper states: “It is proposed that RA is a failure of cell death, but one which is lineage specific to B cells and site specific to synovium.” (Ex. 1035 at 696.) After discussing issues related to B lymphocyte survival and the synovial intimal cells in joint issue (*id.* at 696-97), the paper concludes by referring to “new avenues to explore” in terms of future RA therapies. (*Id.* at 699.)

2. 1998 Edwards Publication

In 1998, Dr. Edwards co-authored another publication titled, “Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody Is Also Antigen” (“Edwards 1998”). (*See* Ex. 1025.) The publication appeared in the British Journal of Rheumatology in February 1998. The publication is prior art under 35 U.S.C. §102(b).

In the Edwards 1998 reference, Dr. Edwards proposed treating RA by killing B cells. (Ex. 1025 at 128-29 (“An alternative strategy may be simpler: to kill all B cells.”).) According to the publication, destroying mature B cells “should allow anti-non-self B-cell clones, but not pathogenic IgG RF-producing clones, to re-emerge.” (*Id.* at 129.) Dr. Edwards also noted, with specific reference to the Maloney 1994 publication and its use of rituximab, that “[r]ecent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects, since B cells are produced rapidly and Ig levels are maintained in the short term.” (*Id.* at 129-30.)

3. 1998 Gryn Letter

In 1998, only a few months after the publication of Edwards 1998, an oncologist named Dr. Jeffrey Gryn wrote to IDEC Pharmaceuticals and proposed a pilot study on the effect of rituximab on autoimmune diseases, including RA (“Gryn”). (*See* Ex. 1026.) The letter is dated May 6, 1998, and it is marked with a “RECEIVED” stamp dated May 14, 1998. (*See id.* at 1.) The patentee submitted Dr. Gryn’s letter in an Information Disclosure Statement, dated November 3, 2000. (Ex. 1007.) The letter is a “printed publication” by virtue of the fact it was sent to a commercial entity (*i.e.*, IDEC Pharmaceuticals) without any confidentiality or other restrictions on use. *See Garret Corp. v. United States*, 422 F.2d 874, 878 (Ct. Cl. 1970) (“While distribution to government agencies and personnel alone may not constitute publication . . . distribution to commercial companies without restriction on use clearly does.”). Moreover, the letter became available as prior art at least by the day it was received—May 14, 1998. *See, e.g.*, MPEP § 2128.02 (“A publication disseminated by mail is not prior art until it is received by at least one member of the public.”). Accordingly, Gryn is prior art under at least 35 U.S.C. §102(a).

Dr. Gryn’s letter evidences what was already recognized by persons of no more than the ordinary level of skill: rituximab was useful for treating RA. (*See* Ex. 1002 at ¶ 44.) Dr. Gryn based his proposed pilot study on the observation that

“[o]ncology patients treated with Rituxin [sic] demonstrate a marked reduction in circulating immunoglobulin levels.” (Ex. 1026 at 2.) Dr. Gryn wrote that rituximab “offers the opportunity to treat [autoimmune] diseases with an agent that affects only B-lymphocytes.” (*Id.* at 2.) He explained:

Since many autoimmune diseases are associated with or caused by antibodies, treatment of these diseases with Rituxin [sic] offers an interesting alternative. I believe that suppression of B-cells with Rituxin [sic] could lead to non-toxic remissions in these diseases.

(*Id.* at 1.)

Dr. Gryn proposed that his pilot study explore the effect of rituximab on “diseases with an autoimmune etiology such as: Rheumatoid Arthritis....” (Ex. 1026 at 2.) Dr. Gryn also noted the “limited toxicity” of rituximab and proposed that it be administered in its “standard dose.” (*Id.*)

C. Methotrexate: the “Gold Standard” and Dominant Therapy for Treating Rheumatoid Arthritis

Methotrexate is an anti-folate drug used in the treatment of autoimmune diseases, including RA; it has also been used at high doses as a treatment for certain types of cancer. (Ex. 1002 at ¶ 46.) Methotrexate is an example of a disease-modifying anti-rheumatic drug (DMARD), a term used generally to describe therapies that improve clinical disease activity and slow the progression of RA, for example, by reducing the rate of damage to bone and cartilage. (*Id.*) The

efficacy and safety of methotrexate as a treatment for RA was clearly established in the literature before the earliest priority date of the '161 patent. (*Id.* at ¶¶ 47-48.)

1. 1995 Kremer Publication

In 1995, Dr. Joel Kremer published a paper titled, “The Changing Face of Therapy for Rheumatoid Arthritis” (“Kremer 1995”). (*See* Ex. 1017.) The publication is prior art under 35 U.S.C. §102(b).

The Kremer 1995 reference states: “In the last decade, the major change in the therapeutic approach to the treatment of patients with RA has been the widespread use and universal acceptance of methotrexate.” (Ex. 1017 at 846.) The paper noted that “recent anecdotal surveys at clinical meetings within the United States indicate that virtually all rheumatologists use methotrexate, and at least half consider the drug to be a first-line agent that should be used before gold salts.” (*Id.* at 846.) The paper commented that “the movement towards the earlier and more widespread use of methotrexate can be viewed as nothing short of revolutionary.” (*Id.* at 847.) As of the date of publication in 1995, Dr. Kremer wrote that “[m]ethotrexate has achieved a position of therapeutic dominance because of its demonstrated efficacy and long-term tolerability.” (*Id.*)

2. 1996 O'Dell Publication

In 1996, O'Dell et al. published a paper titled, "Treatment of Rheumatoid Arthritis with Methotrexate Alone, Sulfasalazine and Hydroxychloroquine, or a Combination of All Three Medications" ("O'Dell 1996"). (*See* Ex. 1004.) The publication is prior art under 35 U.S.C. §102(b).

The O'Dell 1996 reference described a study designed to determine "whether disease modifying drugs were effective as combination therapy for rheumatoid arthritis and whether the combinations studied had better efficacy than methotrexate alone." (Ex. 1004 at 1287.) The paper noted that because "[t]he responses of patients with rheumatoid arthritis to treatment with a single so-called disease-modifying drug, such as methotrexate, are often suboptimal . . . many patients are treated with combinations of these drugs." (*Id.*) Notably, the paper referred to methotrexate alone as "currently the gold standard of treatment for rheumatoid arthritis." (*Id.* at 1290.) The results of the study showed a "50 percent or greater improvement" in patients receiving the combination therapy (also including methotrexate) compared to methotrexate alone. (*Id.*)

D. Combination RA Therapies Involving Methotrexate

In the mid-late 1990s, physicians treating RA patients who did not respond completely to methotrexate would not discontinue treatment, but rather would initially change the route of administration—*e.g.*, from oral to subcutaneous or

intramuscular—and increase the dose. (Ex. 1002 at ¶ 51.) Where RA was not controlled adequately by high doses of methotrexate, physicians would use combination therapies involving methotrexate, as disclosed in the literature. (*Id.* at ¶¶ 52-65.)

1. O’Dell 1997 Publication

In 1997, O’Dell published another paper titled, “Methotrexate Use in Rheumatoid Arthritis” (“O’Dell 1997”). (*See* Ex. 1003.) The publication is prior art under 35 U.S.C. §102(b).

The O’Dell 1997 reference began by saying “[t]o overstate the importance of methotrexate in the contemporary management of rheumatoid arthritis (RA) would be difficult.” (Ex. 1003 at 779.) O’Dell noted that methotrexate was “the disease-modifying antirheumatic drug (DMARD) most commonly used to treat RA.” (*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.” (*Id.*)

The O’Dell 1997 reference discussed the benefits of combination therapies involving methotrexate. On this issue, the paper explained:

Even though few would argue that methotrexate is the single most effective DMARD available, clearly if obtaining or at least approaching remission for patients is the goal, methotrexate alone isn't the answer. Many

clinicians, therefore, have added other DMARDs to methotrexate in patients who have had partial responses, a use of so-called combination therapy.

(*Id.* at 782.) The paper refers to methotrexate as the “cornerstone” of most combinations and “the standard against which combinations should be measured.”

(*Id.* at 790.) Indeed, “[b]ecause 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 included methotrexate.” (*Id.*) According to O’Dell 1997, methotrexate “should be the foundation of most combination therapies” (*Id.* at 792.) The paper concludes: “[c]ontinued research on combinations of DMARDs, as well as combinations that include biologic agents and methotrexate and possibly other DMARDs, is necessary.” (*Id.*)

2. 1997 Pincus Publication

In 1997, Pincus et al. published an editorial titled, “‘No evidence of disease’ in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?” (“Pincus 1997”). (*See* Ex. 1008.) The publication is prior art under 35 U.S.C. §102(b).

The Pincus 1997 reference noted “a strong trend toward the use of combination disease-modifying anti-rheumatic drugs (DMARDs), at least by U.S. rheumatologists.” (Ex. 1008 at 591.) The paper stated that “toxicities of the most

effective DMARD, methotrexate, alone or even in combination, may be less than those of many [alternative treatments].” (*Id.* at 592.) The paper then observed that “[m]any patients with early RA appear to be reasonable candidates for early methotrexate therapy, or ‘combination’ DMARD therapy with methotrexate as the cornerstone.” (*Id.*)

The Pincus 1997 reference also stated that biotechnology products and other RA drugs “should be tested in combination with methotrexate for approval in marketing, particularly as this is how they are likely to be used.” (*Id.* at 593.) Notably, Pincus et al. identified an economic incentive to combine methotrexate with other RA drugs during pharmaceutical development:

While the use of drugs in combination is not a traditional strategy in pharmaceutical development, the fact that more than 50% of patients with RA under the care of rheumatologists in the U.S. take methotrexate suggests that it may be advantageous from both a clinical and a business standpoint to develop most drugs in RA at this time for use in combination with methotrexate.

(*Id.*)

3. Kremer 1998 Publication

In 1998, Joel Kremer published an editorial titled, “Combination Therapy with Biologic Agents in Rheumatoid Arthritis: Perils and Promise” (“Kremer

1998”). (See Ex. 1009.) The publication is prior art under at least 35 U.S.C. §102(a).

Kremer 1998 states that methotrexate was “accepted as the most efficacious and best-tolerated single agent for the treatment of rheumatoid arthritis (RA).” (Ex. 1009 at 1548.) The paper then added that “virtually all” new RA treatments were being tested in combination with methotrexate. (*Id.* (“Virtually all of the new treatment modalities are currently being tested with MTX in patients who have active disease despite an adequate weekly dose of the drug.”).)

With specific reference to biotechnology-derived RA treatments, Kremer 1998 states: “Most of the new biotechnology-derived therapeutic interventions are being studied as both monotherapy and combination therapy with MTX [methotrexate].” (Ex. 1009 at 1548.) The paper even describes the “ideal biotechnology combination study with MTX.” (*See id.* at 1549.) After discussing biologic agents designed to treat RA by targeting a specific molecule (*e.g.*, TNF α and IL-1 β inhibitors), the publication reached the following conclusion:

[T]hese and other biotechnology interventions are, quite reasonably, being empirically combined with MTX while hoping for the best. This approach can, and should, be advocated because our patients simply do not have the time to wait until we determine how all of the new and existing drugs work, let alone how MTX works.

(*Id.* at 1549-50.)

4. 1995 FDA CBER Meeting

In March 1995, the FDA Center for Biologics Evaluation and Research (“CBER”) met to discuss the use of antibodies and other biologics in treating autoimmune diseases, such as RA. The meeting comments were published under the title, “Immunosuppression in Combination with Monoclonal Antibodies,” by Dr. William Schweiterman (“FDA CBER”). (*See* Ex. 1005.) The publication is prior art under 35 U.S.C. §102(b).

The meeting comments discussed using methotrexate as “background therapy” in combination with biologic agents, such as monoclonal antibodies, particularly in phase II clinical studies. During the discussion, one of the doctors noted that methotrexate was “a dominant drug in the U.S.,” and he stated that “the population, from both a practical and commercial standpoint, that we would be interested in looking at [for Phase I and Phase II studies] [are] not patients withdrawn from methotrexate, but rather, incomplete responders on it.” (Ex. 1005 at 294.) On this issue, Dr. Schweiterman responded: “If the Phase I studies off methotrexate are shown to be safe . . . I think it is perfectly appropriate to go into a methotrexate-treated patient population, provided that what you have learned in Phase I is employed in Phase II.” (*Id.* at 295.)

5. Kalden 1997 Publication

In 1997, Dr. Joachim Kalden (from whom a declaration is being submitted in support of this petition) published a paper titled, “Rescue of DMARD failures by means of monoclonal antibodies or biological agents” (“Kalden 1997”) (Ex. 1020). The publication is prior art under 35 U.S.C. §102(b).

The paper stated that, as of early-mid 1997, “[i]nitial attempts [were] presently being conducted to test combination therapies, using monoclonal antibodies directed against the proinflammatory cytokines and cell surface molecules, and long-acting rheumatic drugs such as methotrexate.” (Ex. 1020 at S-91.) The paper commented on recent studies involving combination therapies involving biological agents and methotrexate. For example, the paper stated: “Combining methotrexate and the repeated administration of anti-TNF- α MAb cA2, Kavanaugh *et al.* demonstrated that combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone.” (*Id.* at S-96) (citation omitted.) Dr. Kalden concluded that biological agents might be of “special value” in combinations with methotrexate and other immunosuppressive compounds. (*Id.*)

6. 1998 Draft FDA Guidance and 1999 Final FDA Guidance

In 1998 and 1999, the FDA issued “Guidance for the Industry” regarding “Clinical Development Programs for Drugs, Devices, and biological Products for

the Treatment of Rheumatoid Arthritis (RA).” A draft guidance document was published on August 7, 1998. (Ex. 1011.) The final guidance document was published in February 1999. (Ex. 1012.) Both documents are prior art under at least 35 U.S.C. §102(a).

The pertinent parts of both FDA Guidance documents are identical. Both documents stated that it was “inevitable that new agents [would] be used in combination with methotrexate in clinical practice unless a contraindication exists” and that absent a prohibition on concurrent methotrexate, “data regarding use of the investigational agent in combination with methotrexate [we]re needed to evaluate the potential for immunosuppression from combination therapy.” (Ex. 1011 at 18; Ex. 1012 at 18.)

Put another way, before the earliest priority date of the ’161 patent, the FDA required that new RA treatments be tested in combination with methotrexate. (Ex. 1002 at ¶ 66.) Combining new RA drugs with methotrexate was not only known in the art, it was expected in order to obtain FDA approval. In this light, combining a known biological agent like rituximab with methotrexate (which was also known) to treat RA is not a patentable invention. (*See id.* at ¶¶ 65-68.)

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

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

- 1. “A method of treating rheumatoid arthritis in a human comprising . . . administering to the human more than one intravenous dose of a therapeutically effective amount of [rituximab]” (all claims)⁴**

As of the earliest priority date for the '161 patent, a person of ordinary skill would have been aware of: (i) rituximab's ability to destroy mature B-cells without being toxic to human patients (Exs. 1023, 1024, 1025); and (ii) research showing that B-cells are involved in the pathophysiology of RA (Exs. 1025, 1035, 1036). (*See also* Ex. 1002 at ¶ 70.)

Armed with this information, two separate doctors proposed treating RA with rituximab before the earliest priority date of the '161 patent. The 1998 Edwards reference proposed treating RA by depleting B-cells with anti-B-cell (CD20) antibodies and specifically rituximab (a/k/a IDEC-C2B8). (*See* Ex. 1025 at 129-30). Similarly, Dr. Gryn recognized the benefit of rituximab in the treatment of autoimmune diseases when he proposed trials that would administer

⁴ Claims 5 and 9 of the '161 patent replace the term “rituximab” in claim 1 with: (i) “an antibody that binds to the CD20 antigen on human B lymphocytes;” and (ii) a “wherein” clause stating that “the CD20 antibody is rituximab.” Accordingly, the scope of the three independent claims is identical. (*See* Section V.A.1 *supra*.)

RITUXAN® (*i.e.*, rituximab) to human patients suffering from RA. (*See* Ex. 1026 at 2.) The fact that Edwards 1998 (Ex. 1025) and the Gryn letter (Ex. 1026) both discussed the use of rituximab at about the same time emphasizes that those of no more than the ordinary skill in the art had already thought to use rituximab to treat RA before the earliest priority date. (*See* Ex. 1002 at ¶ 45); *see also* *Geo. M. Martin Co. v. Alliance Machine Sys. Int’l, LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (holding that evidence of simultaneous invention by another supported finding of obviousness).

A person of ordinary skill would also have been aware that rituximab was “formulated for intravenous administration” and that the recommended dosage approved by the FDA was “375 mg/m² given as an IV [intravenous] infusion once weekly for four doses (days 1, 8, 15, and 22).” (*See* Ex. 1006.)

The FDA-approved recommended dosing regimen for rituximab would have been the starting point for a person of ordinary skill using rituximab to treat RA. (Ex. 1002 at ¶ 39.) This is illustrated by Dr. Gryn’s proposal to treat RA with rituximab using the “standard dose” of RITUXAN® over the course of a one-year period. (Ex. 1026 at 2.) The “standard dose” of rituximab at the time of the Gryn letter was the recommended dosage on the FDA-approved label. (*See* Ex. 1002 at ¶ 44.) Indeed, the patentees acknowledged that the logical starting point for using rituximab to treat RA would have been the standard dosing regimen provided on

the FDA label. (*See* Ex. 1001 at 27:59, 28:15, and 29:9 (proposing doses of “375 mg/m² IV days 1, 8, 15, & 22” for treating three separate autoimmune diseases, including rheumatoid arthritis).)

With the possible exception of early Phase I clinical studies designed to identify the safest and most effective dose (*e.g.*, Ex. 1023), a person of ordinary skill would have understood from the prior art that any therapeutically effective dosing regimen for treating RA must involve more than one intravenous dose of rituximab, particularly given the chronic nature of RA. (Ex. 1002 at ¶¶ 72, 74.)

2. “administering to the human methotrexate” (all claims)

The prior art establishes that, as of the earliest priority date for the ’161 patent, methotrexate was the “gold standard” for treating RA (Ex. 1004 at 1290) and had achieved a position of “therapeutic dominance” due to its demonstrated efficacy and long-term tolerability (Ex. 1017 at 847). (*See* Ex. 1002 at ¶ 75.) 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. 1003 at 779.) Indeed, “[t]o overstate the importance of methotrexate in the contemporary management of rheumatoid arthritis (RA) would be difficult.” (*Id.* at 779.) The administration of methotrexate to treat RA patients was well known in the prior art.

3. Combining Rituximab and Methotrexate as Therapeutic Agents for Treating RA (all claims)

Combinations therapies involving monoclonal antibodies and methotrexate were discussed publicly by the FDA as early as 1995, where a representative from the FDA's Center for Biologics Evaluation and Research said, "If the Phase I studies off methotrexate are shown to be safe, and this is agreed upon by the regulatory agency and the sponsor, I think it is perfectly appropriate to go into a methotrexate-treated patient population, provided that what you have learned in Phase I is employed in Phase II." (Ex. 1005 at 295.) The FDA and the rheumatologists who participated in that discussion were well aware of combination therapies for RA that involved biologic agents and methotrexate. (*See id.* at 294-95; Ex. 1002 at ¶ 78.)

A person of ordinary skill at the time of the priority date would be aware that methotrexate was the "cornerstone" and "foundation" for combination RA therapies. (Ex. 1003 at 790, 792; *see also* Ex. 1002 at ¶ 79.) Moreover, a person of ordinary skill would have been aware of studies demonstrating that combination therapies involving methotrexate would be an "important therapeutic approach for RA patients." (*See* Ex. 1020 at S-96 (discussing studies showing the promise of combining drugs with methotrexate to treat RA, including Kavanaugh et al. (Ex. 1019)).) Such experimental data, as well as the initial clinical data regarding combination therapies, led skilled practitioners to conclude that "biological agents

such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as MTX [methotrexate] and other immunosuppressive compounds.” (*Id.*)

The prior art showed that biological agents and other RA drugs “should be tested in combination with methotrexate for approval in marketing, particularly as this is how they are likely to be used.” (Ex. 1008 at 593.) Indeed, the prior art identified a straightforward economic incentive to combine methotrexate with other RA drugs during pharmaceutical development: “[T]he fact that more than 50% of patients with RA under the care of rheumatologists in the U.S. take methotrexate suggests that it may be advantageous from both a clinical and a business standpoint to develop most drugs in RA at this time for use in combination with methotrexate.” (*Id.*)

Because methotrexate was well-accepted as the most efficacious and well-tolerated RA therapy at the relevant time, “virtually all” new RA treatments were being tested in combination with methotrexate. (Ex. 1009 at 1548.) This was also true of biological therapies for RA. (*See id.* (“Most of the new biotechnology-derived therapeutic interventions are being studied as both monotherapy and combination therapy with MTX.”); *see also* Ex. 1016 at 614 (Table I).)

By 1998, the FDA said it was “inevitable” that new therapeutic agents for RA would be used in combination with methotrexate. (Ex. 1011 at 18 (“[S]ince

methotrexate therapy is used to treat many RA patients, it is inevitable that new agents will be used in combination with methotrexate in clinical practice unless a contraindication exists.”.) Indeed, absent a prohibition on concurrent methotrexate, the FDA told those skilled in the art that “data regarding use of the investigational agent in combination with methotrexate are needed to evaluate the potential for immunosuppression from combination therapy.” (*Id.*) Put simply, the FDA told the industry that combining new RA drugs with methotrexate was expected in order to obtain approval for new treatments.

It would have been obvious to a person of ordinary skill as of the priority date to treat RA with rituximab, or any other biologic or drug for treating RA, in combination with methotrexate. (Ex. 1002 at ¶ 77.) The motivation to combine rituximab and other biologic agents with methotrexate can be found in the prior art (*id.*), which described the benefits of such combination therapies for treating RA as discussed above. (Ex. 1020 at S-96 (stating that combination therapies involving biologic agents and methotrexate might be of “special value”).) The prior art also discussed an economic incentive to drug developers to combine new RA treatments with methotrexate. (*E.g.*, Ex. 1008 at 593 (suggesting that the widespread use of methotrexate made it “advantageous from both a clinical and a business standpoint to develop most drugs in RA at this time for use in combination with methotrexate.”).)

Moreover, by the earliest priority date, a person of ordinary skill would have been aware, at minimum, of a synergistic therapeutic result from combining an antibody like rituximab with methotrexate to treat RA. (Ex. 1002 at ¶¶ 67, 82.) Indeed, any such synergistic result would have been completely expected. (*See id.* at ¶ 67; *see also id.* at ¶ 57 (citing Ex. 1021), ¶ 64 (citing Ex. 1018).)

Also well-known was methotrexate's ability to reduce the immune response of anti-drug antibodies, thereby improving the drug's efficacy and its ability to reduce potential allergic responses. (Ex. 1002 at ¶ 83.) When foreign antibodies like rituximab are administered to humans, the immune system in the body produces antibodies to fight the therapeutic drugs. (*Id.*) This immune response can reduce the effectiveness of rituximab in reducing inflammation and treating RA. (*Id.*) In fact, as discussed in the "PRECAUTIONS" section of the FDA label, this was a specific concern associated with rituximab use. (*See* Ex. 1006 at 1). By suppressing the immune response, methotrexate contributes to a synergistic effect that improves the ability of rituximab and similar biologics to treat RA in patients. (Ex. 1002 at ¶ 83.) This was understood before the earliest priority date. (*Id.*)

4. "an antibody that binds to the CD20 antigen on human B lymphocytes" (claims 5 and 9)

It was known in the prior art that rituximab is an antibody that binds to the CD20 antigen on human B lymphocytes. (*See, e.g.,* Ex. 1006 at 1 ("The RITUXAN (Rituximab) antibody is a genetically engineered chimeric

murine/human monoclonal antibody directed against the CD antigen found on the surface of normal and malignant B lymphocytes.”); Ex. 1024 at 2188 (“IDEC-C2B8 [rituximab] is a chimeric monoclonal antibody (MoAb) directed against the B-cell specific antigen CD20”).) This element does nothing more than describe what rituximab is and does. (*See* Ex. 1002 at ¶ 84.)

5. **“wherein the CD20 antibody administration consists of intravenous administration of the CD20 antibody, and the CD20 antibody is rituximab” (claim 5) and “wherein the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab” (claim 9)**

Claims 5 and 9 of the '161 patent each contain “wherein” clauses. The “wherein” clause of claim 9 states that: (i) the CD20 antibody administration be both of a “therapeutically effective amount” and delivered intravenously; and (ii) the CD20 antibody is rituximab. The “wherein” clause of claim 5 does not include the term “therapeutically effective amount” and only states that: (i) the CD20 antibody administration is delivered intravenously; and (ii) the CD20 antibody is rituximab. The “wherein” clauses of claims 5 and 9 do nothing more than make explicit that the CD20 antibody previously referred to in those claims is rituximab and, as a result, claims 5 and 9 are identical in scope to claim 1. In any event, as discussed above, it would have been obvious to administer a therapeutically effective amount of rituximab to treat RA, and it was known that rituximab is administered intravenously. (*See* Section IX.A.1 *supra*; *see also* Ex. 1002 at ¶ 85.)

6. “each administration of rituximab is a dose in the range from about 250 mg/m² to about 1000 mg/m²” (claims 2, 6, and 10)

Claims 2, 6, and 10 recite a broad range of rituximab doses. The recommended dose on the 1997 FDA label falls squarely within this range. (*See* Ex. 1006 at 2 (recommending “375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22)”)). Dr. Gryn also proposed treating patients with this “standard dose” over the course of a one-year period. (*See* Ex. 1026 at 2.) As discussed above, the dosing regimen provided in the 1997 FDA-approved rituximab label would have been the logical starting point for the use of rituximab to treat RA (*see* Section IX.A.1 *supra*; *see also* Ex. 1002 at ¶¶ 39, 73, 86), and this is confirmed by the patentees’ statements in the ’161 patent. (*See* Ex. 1001 at 27:35-67.)

Further, a skilled practitioner would try to optimize the dose of rituximab for treating RA patients by investigating different doses to find the optimal dose for use in clinical practice. (Ex. 1002 at ¶ 87.) The broad range of doses recited in claims 2, 6, and 10 includes many of the preferred doses for rituximab that would have been attempted by a person of ordinary skill. (*Id.*) In fact, two of the five doses tested in the Phase I Maloney et al. study (250 and 500 mg/m²) fall squarely within the claimed range. (*See* Ex. 1023 at 2457.)

7. “administering to the human a glucocorticosteroid” (claims 3, 7, and 11)

Dependent claims 3, 7 and 11 of the '161 patent require the administration of a glucocorticosteroid. Glucocorticosteroids had been used in treating RA patients for many years prior to the filing date of the '161 patent. (*See, e.g.*, Ex. 1034 at 142 (“Oral glucocorticoids are widely used to treat patients with rheumatoid arthritis”).) Glucocorticosteroids (*e.g.*, prednisone and prednisolone) were also combined with methotrexate for the purposes of treating RA before the earliest priority date of the '161 patent. (*See* Ex. 1002 at ¶ 88; Ex. 1022 at 309 (“In a multicentre, double-blind, randomised trial (COBRA), we compared the combination of sulphasalazine (2 g/day), methotrexate (7.5 mg/week), and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) with sulphasalazine alone.”); Ex. 1019 (“Patients continued treatment with MTX for 10/mg/week throughout the trial and were allowed stable does of NSAIDs and prednisone (≤ 7.5 mg/d).”).)

Similarly, a separate paper published in June 1998 by Verhoeven et al., stated: “In early RA patients, step-down bridge therapy that includes corticosteroids leads to much enhanced efficacy at acceptable or low toxicity.” (Ex. 1016 at 612.) The same paper also referred to one study where “prednisolone [a glucocorticosteroid] was added together with methotrexate.” (*Id.* at 613.)

Further, administering a glucocorticoid for the treatment of RA would have been obvious to a person of ordinary skill. (Ex. 1002 at ¶ 89) Glucocorticosteroids were introduced in the treatment of RA soon after their discovery back in 1948. (*Id.*) It was well known that the injection of glucocorticosteroids prior to or concurrent with the infusion of immunoglobulins (*i.e.*, antibodies such as rituximab) will prevent possible adverse side effects. (*Id.*)

8. “administering an initial dose of the rituximab followed by a subsequent dose, where the mg/m^2 dose of the rituximab in the subsequent dose exceeds the mg/m^2 dose of the rituximab in the initial dose” (claims 4, 8, and 12)

Dependent claims 4, 8 and 12 of the '161 patent require that the second dose of rituximab be greater than an initial dose. The claims do not specify the amount of the initial dose or the subsequent dose.

Escalating dosing levels of CD20 antibodies, such as rituximab, were studied in the prior art. The 1997 FDA label provides a “first infusion” and “subsequent infusion,” where the subsequent infusion of rituximab (100 mg/hr) exceeds the initial dose (50 mg/hr). (Ex. 1006 at 2.) In addition, in a May 1998 publication by Tobinai et al., the authors wrote:

A dose-escalation in two steps was employed. The starting dosage [of rituximab] was set at $250 \text{ mg}/\text{m}^2$ /infusion on the basis of the results of the multipledose phase I—II trial conducted in the USA. The dosage was escalated to $375 \text{ mg}/\text{m}^2$ /infusion, if none of three initial

patients or only two or less of six patients enrolled at 250 mg/m² developed critical toxicities.

(Ex. 1013 at 528.) In general, dose escalation studies were quite common before the date of invention. (*See* Ex. 1002 at ¶ 91.)

In any event, increasing the second dose of rituximab would be obvious to a person of ordinary skill. (*Id.* at ¶ 92.) If a patient does not respond adequately to a lower dose, a skilled clinician will increase the dose to reach significant clinical efficacy or to define the patient as a non-responder. (*Id.*) With regard to biologics in clinical trials in the mid-late 1990s, clinicians seeking to determine the efficacy of monoclonal antibodies or fusion proteins tried to determine the optimal dose for RA patients in daily clinical practice. (*Id.* at ¶ 87.)

B. Proposed Combinations of Prior Art

| Claims | Prior Art Combinations |
|----------------------|---|
| 1, 2, 5, 6, 9, 10 | <ul style="list-style-type: none"> • Ex. 1025 or Ex. 1026 in view of Ex. 1003 • Ex. 1025 or Ex. 1026 in view of Ex. 1008 • Ex. 1025 or Ex. 1026 in view of Ex. 1020 • Ex. 1025 or Ex. 1026 in view of Ex. 1003 and Ex. 1006 • Ex. 1025 or Ex. 1026 in view of Ex. 1008 and Ex. 1006 • Ex. 1025 or Ex. 1026 in view of Ex. 1020 and Ex. 1006 |

| Claims | Prior Art Combinations |
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| | <ul style="list-style-type: none"> • Ex. 1025 or Ex. 1026 in view of Ex. 1003 and Ex. 1023 • Ex. 1025 or Ex. 1026 in view of Ex. 1008 and Ex. 1023 • Ex. 1025 or Ex. 1026 in view of Ex. 1020 and Ex. 1023 |
| 3, 7, 11 | <ul style="list-style-type: none"> • Ex. 1025 or Ex. 1026 in view of Ex. 1016 • Ex. 1025 or Ex. 1026 in view of Ex. 1019 • Ex. 1025 or Ex. 1026 in view of Ex. 1022 |
| 4, 8, 12 | <ul style="list-style-type: none"> • Ex. 1025 or Ex. 1026 in view of Ex. 1003 and Ex. 1006 • Ex. 1025 or Ex. 1026 in view of Ex. 1008 and Ex. 1006 • Ex. 1025 or Ex. 1026 in view of Ex. 1020 and Ex. 1006 • Ex. 1025 or Ex. 1026 in view of Ex. 1003 and Ex. 1013 • Ex. 1025 or Ex. 1026 in view of Ex. 1008 and Ex. 1013 • Ex. 1025 or Ex. 1026 in view of Ex. 1020 and Ex. 1013 |

A person of ordinary skill in the art would have been motivated and able to combine the teachings of the above references with predictable results and a reasonable expectation of success. (Ex. 1002 at ¶¶ 96-102, 109-14.) The reason to combine the references is expressly provided in the prior art—namely, to improve treatments for RA patients via combination therapies involving rituximab, methotrexate, and other therapeutic agents, such as glucocorticosteroids.

Before the priority date of the '161 patent, rituximab had been identified as a therapeutic agent for the treatment of RA (Exs. 1025 and 1026) and was known to be safely administered to humans at a wide range of dosing levels (Exs. 1006, 1023, and 1024).

By 1997, the use of combination therapies to treat RA had “increased dramatically” and “over 90% of rheumatologists used combinations” to treat RA. (Ex. 1003 at 789.) The prior art established that “most would agree . . . that methotrexate should be the cornerstone of most combinations,” and that “it is also the standard against which combinations should be measured.” (*Id.* at 790.) Moreover, it was “advantageous from both a clinical and a business standpoint to develop most drugs in RA at [that] time for use in combination with methotrexate.” (Ex. 1008 at 592.) The consensus among persons of ordinary skill was that the combination of biological agents (*e.g.*, rituximab) with methotrexate was of “special value” when treating RA. (Ex. 1020 at S-96.)

Further, the FDA guidance documents concerning treatments for RA observed that studies in RA patients, except those with “very mild disease,” were carried out in the presence of concurrent active therapies, including steroids. (Ex. 1011 at 18; Ex. 1012 at 17.) Combination therapies involving methotrexate had demonstrated so much promise in the prior art that the FDA guidance told the drug development industry that “it is inevitable that new agents [for RA] will be used in

combination with methotrexate in clinical practice unless a contraindication exists.” (Ex. 1011 at 18; Ex. 1012 at 18.) In fact, absent a prohibition on concurrent methotrexate, the FDA required “data regarding the use of the investigational [RA] agent in combination with methotrexate” to “evaluate the potential for immunosuppression from combination therapy.” (*Id.*)

C. Claim Charts Comparing the Challenged Claims Against the Prior Art

| Comparison to U.S. Patent No. 7,820,161 | |
|---|---|
| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| 1. A method of treating rheumatoid arthritis in a human comprising: | <p>Ex. 1025 (Edwards 1998): “Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody Is Also Antigen” (p126); “An alternative strategy may be simpler: to kill all B cells.” (p129); “This may well be what happens when subjects with RA treated with high-dose cyclophosphamide prior to bone marrow transplantation go into long-term remission.” (p129)</p> <p>Ex. 1026 (Gryn): “Proposed Investigation: Perform a pilot study on the effect of <u>Rituxin</u> [sic] diseases with an autoimmune etiology such as: Rheumatoid Arthritis . . .” (p2).</p> |
| (a) administering to the human more than one intravenous dose of a therapeutically effective amount of rituximab; and | <p>Ex. 1025 (Edwards 1998): “An alternative strategy may be simpler: to kill all B cells . . . Recent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects [37, 38], since B cells are produced rapidly and Ig levels are maintained in the short term.” (pp 128-29); “37. Maloney DG, Liles TM, Czerwinski DK <i>et al.</i> Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. <i>Blood</i> 1994; 84:2457-66.” (p 130).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
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| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| | <p>Ex. 1026 (Gryn): “<u>Rituxin</u> [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocytes” (p2); “<u>Rituxin</u> [sic] will be given in its standard dose.” (p2).</p> <p>Ex. 1006 (FDA Label): “The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.” (p1); “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22.” (p2).</p> <p>Ex. 1023 (Maloney 1994): “In this phase I clinical trial, 15 patients (3 per dose level) with relapsed low-grade B-cell lymphoma were treated with a single dose (10, 50, 100, 250, or 500 mg/m²) of antibody administered intravenously . . . The results of this single-dose trial have been used to design a multiple-dose phase I/II study.” (p2457); “Based on these observations of safety and tumor responses to a single infusion of this chimeric anti-CD20 MoAb, a phase I/II trial using four weekly doses of antibody in patients with relapsed B-cell NHL has been initiated.” (p2465).</p> |
| (b) administering to the human methotrexate. | <p>Ex. 1003 (O’Dell 1997): “Methotrexate was not approved by the FDA for use in RA until 1988; it is now not only the most commonly used but also the first prescribed DMARD by most rheumatologists in the United States for the treatment of RA. It has achieved this distinction because of both its efficacy and tolerability.” (p779); “Many clinicians, therefore, have added other DMARDs to methotrexate in patients who have had partial responses, a use of so-called combination therapy.” (pp 782-83); “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, the combination therapies most commonly used in clinical practice include methotrexate.” (p790); “Because</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
|--|---|
| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| | <p>methotrexate is the most effective DMARD available, it should be the foundation of most combination therapies . . . Continued research on combinations of DMARDs, as well as combinations that include biologic agents and methotrexate and possibly other DMARDs, is necessary.” (p792).</p> <p>Ex. 1008 (Pincus): “Many patients with early RA appear to be reasonable candidates for early methotrexate therapy, or ‘combination’ DMARD therapy with methotrexate as the cornerstone. If methotrexate is not optimally effective as a single drug, other DMARDs should be added or substituted within months.” (p592); “Toxicities of the most effective DMARD, methotrexate, alone or even in combination, may be less than those of many NSAIDs.” (p592); “The fact that more than 50% of patients with RA under the care of rheumatologists in the U.S. take methotrexate suggests that it may be advantageous from both a clinical and a business standpoint to develop most drugs in RA at this time for use in combination with methotrexate.” (p593).</p> <p>Ex. 1016 (Verhoeven): Table I (p614).</p> <p>Ex. 1020 (Kalden): “Combining methotrexate and the repeated administration of anti-TNF-a MAb cA2, Kavanaugh <i>et al.</i> demonstrated that combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone.” (p S-96.); “From these experimental, as well as initial clinical data, it can be concluded that biological agents such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as MTX and other immunosuppressive compounds.” (p S-96).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
|--|--|
| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| <p>2. The method of claim 1, wherein each administration of the rituximab is a dose in the range from about 250 mg/m² to about 1000 mg/m².</p> | <p>Ex. 1026 (Gryn): “<u>Rituxin</u> [sic] will be given in its standard dose.” (p2).</p> <p>Ex. 1006 (FDA Label): “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22.” (p2).</p> <p>Ex. 1023 (Maloney 1994): “In this phase I clinical trial, 15 patients (3 per dose level) with relapsed low-grade B-cell lymphoma were treated with a single dose (10, 50, 100, 250, or 500 mg/m²) of antibody administered intravenously . . . The results of this single-dose trial have been used to design a multiple-dose phase I/II study.” (p2457); “Based on these observations of safety and tumor responses to a single infusion of this chimeric anti-CD20 MoAb, a phase I/II trial using four weekly doses of antibody in patients with relapsed B-cell NHL has been initiated.” (p2465).</p> |
| <p>3. The method of claim 1, comprising administering to the human a glucocorticosteroid.</p> | <p>Ex. 1034 (Kirwan): “Oral glucocorticoids are widely used to treat patients with rheumatoid arthritis”) (p142).</p> <p>Ex. 1019 (Kavanaugh): “[M]any clinicians utilize MTX as initial therapy for RA patients. We therefore undertook a randomized, double-blind, placebo controlled study of a chimeric α-TNF mAb (cA2) in RA patients who had active disease despite receiving \geq 3 months therapy with MTX Patients continued treatment with MTX 10 mg/week throughout the trial and were allowed stable doses of NSAIDs and prednisone (\leq 7.5 mg/d).”</p> <p>Ex. 1022 (Boers): “In a multicentre, double-blind, randomised trial (COBRA), we compared the combination of sulphasalazine (2 g/day), methotrexate (7.5 mg/week), and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) with sulphasalazine alone.” (p309).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
|---|---|
| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| | <p>Ex. 1016 (Verhoeven): “In early RA patients, step-down bridge therapy that includes corticosteroids leads to much enhanced efficacy at acceptable or low toxicity.” (p612); “prednisolone was added together with methotrexate.” (p613); Table I (p614).</p> |
| <p>4. The method of claim 1, comprising administering an initial dose of the rituximab followed by a subsequent dose, where the mg/m² dose of the rituximab in the subsequent dose exceeds the mg/m² dose of the rituximab in the initial dose.</p> | <p>Ex. 1006 (FDA Label): “First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr . . . Subsequent Infusions: Subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated.” (p2).</p> <p>Ex. 1013 (Tobinai): “A dose-escalation in two steps was employed. The starting dosage was set at 250 mg/m² infusion on the basis of the results of the multipledose phase I—II trial conducted in the USA. The dosage was escalated to 375 mg/m²/infusion, if none of three initial patients or only two or less of six patients enrolled at 250 mg/m² developed critical toxicities.” (p528).</p> |
| <p>5. A method of treating rheumatoid arthritis in a human comprising:</p> | <p>Ex. 1025 (Edwards 1998): “Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody Is Also Antigen” (p126); “An alternative strategy may be simpler: to kill all B cells.” (p129); “This may well be what happens when subjects with RA treated with high-dose cyclophosphamide prior to bone marrow transplantation go into long-term remission.” (p129).</p> <p>Ex. 1026 (Gryn): “Proposed Investigation: Perform a pilot study on the effect of <u>Rituxin</u> [sic] diseases with an autoimmune etiology such as: Rheumatoid Arthritis” (p2).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
|--|--|
| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| <p>(a) administering to the human more than one intravenous dose of a therapeutically effective amount of an antibody that binds to the CD20 antigen on human B lymphocytes; and</p> | <p>Ex. 1025 (Edwards 1998): “An alternative strategy may be simpler: to kill all B cells . . . Recent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects [37, 38], since B cells are produced rapidly and Ig levels are maintained in the short term.” (pp 128-29); “37. Maloney DG, Liles TM, Czerwinski DK <i>et al.</i> Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. <i>Blood</i> 1994; 84:2457-66.” (p 130).</p> <p>Ex. 1026 (Gryn): “<u>Rituxin</u> [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocytes” (p2); “<u>Rituxin</u> [sic] will be given in its standard dose.” (p2).</p> <p>Ex. 1006 (FDA Label): “The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.” (p1); “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22.” (p2).</p> <p>Ex. 1023 (Maloney 1994): “In this phase I clinical trial, 15 patients (3 per dose level) with relapsed low-grade B-cell lymphoma were treated with a single dose (10, 50, 100, 250, or 500 mg/m²) of antibody administered intravenously . . . The results of this single-dose trial have been used to design a multiple-dose phase I/II study.” (p2457); “Based on these observations of safety and tumor responses to a single infusion of this chimeric anti-CD20 MoAb, a phase I/II trial using four weekly doses of antibody in patients with relapsed B-cell NHL has been initiated.” (p2465).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
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| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| <p>(b) administering to the human methotrexate;</p> | <p>Ex. 1003 (O'Dell 1997): "Methotrexate was not approved by the FDA for use in RA until 1988; it is now not only the most commonly used but also the first prescribed DMARD by most rheumatologists in the United States for the treatment of RA. It has achieved this distinction because of both its efficacy and tolerability." (p779); "Many clinicians, therefore, have added other DMARDs to methotrexate in patients who have had partial responses, a use of so-called combination therapy." (pp 782-83); "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, the combination therapies most commonly used in clinical practice include methotrexate." (p790); "Because methotrexate is the most effective DMARD available, it should be the foundation of most combination therapies . . . Continued research on combinations of DMARDs, as well as combinations that include biologic agents and methotrexate and possibly other DMARDs, is necessary." (p792).</p> <p>Ex. 1008 (Pincus): "Many patients with early RA appear to be reasonable candidates for early methotrexate therapy, or 'combination' DMARD therapy with methotrexate as the cornerstone. If methotrexate is not optimally effective as a single drug, other DMARDs should be added or substituted within months." (p592); "Toxicities of the most effective DMARD, methotrexate, alone or even in combination, may be less than those of many NSAIDs." (p592); "The fact that more than 50% of patients with RA under the care of rheumatologists in the U.S. take methotrexate suggests that it may be advantageous from both a clinical and a business standpoint to develop most drugs in RA at this time for use in combination with methotrexate." (p593).</p> <p>Ex. 1016 (Verhoeven): Table I (p614).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
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| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| | <p>Ex. 1020 (Kalden): “Combining methotrexate and the repeated administration of anti-TNF-a MAb cA2, Kavanaugh <i>et al.</i> demonstrated that combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone.” (p S-96.); “From these experimental, as well as initial clinical data, it can be concluded that biological agents such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as MTX and other immunosuppressive compounds.” (p S-96).</p> |
| <p>wherein the CD20 antibody administration consists of intravenous administration of the CD20 antibody, and the CD20 antibody is rituximab.</p> | <p>Ex. 1025 (Edwards 1998): “An alternative strategy may be simpler: to kill all B cells . . . Recent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects [37, 38], since B cells are produced rapidly and Ig levels are maintained in the short term.” (pp 128-29); “37. Maloney DG, Liles TM, Czerwinski DK <i>et al.</i> Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. <i>Blood</i> 1994; 84:2457-66.” (p 130).</p> <p><i>See</i> Ex. 1001 ('161 patent): “The terms ‘rituximab’ or ‘RITUXAN®’ herein refer to the genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen and designated ‘C2B8’ in U.S. Pat. No. 5,736,137” (8:61-64).</p> <p>Ex. 1026 (Gryn): “<u>Rituxin</u> [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocytes” (p2); “<u>Rituxin</u> [sic] will be given in its standard dose.” (p2).</p> <p>Ex. 1006 (FDA Label): “RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration.” (p1); “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
|---|--|
| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| | once weekly for four doses (days 1, 8, 15, and 22.” (p2). |
| 6. The method of claim 5, wherein each administration of the antibody is a dose in the range from about 250 mg/m ² to about 1000 mg/m ² . | <i>See claim 2 above.</i> |
| 7. The method of claim 5, comprising administering to the human a glucocorticosteroid. | <i>See claim 3 above.</i> |
| 8. The method of claim 5, comprising administering an initial dose of the antibody followed by a subsequent dose, where the mg/m ² dose of the antibody in the subsequent dose exceeds the mg/m ² dose of the antibody in the initial dose. | <i>See claim 4 above.</i> |
| 9. A method of treating rheumatoid arthritis in a human comprising: | Ex. 1025 (Edwards 1998): “Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody Is Also Antigen” (p126); “An alternative strategy may be simpler: to kill all B cells.” (p129); “This may well be what happens when subjects with RA treated with high-dose cyclophosphamide prior to bone marrow transplantation go into long-term remission.” (p129). |

| Comparison to U.S. Patent No. 7,820,161 | |
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| | <p>Ex. 1026 (Gryn): “Proposed Investigation: Perform a pilot study on the effect of <u>Rituxin</u> [sic] diseases with an autoimmune etiology such as: Rheumatoid Arthritis . . .” (p2); “Since many autoimmune diseases are associated with or caused by antibodies, treatment of these diseases with Rituxin [sic] offers an interesting alternative. I believe that suppression of B-cells with Rituxin could lead to non-toxic remissions in these diseases.” (p1).</p> |
| <p>(a) administering to the human more than one intravenous dose of a therapeutically effective amount of an antibody that binds to the CD20 antigen on human B lymphocytes; and</p> | <p>Ex. 1025 (Edwards 1998): “An alternative strategy may be simpler: to kill all B cells . . . Recent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects [37, 38], since B cells are produced rapidly and Ig levels are maintained in the short term.” (pp 128-29); “37. Maloney DG, Liles TM, Czerwinski DK <i>et al.</i> Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. <i>Blood</i> 1994; 84:2457-66.” (p 130).</p> <p>Ex. 1026 (Gryn): “Oncology patients treated with <u>Rituxin</u> [sic] demonstrate a marked reduction in circulating immunoglobulin levels. Many autoimmune diseases are associated or caused by humoral factors. Rheumatoid factor in rheumatoid arthritis, anti-platelet antibodies in ITP, and Anti-Nuclear Antibodies in Lupus are examples of these . . . <u>Rituxin</u> [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocytes” (p2); “<u>Rituxin</u> [sic] will be given in its standard dose.” (p2).</p> <p>Ex. 1006 (FDA Label): “The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.” (p1); “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22.” (p2).</p> <p>Ex. 1023 (Maloney 1994): “In this phase I clinical trial, 15</p> |

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| | <p>patients (3 per dose level) with relapsed low-grade B-cell lymphoma were treated with a single dose (10, 50, 100, 250, or 500 mg/m²) of antibody administered intravenously . . . The results of this single-dose trial have been used to design a multiple-dose phase I/II study.” (p2457); “Based on these observations of safety and tumor responses to a single infusion of this chimeric anti-CD20 MoAb, a phase I/II trial using four weekly doses of antibody in patients with relapsed B-cell NHL has been initiated.” (p2465).</p> |
| <p>(b) administering to the human methotrexate;</p> | <p>Ex. 1003 (O’Dell 1997): “Methotrexate was not approved by the FDA for use in RA until 1988; it is now not only the most commonly used but also the first prescribed DMARD by most rheumatologists in the United States for the treatment of RA. It has achieved this distinction because of both its efficacy and tolerability.” (p779); “Many clinicians, therefore, have added other DMARDs to methotrexate in patients who have had partial responses, a use of so-called combination therapy.” (pp 782-83); “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, the combination therapies most commonly used in clinical practice include methotrexate.” (p790); “Because methotrexate is the most effective DMARD available, it should be the foundation of most combination therapies . . . Continued research on combinations of DMARDs, as well as combinations that include biologic agents and methotrexate and possibly other DMARDs, is necessary.” (p792).</p> <p>Ex. 1008 (Pincus): “Many patients with early RA appear to be reasonable candidates for early methotrexate therapy, or ‘combination’ DMARD therapy with methotrexate as the cornerstone. If methotrexate is not optimally effective as a single drug, other DMARDs should be added or substituted within months.” (p592); “Toxicities of the most effective DMARD, methotrexate, alone or even in combination, may</p> |

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| | <p>be less than those of many NSAIDs.” (p592).</p> <p>Ex. 1016 (Verhoeven): Table I (p614).</p> <p>Ex. 1020 (Kalden): “Combining methotrexate and the repeated administration of anti-TNF-a MAb cA2, Kavanaugh <i>et al.</i> demonstrated that combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone.” (p S-96.); “From these experimental, as well as initial clinical data, it can be concluded that biological agents such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as MTX and other immunosuppressive compounds.” (p S-96).</p> |
| <p>wherein the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab.</p> | <p>Ex. 1025 (Edwards 1998): “An alternative strategy may be simpler: to kill all B cells . . . Recent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects [37, 38], since B cells are produced rapidly and Ig levels are maintained in the short term.” (pp 128-29); “37. Maloney DG, Liles TM, Czerwinski DK <i>et al.</i> Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. <i>Blood</i> 1994; 84:2457-66.” (p 130).</p> <p>Ex. 1026 (Gryn): “<u>Rituxin</u> [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocytes” (p2); “<u>Rituxin</u> [sic] will be given in its standard dose.” (p2).</p> <p>Ex. 1006 (FDA Label): “RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration.” (p1); “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22.” (p2).</p> |

| Comparison to U.S. Patent No. 7,820,161 | |
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| '161 Patent Claims | Exemplary Disclosure in Prior Art |
| 10. The method of claim 9, wherein each administration of the antibody is a dose in the range from about 250 mg/m ² to about 1000 mg/m ² . | <i>See</i> claims 2 and 6 above. |
| 11. The method of claim 9, comprising administering to the human a glucocorticosteroid. | <i>See</i> claims 3 and 7 above. |
| 12. The method of claim 9, comprising administering an initial dose of the antibody followed by a subsequent dose, where the mg/m ² dose of the antibody in the subsequent dose exceeds the mg/m ² dose of the antibody in the initial dose. | <i>See</i> claims 4 and 8 above. |

X. DR. VAN VOLLENHOVEN’S OPINIONS FAIL TO ESTABLISH UNEXPECTED RESULTS

As an initial matter, “where a claimed invention represents no more than the predictable use of prior art elements according to established functions . . . evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness.” *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1344

(Fed. Cir. 2013). “For objective evidence [of non-obviousness] to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.” *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). “[O]bjective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.” *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (quoting *In re Grasselli*, 713 F.3d 731, 743 (Fed. Cir. 1983)). Moreover, “weak secondary considerations generally do not overcome a strong prima facie case of obviousness.” *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010).

Dr. van Vollenhoven submitted a Rule 132 declaration on July 30, 2007, in which he argued: “I believe that one would not have been able to predict that continued treatment with MTX [methotrexate] would extend the therapeutic response to rituximab in patients in which MTX alone had proved ineffective prior to this trial.” (Ex. 1014 at ¶ 34.) Dr. van Vollenhoven’s opinions were based on the results of a clinical study published in 2004 (“Edwards et al. 2004”) (Ex. 1033).

As discussed in detail in Dr. Kalden’s supporting declaration submitted herewith, the “extend[ed] therapeutic response” characterized by Dr. van Vollenhoven as unpredictable was not only predictable, it was entirely expected. This is true for at least three reasons. First, the “extended therapeutic response” of

a biologic agent (such as rituximab), when combined with methotrexate to treat RA, had been observed and was well-known before the earliest priority date of the '161 patent. (Ex. 1002 at ¶¶ 95-99.) Second, it was also well-known before the earliest priority date of the '161 patent that one of the reasons why an “extended therapeutic response” was observed is due to methotrexate’s ability to suppress a patient’s immune response to the biologic agent—the so-called anti-drug antibody response (or HAMA/HACA response). (*Id.* at ¶ 100.) As discussed by Dr. Kalden, practitioners were aware long before the earliest priority date of the '161 patent that rituximab could elicit just such a HAMA/HACA response in a patient. (*Id.* at ¶ 101.) This is why the 1997 FDA-approved rituximab label cautions practitioners about rituximab’s ability to induce a HAMA/HACA response in its “PRECAUTIONS” section. (Ex. 1006 at 1.) Third, Dr. van Vollenhoven based his conclusions on Ex. 1033. Assuming that one could conclude from Ex. 1033 that there existed an “extended therapeutic response” when rituximab was combined with methotrexate, it is clear from the conditions of the study that the “extended therapeutic response” cannot be extended across the full scope of the claims because: (i) unexpected results were only seen “after 24 weeks,” whereas the challenged claims require only one dose of methotrexate and more than one dose of rituximab; and (ii) the clinical study applied only to a small subset of the patient population covered by the challenged claims. (*See* Ex. 1002 at ¶¶ 103-

107.) Therefore, the purported unexpected result identified by Dr. van Vollenhoven is not commensurate in scope with the claims. (*Id.* at ¶¶ 106-107.)

XI. CONCLUSION

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

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

Dated: December 15, 2014

Respectfully submitted,
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Attachment A: Certificate of Service

CERTIFICATE OF SERVICE

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

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**Attachment B: List of Evidence
and Exhibits Relied upon in the Petition**

| Exhibit | Reference |
|----------------|--|
| 1001 | U.S. Patent No. 7,820,161 |
| 1002 | Declaration of Joachim R. Kalden, M.D, in Support of the Petition for Inter Partes Review of U.S. Patent. No. 7,820,161, dated Dec. 8, 2014 |
| 1003 | O'Dell J, <i>Methotrexate Use in Rheumatoid Arthritis</i> , Rheumatic Disease Clinics of North America, Vol. 23, No. 4, pp 779-796 (1997) |
| 1004 | O'Dell J et al., <i>Treatment of Rheumatoid Arthritis with Methotrexate Alone, Sulfasalazine and Hyrdoxychloroquine, or a Combination of All Three Medications</i> , Treatment of Rheumatoid Arthritis, Vol. 334 No. 20, pp 1287-1291 (1996) |
| 1005 | Schwieterman W, <i>Immunosuppression in Combination with Monoclonal Antibodies</i> , Biologic Agents in Autoimmune Disease, pp 291-298 (Mar. 2-5, 1995) |
| 1006 | 1997 Product Label for RITUXAN® |

| Exhibit | Reference |
|---------|--|
| 1007 | Information Disclosure Statement (November 3, 2000) |
| 1008 | Pincus T et al., <i>“No evidence of disease” in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?</i> , Clinical and Experimental Rheumatology, 15: 591-596 (1997) |
| 1009 | Kremer J, <i>Combination Therapy with Biologic Agents in Rheumatoid Arthritis: Perils and Promise</i> , Arthritis & Rheumatism, Vol. 41, No. 9, pp 1548-1551 (1998) |
| 1010 | Applicants’ Declaration Pursuant to 37 C.F.R. § 1.131 (May 21, 2003) |
| 1011 | Draft Guidance, Arthritis Advisory Committee, Food and Drug Administration, Center for Drug Evaluation and Research (Aug. 7, 1998) |
| 1012 | Guidance for Industry, Arthritis Advisory Committee, Food and Drug Administration, Center for Drug Evaluation and Research (Feb. 1999) |

| Exhibit | Reference |
|---------|---|
| 1013 | Tobinai K et al., <i>Feasibility and pharmacokinetic study of a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab) in relapsed B-cell lymphoma</i> , <i>Annals of Oncology</i> 9: 527-534 (1998) |
| 1014 | Declaration of Ronald van Vollenhoven (Jul. 30, 2007) |
| 1015 | Second Declaration of Ronald van Vollenhoven (Jan. 19, 2010) |
| 1016 | Verhoeven AC et al., <i>Combination Therapy in Rheumatoid Arthritis: Updated Systematic Review</i> , <i>British Journal of Rheumatology</i> , 37: 612-619 (1998) |
| 1017 | Kremer J, <i>The Changing Face of Therapy for Rheumatoid Arthritis</i> , <i>Rheumatic Disease Clinics of North America</i> , Vol. 21, No. 3, pp. 845-852 (1995) |
| 1018 | Kalden JR et al., <i>Biologic agents in the treatment of inflammatory rheumatic diseases</i> , <i>Current Opinion in Rheumatology</i> , 9:206-212 (1997) |

| Exhibit | Reference |
|---------|---|
| 1019 | Kavanaugh AF et al., <i>Anti-TNF-α Monoclonal Antibody (mAb) Treatment of Rheumatoid Arthritis (RA) Patients with Active Disease on Methotrexate (MTX); Results of a Double-Blind, Placebo Controlled Multicenter Trial</i> , <i>Arthritis Rheum.</i> ; Vol. 39, No. 9 (suppl) (1996) |
| 1020 | Kalden JR, <i>Rescue of DMARD failures by means of monoclonal antibodies or biological agents</i> , <i>Clinical and Experimental Rheumatology</i> , 15 (Suppl. 17): S91-S98 (1997) |
| 1021 | Maini R et al., <i>Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis</i> , <i>Arthritis & Rheumatism</i> , Vol. 41, No. 9, pp. 1552-1563 (1998) |
| 1022 | Boers M et al., <i>Randomised Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine with Sulphasalazine Alone in Early Rheumatoid Arthritis</i> , <i>The Lancet</i> , 350: 309-318 (1997) |

| Exhibit | Reference |
|---------|---|
| 1023 | Maloney DG et al., <i>Phase I Clinical Trial Using Escalating Single Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma</i> , Blood, Vol. 84, No. 8, pp. 2457-2466 (1994) |
| 1024 | Maloney D et al., <i>IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma</i> , Blood, Vol. 90, No. 6, pp. 2188-2195 (1997) |
| 1025 | Edwards JCW et al., <i>Rheumatoid Arthritis: the Predictable Effect of Small Immune Complexes in which Antibody Is Also Antigen</i> , British Journal of Rheumatology, 37: 126-130 (1998) |
| 1026 | Letter from Dr. Jeffrey Gryn to Cooper Cancer Institute, dated May 6, 1998 |
| 1027 | U.S. Patent Application Ser. No. 09/564,288 |
| 1028 | Request for Continued Examination (Jun. 20, 2006) |
| 1029 | '161 Prosecution History: Office Action (Feb. 7, 2007) |

| Exhibit | Reference |
|---------|---|
| 1030 | '161 Prosecution History: Response and Amendment (Dec. 5, 2007) |
| 1031 | '161 Prosecution History: Office Action (Jun. 29, 2009) |
| 1032 | '161 Prosecution History: Amendment and Reply (Dec. 29, 2009) |
| 1033 | Edwards JCW et al., <i>Efficacy of B-Cell-Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis</i> , N Engl J Med, Vol. 350, No. 25, pp 2572-2581 (2004) |
| 1034 | Kirwan J, <i>The Effect of Glucocorticoids on Joint Destruction in Rheumatoid Arthritis</i> , N Engl J Med, Vol. 333, No. 3, pp 142-146 (1995) |
| 1035 | Edwards JCW et al., <i>Is rheumatoid arthritis a failure of B cell death in synovium?</i> , Annals of the Rheumatic Diseases, 54; 696-700 (1995) |
| 1036 | L.S. De Clerk, <i>B Lymphocytes and Humoral Immune Responses in Rheumatoid Arthritis</i> , Clinical rheumatology, 14, Suppl. No. 2, pp. 14-18 (1995) |