Paper No.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Genentech, Inc. 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

TABLE OF CONTENTS

I. PRELIMINARY STATEMENT 1

II. MANDATORY NOTICES 4

A. Real Parties-in-Interest or Privies 4

B. Related Matters 4

C. Lead and Back-Up Counsel 4

D. Service Information 4

III. CERTIFICATION OF GROUNDS FOR STANDING 5

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED 5

V. SUMMARY OF THE '161 PATENT AND PROSECUTION HISTORY 5

A. The Claims of the '161 Patent 6

1. Independent Claims 1, 5, and 9 6

2. Dependent Claims 2-4, 6-8, and 10-12 7

B. Specification of the '161 Patent 9

C. Prosecution History of the '161 Patent 10

1. The Patentees Were Not Successful in Their Attempt to Patent the Treatment of RA with Rituximab Alone 10

2. The Patentees Canceled the Original Claims Directed to Treating RA with Rituximab Alone in the Face of Edwards 1998 and Other Art 11

3. The Patentees' Rule 131 Declaration Alleging Prior Invention Related Only to Cancelled Claims Directed to a Single Therapeutic Agent 12

VI. CLAIM CONSTRUCTION 13

VII. LEVEL OF ORDINARY SKILL 14

VIII. THE STATE OF THE PRIOR ART 15

A. Rituximab and the Depletion of B-Cells 15

1. 1997 FDA-Approved RITUXAN® Product Insert 15

2. 1994 Maloney et al. Publication 17

3. 1997 Maloney et al. Publication 17

B. Treating RA with Rituximab By Destroying Mature B-Cells 18

1. 1995 Edwards Publication 18

2. 1998 Edwards Publication 19

3. 1998 Gryn Letter 20

C. Methotrexate: the "Gold Standard" and Dominant Therapy for Treating Rheumatoid Arthritis 21

1. 1995 Kremer Publication 22

2. 1996 O'Dell Publication 23

D. Combination RA Therapies Involving Methotrexate 23

1. O'Dell 1997 Publication 24

2. 1997 Pincus Publication 25

3. Kremer 1998 Publication 26

4. 1995 FDA CBER Meeting 28

5. Kalden 1997 Publication 29

6. 1998 Draft FDA Guidance and 1999 Final FDA Guidance 29

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE 31

A. No Differences Exist Between the Challenged Claims and the Prior Art 31

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) 31

2. "administering to the human methotrexate" (all claims) 33

3. Combining Rituximab and Methotrexate as Therapeutic Agents for Treating RA (all claims) 34

4. "an antibody that binds to the CD20 antigen on human B lymphocytes" (claims 5 and 9) 37

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) 38

6. "each administration of rituximab is a dose in the range from about 250 mg/m^2 to about 1000 mg/m^2" (claims 2, 6, and 10) 39

7. "administering to the human a glucocorticosteroid" (claims 3, 7, and 11) 40

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) 41

B. Proposed Combinations of Prior Art 42

C. Claim Charts Comparing the Challenged Claims Against the Prior Art 45

X. DR. VAN VOLLENHOVEN'S OPINIONS FAIL TO ESTABLISH UNEXPECTED RESULTS.....57

XI. CONCLUSION.....60

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 Pharmaceuticals[2] 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 rituximab;	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 an antibody	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 an antibody

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

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/m^2 to about 1000 mg/m^2.” 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 rituximab 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 antibody 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 antibody 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 rituximab 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 antibody 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 antibody 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/m^2 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/m^2 to about 1000 mg/m^2.” The broadest reasonable

interpretation of these claims would include doses ranging from some amount less than 250 mg/m^2 to some amount greater than 1000 mg/m^2.

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/m^2 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/m^2 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/m^2 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.*, TNFα and IL-1β 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-a 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/m^2 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/m^2 to about 1000 mg/m^2" (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/m^2 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/m^2) 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 mg/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 mg/m^2/infusion, if none of three initial

> patients or only two or less of six patients enrolled at 250 mg/m^2 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	• 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
	• 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	• 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	• 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:	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 cyclophopsphamide prior to bone marrow transplantation go into long-term remission." (p129) Ex. 1026 (Gryn): "Proposed Investigation: Perform a pilot study on the effect of Rituxin [sic] diseases with an autoimmune etiology such as: Rheumatoid Arthritis . . ." (p2).
(a) administering to the human more than one intravenous dose of a therapeutically effective amount of rituximab; and	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 *et al.* Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 1994; 84:2457-66." (p 130).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
	Ex. 1026 (Gryn): "Rituxin [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocyes" (p2); "Rituxin [sic] will be given in its standard dose." (p2). 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). 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).
(b) administering to the human methotrexate.	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

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
	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). 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). Ex. 1016 (Verhoeven): Table I (p614). Ex. 1020 (Kalden): "Combining methotrexate and the repeated administration of anti-TNF-a 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." (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).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
2. The method of claim 1, wherein each administration of the rituximab is a dose in the range from about 250 mg/m^2 to about 1000 mg/m^2.	Ex. 1026 (Gryn): "Rituxin [sic] will be given in its standard dose." (p2). 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). 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).
3. The method of claim 1, comprising administering to the human a glucocorticosteroid.	Ex. 1034 (Kirwan): "Oral glucocorticoids are widely used to treat patients with rheumatoid arthritis . . . .") (p142). 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 ≥ 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 (≤ 7.5 mg/d)." 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).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
	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).
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 rituximab in the subsequent dose exceeds the mg/m^2 dose of the rituximab in the initial dose.	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). 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).
5. 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 cyclophopsphamide prior to bone marrow transplantation go into long-term remission." (p129). Ex. 1026 (Gryn): "Proposed Investigation: Perform a pilot study on the effect of Rituxin [sic] diseases with an autoimmune etiology such as: Rheumatoid Arthritis . . . ." (p2).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
(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	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 *et al.* Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 1994; 84:2457-66." (p 130). Ex. 1026 (Gryn): "Rituxin [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocytes" (p2); "Rituxin [sic] will be given in its standard dose." (p2). 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). 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).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
(b) administering to the human methotrexate;	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). 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). Ex. 1016 (Verhoeven): Table I (p614).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
	Ex. 1020 (Kalden): "Combining methotrexate and the repeated administration of anti-TNF-a 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." (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).
wherein the CD20 antibody administration consists of intravenous administration of the CD20 antibody, and the CD20 antibody is rituximab.	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 *et al.* Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 1994; 84:2457-66." (p 130). *See* 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). Ex. 1026 (Gryn): "Rituxin [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocyes" (p2); "Rituxin [sic] will be given in its standard dose." (p2). 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

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.	*See* claim 2 above.
7. The method of claim 5, comprising administering to the human a glucocorticosteroid.	*See* claim 3 above.
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.	*See* claim 4 above.
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 cyclophopsphamide prior to bone marrow transplantation go into long-term remission." (p129).

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
	Ex. 1026 (Gryn): "Proposed Investigation: Perform a pilot study on the effect of Rituxin [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).
(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	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 *et al*. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 1994; 84:2457-66." (p 130). Ex. 1026 (Gryn): "Oncology patients treated with Rituxin [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 . . . Rituxin [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocyes" (p2); "Rituxin [sic] will be given in its standard dose." (p2). 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). Ex. 1023 (Maloney 1994): "In this phase I clinical trial, 15

Comparison to U.S. Patent No. 7,820,161	
'161 Patent Claims	**Exemplary Disclosure in Prior Art**
	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).
(b) administering to the human methotrexate;	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). 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

Comparison to U.S. Patent No. 7,820,161	
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	be less than those of many NSAIDs." (p592). Ex. 1016 (Verhoeven): Table I (p614). Ex. 1020 (Kalden): "Combining methotrexate and the repeated administration of anti-TNF-a 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." (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).
wherein the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab.	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 *et al.* Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 1994; 84:2457-66." (p 130). Ex. 1026 (Gryn): "Rituxin [sic] offers the opportunity to treat these diseases with an agent that affects only B-lymphocyes" (p2); "Rituxin [sic] will be given in its standard dose." (p2). 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).

Comparison to U.S. Patent No. 7,820,161	
'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.	*See* claims 2 and 6 above.
11. The method of claim 9, comprising administering to the human a glucocorticosteroid.	*See* 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.	*See* 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,
Proskauer Rose LLP

/s/ Siegmund Y. Gutman
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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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/s/ Gerald Worth
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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, *Methotrexate Use in Rheumatoid Arthritis*, Rheumatic Disease Clinics of North America, Vol. 23, No. 4, pp 779-796 (1997)
1004	O'Dell J et al., *Treatment of Rheumatoid Arthritis with Methotrexate Alone, Sulfasalazine and Hyrdoxychloroquine, or a Combination of All Three Medications*, Treatment of Rheumatoid Arthritis, Vol. 334 No. 20, pp 1287-1291 (1996)
1005	Schwieterman W, *Immunosuppression in Combination with Monoclonal Antibodies*, 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)
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Exhibit	Reference
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Paper No.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Genentech, Inc.
Patent Owner

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

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

Inter Partes Review No. TBD

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I. PRELIMINARY STATEMENT 1

II. MANDATORY NOTICES 4

A. Real Parties-in-Interest or Privies 4

B. Related Matters 4

C. Lead and Back-Up Counsel 4

D. Service Information 4

III. CERTIFICATION OF GROUNDS FOR STANDING 5

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED 5

V. SUMMARY OF THE '838 PATENT AND PROSECUTION HISTORY 5

A. The Claims of the '838 Patent 6

1. Independent Claims 1, 2, 8, 10, and 11 6

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

B. Specification of the '838 Patent 7

C. Prosecution History of the '838 Patent 9

VI. CLAIM CONSTRUCTION 10

A. The Preamble Phrase "who experiences an inadequate response to a TNFα-inhibitor" Is Not Limiting 11

B. Two 1000 mg Doses of the CD20 Antibody Must Necessarily Be "an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond" 13

C. The "Wherein" Clauses Relating to the Clinical Results of the Claimed Treatment Have No Patentable Weight 14

D. The Preamble "[a] method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive procession at weeks 24 and beyond" Is Not Limiting 16

VII. LEVEL OF ORDINARY SKILL 17

VIII. THE STATE OF THE PRIOR ART 18

A. RA Treatments and the American College of Rheumatology (ACR) Criteria 18

B. Treating RA with Anti-CD20 Antibody Rituximab 19

1. The Work of Dr. Edwards 20

2. Genentech's 2000 PCT Application (Curd et al.) 25

3. The De Vita Study 26

4. The Tuscano Abstract 27

C. TNFα-Inhibitors and Non-Responders 28

D. Combination Therapies Involving Methotrexate and Corticosteroids 30

1. Methotrexate 30

2. Corticosteroids 31

3. Combination Therapies Involving Methotrexate and Corticosteroids 32

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE 35

A. No Differences Exist Between the Challenged Claims and the Prior Art 35

1. "A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor" (claims 1, 2, 8, and 10) 35

2. "administering to the patient an antibody that binds to CD20," "wherein the antibody comprises rituximab," and "administering to the patient rituximab" (claims 1, 2, 3, 8) 39

3. "wherein the antibody is administered as two intravenous doses of 1000mg" and "wherein rituximab is administered as two intravenous doses of 1000 mg" (all claims) 41

4. "administering to the patient an antibody . . . in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 or beyond" (claim 2) 45

5. "wherein the patient has no erosive progression at weeks 24 and beyond," "wherein the clinical response is ACR50 at week 24," "wherein the clinical response is ACR70 at week 24," wherein the clinical response is no erosive progression at weeks 24 and beyond" (claims 10, 12-14) 47

6. "A method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences and inadequate response to a TNFα-inhibitor" (claim 11) 49

7. "wherein the patient is further treated with concomitant methotrexate (MTX)," "administering methotrexate to the patient," and "administering to the patient rituximab, and methotrexate" (claims 4, 9, 10, and 11) 50

8. "wherein the patient is further treated with a corticosteroid regimen" and "wherein the corticosteroid regimen consists of methylprednisolone and prednisone" (claims 5 and 6) 52

9. "wherein the CD20 antibody is the only B-cell surface marker antibody administered to the patient" (claim 7) 54

B. Proposed Combinations of Prior Art 54

1. Edwards VI (Ex. 1003) and Genentech Press Release (Ex. 1004) Anticipate Claims 1-5 and 7-14 54

2. All Challenged Claims Are Rendered Obvious by the Prior Art 55

X. SECONDARY CONSIDERATIONS 57

XI. CONCLUSION 60

I. PRELIMINARY STATEMENT

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

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

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

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

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

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

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

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

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

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

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

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

II. MANDATORY NOTICES

A. Real Parties-in-Interest or Privies

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

B. Related Matters

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

C. Lead and Back-Up Counsel

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III. CERTIFICATION OF GROUNDS FOR STANDING

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

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

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

V. SUMMARY OF THE ’838 PATENT AND PROSECUTION HISTORY

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

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

A. The Claims of the '838 Patent

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

Claims 1, 2, 8, and 10 share the same preamble: "[a] method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor." The preamble of claim 11 is somewhat different: "[a] method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα-inhibitor." As explained below, the preamble phrase "who experiences an inadequate response to a TNFα-inhibitor," which appears in all of the challenged claims, is not a limitation. *See* Section VI.A *infra*. Nor is the preamble of claim 11 a limitation on claim scope. *See* Section VI.D *infra*.

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

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

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

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

B. Specification of the ’838 Patent

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

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

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

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

> [T]he invention is not limited to a prior therapy step with such a TNFα-inhibitor; for instance, the patient may be considered to be prone to experience a toxicity, e.g. cardiac toxicity, with a TNFα-inhibitor before therapy therewith has begun, or the patient may be determined to be one who is unlikely to respond to therapy with a TNFα-inhibitor.

(*Id*. at 28:55-61.)

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

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

C. Prosecution History of the ’838 Patent

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

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

VI. CLAIM CONSTRUCTION

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

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

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

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

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

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

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

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

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

> [T]he invention is not limited to a prior therapy step with such a TNFα-inhibitor; for instance, the patient may be considered to be prone to experience a toxicity, e.g. cardiac toxicity, with a TNFα-inhibitor before therapy therewith has begun, or the patient may be determined to be one who is unlikely to respond to therapy with a TNFα-inhibitor.

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

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

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

B. Two 1000 mg Doses of the CD20 Antibody Must Necessarily Be "an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond"

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

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

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

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

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

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

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

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

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

> The wherein clauses do not inform the mechanics of how the "administering" or "contacting" steps are performed; rather, the wherein clauses merely characterize the result of that step. Therefore, the wherein clause is not entitled to weight in construing the claims.

Id.

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

D. The Preamble "[a] method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive procession at weeks 24 and beyond" Is Not Limiting

The preamble of claim 11 reads: "[a] method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα-inhibitor." The preamble merely states the purpose or intended use of the invention, which is set forth fully in the body of the claim. The broadest reasonable construction of claim 11 is that the preamble is not a limitation on the scope of the claim.

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

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

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

VII. LEVEL OF ORDINARY SKILL

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

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

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

VIII. THE STATE OF THE PRIOR ART

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

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

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

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

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

B. Treating RA with Anti-CD20 Antibody Rituximab

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

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

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

1. The Work of Dr. Edwards

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

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

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

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

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

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

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

According to Edwards IV, "[a]n open study of B-lymphocyte depletion was undertaken in rheumatoid arthritis (RA) patients to test the hypothesis that B lymphocytes may be essential to disease perpetuation." (Ex. 1022 at 205.) The paper reports that "[f]ive patients with refractory RA were treated with a monoclonal anti-CD20 antibody, cyclophosphamide and prednisolone and followed for 12-17 months." (*Id.*) All patients received four IV infusions of rituximab on day 2 (300 mg), day 8 (600 mg), day 15 (600 mg), and day 22 (600 mg), for a total dose of 2100 mg. (*Id.* at 206.) Patients also received oral administrations of prednisolone. (*Id.*) The results of the study showed that "[a]t 26 weeks all patients satisfied the American College of Rheumatology ACR50 and patients 1-3 the ACR70 criteria of improvement without further therapy." (*Id.*) The paper concludes that "[t]hese finding are consistent with the concept that RA is critically dependent on B lymphocytes and suggest that B-lympocyte depletion may be a safe and effective therapy." (*Id.*)

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

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

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

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

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

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

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

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

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

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

The Curd PCT Publication described the intravenous administration of more than one dose of rituximab for treating RA. (*See, e.g., id.* at 25:17-18 ("RITUXAN® is administered intravenously (IV) to the RA patient according to any of the following dosing schedules . . . [showing various doses on days 1, 8, 15 & 22].").) The Curd PCT Publication also allowed for multiple doses in a broad range: "Suitable dosages for [RITUXAN®] are, for example, in the range from about 20mg/m^2 to about 1000mg/m^2." (*Id.* at 23:18-19.) Those relative doses

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

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

3. The De Vita Study

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

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

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

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

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

4. The Tuscano Abstract

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

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

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

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

C. TNFα-Inhibitors and Non-Responders

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

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

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

In 2001, a separate publication by Seymour et al. reported similar response rates for TNFα-inhibitors etanercept and infliximab. (Ex. 1011 at 201 ("There are currently no predictors of a good response to anti-TNF drugs and a percentage of patients fail to respond to treatment (25% to 38% of etanercept [Enbrel®] patients; 21% to 42% of infliximab [Remicade®] patients).").) The paper estimated that

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

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

D. Combination Therapies Involving Methotrexate and Corticosteroids

1. Methotrexate

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

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

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

2. Corticosteroids

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

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

3. Combination Therapies Involving Methotrexate and Corticosteroids

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

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

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

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

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

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

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

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

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

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

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

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

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

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

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

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

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

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

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

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

(Ex. 1009 (emphasis added).)

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

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

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

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

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

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

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

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

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

In 2000, the published Curd PCT Publication described the intravenous administration of more than one dose of rituximab for the purpose of treating RA. *See* Section VIII.B.2 *supra*. The Curd PCT Publication described the intravenous administration of more than one dose of rituximab for treating RA. (*See, e.g.*, Ex. 1005 at 25:17-18 ("RITUXAN® is administered intravenously (IV) to the RA patient according to any of the following dosing schedules . . . [showing various doses on days 1, 8, 15 & 22].").)

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

In 2002, Tuscano published an abstract titled, "Successful Treatment of Infliximab-Refractory Rheumatoid Arthritis with Rituximab." *See* Section VIII.B.4 *supra*. The abstract "describe[d] the initial data of a clinical trial using rituximab alone for the treatment of erosive RA in patients that have previously failed multiple DMARD's including infliximab." (Ex. 1008.)

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

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

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

The Curd PCT Publication disclosed multiple IV doses of rituximab in a range that includes 1000 mg. The reference states, in pertinent part, "[O]ne may administer . . . one or more subsequent dose(s) . . . and the subsequent dose may be in the range from about 250mg/m^2 to about 1000mg/m^2." (Ex. 1005 at 23:23-27.) This dosing range corresponds to absolute doses of about 32 mg to about 1600 mg for an average patient, assuming an average body surface area of 1.6 m^2. (*See* Ex. 1002 at ¶ 84.) The Curd PCT Publication creates a presumption of obviousness because the range of possible rituximab doses disclosed in the prior art includes the claimed 1000 mg amount. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1332 (Fed. Cir. 2004) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness"); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed

invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations").

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

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

In *Hoffmann La Roche v. Apotex*, the Federal Circuit Court of Appeals held that it was obvious to select once monthly dosing of a known drug by scaling up a known daily dosing regimen. 748 F.3d at 1329-35. Specifically, the Court held that it was obvious to select once monthly oral dosing of ibandronate (a drug for

treating osteoporosis) at 150 mg, concluding that "it was reasonable to expect that a once monthly dose of 150 mg would have roughly the same efficacy as a daily dose of 5 mg." *Id.* at 1332-33. Further, evidence supporting superior efficacy for that dose "does not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg." *Id.* at 1334. Here, the prior art established at least a reasonable expectation of success using two intravenous doses of rituximab to treat RA. (Ex. 1002 at ¶ 88.)

The prior art also provided substantial guidance as to the total dose that would produce effective results. (Ex. 1002 at ¶ 87.) The results of Edwards IV demonstrated the efficacy of four weekly doses of rituximab totaling 2100 mg. (Ex. 1022 at 206, 207 ("A simple binomial analysis indicates that further, similar cases treated in the same way can be expected with 95% confidence to have a minimum chance of 47.8% of achieving ACR50 6 months after B-lymphocyte depletion . . . the same percentage figures can be applied to ACR70 at 18 months.").) In light of similar evidence, the Federal Circuit concluded "it was reasonable to expect that a once monthly dose of 150 mg would have roughly the same efficacy as a daily dose of 5 mg." *Hoffmann-La Roche*, 748 F.3d at 1333.

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

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

4. "administering to the patient an antibody . . . in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 or beyond" (claim 2)

Claim 2 includes two separate elements regarding the amount of antibody administered to the patient. First, the claim requires the administration of an antibody in an amount effective to provide certain clinical responses in patient (*e.g.*, ACR50 at week 24). Second, the claim requires the administration of two 1000 mg doses of the antibody. In order to reconcile these two elements, two 1000 mg doses of the antibody must be an amount sufficient to provide the required clinical responses. *See* Section VI.B *supra*. This is confirmed by the patent's specification. The lone example in the '838 patent identifies two "therapeutically effective" dosing regimens of CD20 antibody: (1) two bi-weekly 1000 mg doses; and (2) four weekly doses of 375 mg/m^2. (*See* Ex. 1001 at 31:29-31 ("Patients are treated with a therapeutically effective dose of the CD20 antibody, for instance, 1000 mg i.v. on Days 1 and 15, or 375 mg/m^2 i.v. weekly x 4.").) The specification identifies "potential secondary endpoints" for these treatments, including "[p]roportion of patients with ACR50 and 70 responses at Week 24." (*Id.* at 32:3-6.)

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

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

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

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

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

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

The lone example in the specification of the '838 patent confirms that the co-administration of rituximab and methotrexate produces the required clinical responses. The example identifies the dosing levels for rituximab and methotrexate (MTX). (*See* Ex. 1001 at 31:29-33 ("Patients are treated with a therapeutically effective dose of the CD20 antibody, for instance, 1000 mg i.v. on Days 1 and 15, or 375 mg/m^2 i.v. weeklyx4. Patients may also receive concomitant MTX (10-25 mg/week per oral (p.o.) or parenteral) . . . .").) The example then identifies "potential secondary endpoints" for these treatments, including a "[p]roportion of patients with ACR50 and 70 responses at Week 24." (*Id*. at 32:3-6.)

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

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

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

6. "A method of achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond, in a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα-inhibitor" (claim 11)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

B. Proposed Combinations of Prior Art

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

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

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

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

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

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

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

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

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

X. SECONDARY CONSIDERATIONS

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

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

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

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

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

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

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

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

XI. CONCLUSION

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

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

Dated: December 15, 2014

Respectfully submitted,
Proskauer Rose LLP

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Attachment A: Certificate of Service

CERTIFICATE OF SERVICE

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

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

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

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

Exhibit	Reference
1011	Seymour H E et al., *Anti-TNF agents for rheumatoid arthritis*, Br J Clin Pharmacol, 51, 201-208 (2001)
1012	1997 Product Label for RITUXAN®
1013	Pincus T et al., *"No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?*, Clinical and Experimental Rheumatology, 15: 591-596 (1997)
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Exhibit	Reference
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Exhibit	Reference
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Exhibit	Reference
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Paper No.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Biogen Idec, Inc.
Patent Owner

Patent No. 8,329,172 B2
Issued: December 11, 2012
Filed: August 18, 2007
Inventor: Antonio J. Grillo-López

Title: COMBINATION THERAPIES FOR B-CELL LYMPHOMAS COMPRISING ADMINISTRATION OF ANTI-CD20 ANTIBODY

Inter Partes Review No. TBD

PETITION FOR INTER PARTES REVIEW

TABLE OF CONTENTS

Page

I. PRELIMINARY STATEMENT 1

II. MANDATORY NOTICES 4

A. Real Parties-in-Interest or Privies 4

B. Related Matters 5

C. Lead and Back-Up Counsel 5

D. Service Information 5

III. CERTIFICATION OF GROUNDS FOR STANDING 5

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED 6

V. SUMMARY OF THE '172 PATENT AND PROSECUTION HISTORY 6

A. The '172 Patent's Issued Claim 7

B. The Claims Upon Which Issued Claim 1 of the '172 Patent is Based 8

C. Claim 1 Is Not Entitled to the '180 Provisional Application's Early Filing Date 8

D. Prosecution of the Challenged Claim Did Not Address Prior Art That Discussed "Maintenance Therapy" Following Chemotherapy to Treat Non-Hodgkins Lymphoma 10

E. Patentee's Failed Attempt to Demonstrate Unexpected Results 11

VI. CLAIM CONSTRUCTION 12

A. "A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising" 12

B. "administering to the patient chemotherapy consisting of CVP therapy to which the patient responds." 12

C. "followed by rituximab maintenance therapy" 13

D. "wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years." 15

VII. LEVEL OF ORDINARY SKILL 15

VIII. THE STATE OF THE PRIOR ART 16

A. Chemotherapy for Low Grade Non-Hodgkin's B-cell Lymphoma 16

B. Maintenance therapy for LG-NHL 19

1. Maintenance therapy with interferon 19

2. The German Low-Grade Lymphoma Study Group trial as reported in 1994 and 1996—CVP followed by interferon maintenance therapy 20

C. Treating B-cell Lymphoma with Rituximab 21

1. 1994 Maloney et al. Publication 22

2. The July 1997 FDA Biological Response Modifiers Advisory Committee Hearing 22

3. 1997 FDA-Approved RITUXAN® Product Insert 25

4. 1998 McLaughlin et al. Publication 25

5. The ECOG 4494 and ECOG 1496 Clinical Trials 28

IX. THE CHALLENGED CLAIM IS UNPATENTABLE 31

A. Claim 1 is anticipated by ECOG 1496 31

B. Claim 1 of the '172 patent is obvious 32

1. Those of ordinary skill in the art were motivated to identify an effective and tolerable maintenance therapy for treating LG-NHL 32

2. Rituximab was known to possess properties that would be beneficial for maintenance therapy 33

3. All the elements of claim 1 were known in the prior art, and one of ordinary skill in the art was motivated to combine them with a reasonable expectation of success 35

C. Proposed Combinations of Prior Art That Anticipate and Render Obvious Claim 1 of the '172 Patent 38

1. ECOG 1496 (Ex. 1003) Anticipates Claim 1 38

2. ECOG 4494 (Ex. 1004) Renders Obvious Claim 1 38

3. ECOG 4494 (Ex. 1004) In Combination with Unterhalt 1996 (Ex. 1006) Renders Obvious Claim 1 40

4. ECOG 4494 (Ex. 1004) In Combination with the FDA Transcript (Ex. 1007) Renders Obvious Claim 1 41

5. McNeil (Ex. 1005) Renders Obvious Claim 1 42

6. McNeil (Ex. 1005) In Combination with the 1997 Rituxan® Label (Ex. 1008) Renders Obvious Claim 1 43

7. Either McNeil (Ex. 1005) Alone (or McNeil In Combination With the 1997 Rituxan® Label (Ex. 1008)) In Combination With Unterhalt (Ex. 1006) Renders Obvious Claim 1 44

8. McNeil (Ex. 1005) Alone (or McNeil In Combination with the 1997 Rituxan® Label (Ex. 1008)) In Combination With the 1997 FDA Transcript (Ex. 1007) Renders Obvious Claim 1 45

9. McLaughlin (Ex. 1009) Renders Obvious Claim 1 45

10. McLaughlin 1998 (Ex. 1009) In Combination with McNeil (Ex. 1005) Renders Obvious Claim 1 48

D. Claim Chart Comparing the Challenged Claim to the Prior Art 49

X. HOCHSTER FAILS TO ESTABLISH UNEXPECTED RESULTS 56

XI. CONCLUSION 60

I. PRELIMINARY STATEMENT

The challenged, and only, claim of U.S. Patent No. 8,329,172 ("the '172 patent") (Ex. 1001) relates to a method of treating low-grade B-cell non-Hodgkin's lymphoma (sometimes referred to as "LG-NHL") by administering two different agents—CVP and rituximab— both of which were known and used to treat LG-NHL long before the earliest priority date of the '172 patent. CVP (a/k/a COP)[1] is a combination chemotherapy regimen that traditionally had been used for the treatment of LG-NHL. Rituximab is an antibody that had already been FDA approved to treat LG-NHL, and had been marketed under the tradename RITUXAN®. The claim is generally directed to administering CVP therapy to which a patient responds, followed by administrations of rituximab every 6 months, so as to provide maintenance therapy for 2 years.

The precise method claimed had been described in an anticipatory printed publication—ECOG 1496 (Ex. 1003)—more than one year before the earliest priority date to which the '172 patent is entitled. ECOG 1496 is the protocol for a clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG), a well-known organization that is publicly supported by the National Cancer

[1] CVP is a combination of the drugs cyclophosphamide, vincristine, and prednisone. Because the drug vincristine is also known as oncovin, CVP therapy is also sometimes referred to by the acronym "COP."

Institute ("NCI") of the U.S. National Institutes of Health. ECOG is a cooperative group made up of a network of physicians and researchers at numerous private and public institutions who are engaged in oncology research, including clinical trials. The protocols of, and results obtained from, clinical trials conducted by ECOG are publicly available and disseminated. ECOG 1496 is one such publication.

Each element of the challenged claim had also been extensively discussed in other literature published more than one year before the earliest priority date of the '172 patent. For example, ECOG 4494 (Ex. 1004), another clinical trial protocol published by ECOG, and McNeil (Ex.1005), both described the use of a similar chemotherapy combination (CHOP), followed by the precise rituximab maintenance therapy recited in the claim, to treat non-Hodgkin's lymphoma. CHOP is identical to the CVP chemotherapy recited in the challenged patent claim, except that it has one additional ingredient, hydroxydaunorubicin—the "H" in CHOP, which was known to be toxic and not beneficial for the treatment of LG-NHL.

McLaughlin (Ex.1009) is acknowledged by the patent owner, Biogen Idec, as having successfully provided the foundation for, and encouraged the use of, the patent's claimed method of using rituximab maintenance therapy for the treatment of LG-NHL. Specifically, Biogen Idec states on its website for RITUXAN® that "B-cell depletion observed in the McLaughlin trial ***formed the basis*** for the ECOG

1496 dosing strategy following first-line CVP induction in low-grade NHL." (emphasis added). The ECOG 1496 dosing strategy for which McLaughlin "formed the basis" is the precise dosing strategy of claim 1 of the '172 patent. Indeed, McLaughlin strongly encouraged the treatment of LG-NHL by using rituximab maintenance therapy following prior chemotherapy, including CVP. It further shows that the standard course of rituximab therapy is effective to deplete B-cells for at least 6 months, the same interval between administrations of rituximab maintenance therapy that is recited in claim 1.

Other prior art encouraged the use of biologic therapeutics (of which rituximab is an example) as maintenance therapy for as long as possible, including for two years or more, following CVP therapy for the treatment of LG-NHL (*see, e.g.*, Unterhalt 1996 (Ex. 1006)). And still other publications describe the use of CVP to treat a form of LG-NHL, followed by multiple courses of rituximab therapy (*see, e.g.*, 1997 FDA Transcript (Ex. 1007)).

All the elements of the single '172 patent claim were thus well known to a person of ordinary skill, who had a strong reason to combine them. Among other things, encouraging data from studies where biologic therapeutics (such as interferon[2]) were used as maintenance therapy, following CVP therapy, for the

[2] Interferon is a hormone made by white blood cells to stimulate the immune system.

treatment of LG-NHL, provided those of ordinary skill with much more than a reasonable expectation of success. This was particularly the case given rituximab's well-known advantages over other such biologic therapeutics, including rituximab's better toxicity profile. Ex. 1002 at ¶¶ 65-69.[3]

Notably, publications disclosing maintenance therapy for the treatment of LG-NHL were not cited during prosecution of the '172 patent. Such publications, however, provide the foundation for the current petition. Indeed, in Europe, the patentee surrendered a claim similar to the '172 patent claim in light of prior art publications that discussed maintenance therapy for the treatment of LG-NHL with various biologics including interferon and rituximab. Ex. 1057.

For all the reasons discussed herein, and in the supporting declaration by Dr. Michael L. Grossbard (Ex. 1002), claim 1 of the '172 patent should be held unpatentable as anticipated and/or obvious.

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")

[3] All page numbers cited herein refer to the original pagination of the exhibits.

B. Related Matters

Simultaneously with this petition, Petitioner has filed petitions for *Inter Partes* Review against United States Patent Nos. 7,820,161 and 7,976,838. The following patents and patent applications may claim the benefit of the priority of the filing date of U.S. Patent No. 8,329,172: 6,455,043, USSN 13/524837, USSN 13/868753, USSN 14/070256, and USSN 13/524896.

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 claim 1, the only issued claim of the ’172 patent (Ex. 1001), as unpatentable under 35 U.S.C. §§ 102 and 103 on the specific grounds set forth in Section IX below. This petition is supported by the Declaration of Michael L. Grossbard, M.D. (Ex.1002). The petition and supporting declaration show that there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claim. *See* 35 U.S.C. § 314(a).

V. SUMMARY OF THE ’172 PATENT AND PROSECUTION HISTORY

The ’172 patent names Antonio J. Grillo-López as the sole inventor and Biogen Idec as the assignee. Ex. 1001. The ’172 patent issued on December 11, 2012 from application ser. no. 11/840,956 (Ex. 1058, “the ’956 application”), which was filed on August 18, 2007 but claimed priority, through a series of continuation applications, to U.S. patent application ser. no. 09/372,202 (“the ’202 application”), filed on August 11, 1999. The ’202 application claimed priority to provisional application ser. no. 60/096,180 (Ex. 1059, “the ’180 provisional application”), which was filed even earlier on August 11, 1998. As explained below, however, the ’180 provisional application does not provide adequate § 112 support for the ’172 patent’s issued claim. Hence, August 11, 1999, the filing date

of the ’202 Application, is the earliest possible effective filing date for claim 1 of the ’172 patent.

Any publication prior to August 11, 1998 therefore qualifies as prior art under 35 U.S.C. §102(b) (“the 102(b) date”).

A. The ’172 Patent’s Issued Claim

Claim 1, the ’172 patent’s only claim, recites a method of treating LG-NHL patients with two known LG-NHL treatments, (i) CVP chemotherapy and (ii) rituximab. The claim reads as follows (emphasis added):

> 1. A method of treating low grade B-cell non-Hodgkin’s lymphoma in a human patient comprising **administering to the patient chemotherapy consisting of CVP therapy** to which the patient responds, **followed by rituximab maintenance therapy**, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 **every 6 months, and wherein the maintenance therapy is provided for 2 years**.[4]

The claim’s recited schedule of four weekly doses of 375 mg/m^2 had already been established as the recommended dosing schedule for RITUXAN® at least as early as RITUXAN®’s 1997 label. Ex. 1008; *see* section VIII C.3 below.

[4] Except as noted, all emphases in quotations have been added.

B. The Claims Upon Which Issued Claim 1 of the ’172 Patent is Based

Claim 1 of the ’172 patent originated from claims 41-43, which were added to the ‘956 application on October 31, 2007, *more than eight years after* the ’202 application had been filed. *See* Ex. 1060 at 4. Those new claims read:

> 41. A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising administering to the patient CVP therapy followed by rituximab maintenance therapy, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months.
>
> 42. A method according to claim 42, wherein the patient exhibits a response to the CVP therapy.
>
> 43. A method according to claim 42, wherein the maintenance therapy is provided for 2 years.

Claim 41 was later amended to incorporate the elements of claims 42 and 43, and subsequently issued as claim 1 of the ’172 patent. *See* Ex. 1061 at 2, 5.

C. Claim 1 Is Not Entitled to the ’180 Provisional Application’s Early Filing Date

When the applicants added new claims 41-43 they did not cite for support to any disclosure in the earlier ’180 provisional application. Instead, for support, they referenced “page 28, lines 16-21” of the ’956 application, Ex. 1060 at 5, which corresponds to the passage at column 13, lines 8-16 of the issued ’172 patent and reads as follows:

> A Phase III study conducted by ECOG in patients with low-grade NHL is comparing the combination of cyclophosphamide and fludarabine (Arm A) with standard CVP therapy (Arm B). In the randomization to Arm A or Arm B, patients are stratified by age, tumor burden, histology, and B symptoms. Responders in both arms will undergo a second randomization to Rituximab maintenance therapy (375 mg/m^2 weekly times 4 every 6 months for 2 years (Arm C) or to observation (Arm D).

The ’180 provisional application does not contain the above passage. In fact, the ’180 provisional application (Ex. 1059) consists entirely of a compilation of a published article, several abstracts and a poster presentation, followed by two pages of claims. Nothing in that compilation describes the specific combination claimed in the ’172 patent.

Accordingly, the ’180 provisional application does not provide adequate § 112 support for claims 41-43 presented in the ’956 application and, for at least the same reasons, it does not provide adequate § 112 support for issued claim 1 of the’172 patent. The patent examiner agreed, noting that “[t]he claimed inventions [including then-pending claims 41-43] are not disclosed in parent application 60/096180. Therefore, regarding the application of prior art, the instant application is not entitled to priority to said application.” Ex. 1062 at 4. The applicants never traversed that statement and, by not doing so, effectively conceded the Office’s position on priority. In view of this, the earliest priority date to which claim 1 of

the ’172 patent is entitled is the filing date of the ‘202 application—August 11, 1999. Any publication on or before August 11, 1998, for example, is therefore prior art under § 102(b).

D. Prosecution of the Challenged Claim Did Not Address Prior Art That Discussed “Maintenance Therapy” Following Chemotherapy to Treat Non-Hodgkins Lymphoma

Claims 41-43 were rejected as obvious during prosecution of the ’956 Application before being finally allowed to issue as claim 1 of the’172 patent. In contrast to the art upon which this petition is based, however, none of the art cited by the Examiner during prosecution discusses the use of “maintenance therapy” following chemotherapy (*e.g.*, CVP or CHOP) to treat non-Hodgkins lymphoma, much less low grade non-Hodgkins lymphoma.

For example, on February 29, 2012, in the last rejection of claim 41 (which is the predecessor to the challenged claim) before allowance, the Examiner cited two different combinations of references as the bases for obviousness rejections. Ex. 1063 at 7-11. In each combination of references, the Examiner relies on “IDEC Pharmaceuticals Press Release (12/9/96)” as the primary reference. As characterized by the Examiner, the press release

> discloses that it is desirable to use rituximab in combination with other anti-cancer treatments. Said reference does not disclose use of rituximab in combination with CVP (aka COP).

Id. at 7. None of the cited references were described as discussing maintenance therapy. Indeed, in its May 22, 2012 Response, the applicant stated that a "prima facie case for obviousness has not been made out as to claim 41," and further noted that "[t]he Examiner has not shown how the combined art teaches the aspects of claim 41 bolded above [including maintenance therapy]." Ex. 1064 at 4.

In contrast to the references cited during prosecution, this petition cites a number of references that describe maintenance therapy for treating NHL, including at least the following § 102(b) prior art—ECOG 1496 (Ex. 1003); ECOG 4494 (Ex.1004); McNeil (Ex.1005); Unterhalt 1996 (Ex.1006); and McLaughlin (Ex.1009).

E. Patentee's Failed Attempt to Demonstrate Unexpected Results

In its May 22, 2012 Response, the applicant attempted to use Hochster to demonstrate unexpected results associated with the claimed method. Ex. 1064 at 7-10. However, as discussed in greater detail below (*see* Section X), the Examiner did not rely on, and the applicant did not attempt to demonstrate unexpected results over, prior art that described the use of maintenance therapy to treat LG-NHL. Indeed, such prior art shows that the results that the applicant characterizes as "unexpected" were, in fact, entirely expected. Ex.1002 at ¶¶ 113-121, 137-140. In any event, the results relied upon by the applicant are otherwise insufficient to impart patentability to the '172 patent claim.

VI. CLAIM CONSTRUCTION

Because the ’172 patent has not yet expired, the challenged claim should be given its broadest reasonable construction in light of the specification of the patent. 37 C.F.R. § 42.100(b).

A. “A method of treating low grade B-cell non-Hodgkin’s lymphoma in a human patient comprising”

Under the broadest reasonable construction standard, the “comprising” language of the claim encompasses, among other things, additional forms of treatment that may be administered to the patient as long as the patient is administered “chemotherapy consisting of CVP therapy to which the patient responds followed by rituximab maintenance therapy . . . .”

B. “administering to the patient chemotherapy consisting of CVP therapy to which the patient responds.”

Under the broadest reasonable construction standard, “chemotherapy consisting of CVP” means that the chemotherapy to which the patient responds, and which is followed by rituximab maintenance therapy, must be CVP. A patient who responds to “chemotherapy consisting of CVP” will have a response, including, for example, a complete response (CR) or a partial response (PR). Ex.1002 at ¶¶ 29-30, 38-39. When a patient has a complete response or complete remission (CR), the patient will have only minimal residual disease (MRD). *Id*. at ¶¶ 29, 57. When a patient has a partial response or partial remission (PR), the patient will have a substantially reduced tumor burden. *Id*. at ¶ 29. A patient with a

CR or PR will have a lower tumor burden relative to that which existed prior to the CVP chemotherapy. *Id.* at ¶¶ 29-30,38-39. The specification is consistent with this definition and explains that a patient who responds to CVP can have a response that includes a complete response (CR) or a partial response (PR):

> Complete response required the regression of all lymph nodes to <1×1 cm2 demonstrated on two occasions at least 28 days apart on neck, chest abdomen, and pelvic CT scans, resolution of all symptoms and signs of lymphoma, and normalization of bone marrow, liver, and spleen. Partial response required a ≧50% decrease in the sum of the products of perpendicular measurements of lesions without any evidence of progressive disease for at least 28 days. Patients who did not achieve a CR or PR were considered non-responders, even if a net decrease (>50%) of measurable disease was observed.

Ex. 1001 at col. 9, lines 14-25.

C. "followed by rituximab maintenance therapy"

"Followed by" means that the "rituximab maintenance therapy" is administered at any time after the patient has responded to the chemotherapy consisting of CVP therapy, for example, after a CR or PR. Ex. 1002 at ¶ 62. "Rituximab" refers to the chimeric, anti-CD20 antibody also known as C2B8, for example. An example of such an antibody is RITUXAN®, which has been commercially marketed since at least 1997. Ex. 1001 at col. 1, lines 47-50 and col. 2, lines 59-60.

"Maintenance therapy" is not specifically defined in the '172 patent. One of ordinary skill in the art would understand that "maintenance therapy" means treating a patient who has responded to "chemotherapy consisting of CVP" for the purpose of treating the MRD (for patients who responded with CR), prolonging the remission and/or preventing relapse. Ex. 1002 at ¶¶ 32, 42, 113-114. In the context of claim 1, "maintenance therapy" refers to administering rituximab after "chemotherapy consisting of CVP" for the purpose of treating the patient's MRD (for patients who responded with CR), prolonging remission, and/or to prevent relapse. *Id.* This is consistent with statements made in prior art publications. *See* Ex. 1030 at 613 ("The aim [of BCG maintenance] was to control, after complete remission, the residual and undetectable lymphoma cells"); Ex. 1029 at 96 ("BCG seems useful as maintenance treatment in preventing relapse in all varieties of non-Hodgkin's lymphomas"); Ex. 1033 at Abstract ("The best results have been reported when IFN [interferon] was used as maintenance therapy in patients with minimal residual disease or complete remission"); Ex. 1033 at 154 ("Because relapse remains as the most important problem in patients with low-grade lymphoma, IFN [interferon] has been tested as a maintenance therapy in patients who have achieved CR or a good partial response (GPR)"); Ex. 1065 at 1163, col. 1 ("We and others are conducting studies on the role of maintenance therapy in prolonging remission in low grade NHL."). The foregoing interpretation is also

consistent with the patentee's statements, during prosecution, arguing that the specification teaches maintenance therapy. *See, e.g.*, Ex. 1066 at 5 ("The benefits of such 'sequential' treatment regimes for prolonging remission or preventing relapse were disclosed . . . Thus, the specification read as a whole clearly described the presently claimed invention, including 'maintenance therapy' as in claim 41…."). In other words, the applicants associated "maintenance therapy" with prolonging remission or preventing relapse.

D. "wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years."

According to the 1997 FDA label for RITUXAN®, the standard course of rituximab therapy for treating LG-NHL is four weekly administrations at a dose of 375 mg/m^2 each. Ex. 1008 at 2, col. 1. Hence, according to the '172 patent claim, a course of rituximab maintenance therapy is provided every 6 months and must continue for at least two years, but can continue for a longer period of time due to the "comprising" transition language of the claim.

VII. LEVEL OF ORDINARY SKILL

LG-NHL is a chronic, incurable cancer that has been the subject of substantial research and published literature as seen from the numerous publications cited in the '172 patent. *See* Ex. 1002 at ¶ 35. Many doctors in the field participate in clinical trials involving new drugs and methods of treatment.

For this reason, hematologists and oncologists tend to be well informed about current trends and developing therapies for treating LG-NHL. *Id.* This was true in the 1990s and remains true today. *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 hematologist, oncologist, and/or medical researcher who understood the pathophysiology of NHL diseases and was knowledgeable about methods for treating NHL patients through experience in treating such patients and/or the medical literature. *See Id.* at ¶ 36. For convenience, persons having this ordinary level of skill are sometimes referred to as "oncologists" in this petition.

VIII. THE STATE OF THE PRIOR ART

A. Chemotherapy for Low Grade Non-Hodgkin's B-cell Lymphoma

B-cell lymphoma is a malignant disease characterized by uncontrolled growth of B-cells. B-cells, which are also known as "B lymphocytes," are white blood cells that secrete antibodies when they mature. Non-Hodgkin's lymphoma ("NHL") is a type of B-cell lymphoma. Low grade or "indolent" NHL grows more slowly than high and intermediate grade lymphomas, which are also referred to as "aggressive" lymphomas. Low grade NHL often affects follicular B-cells in the lymph nodes. Ex. 1002 at ¶¶ 51-54.

Chemotherapeutic drugs that target rapidly dividing cells are used to treat malignant diseases such as NHL. Ex. 1002 at ¶ 40. One common strategy is to use a combination of drugs with different mechanisms of action in order to increase efficacy by attacking multiple targets found in malignant cells and reduce the chance of developing of drug-resistant cells. Two closely related chemotherapy regimens were considered during prosecution of the '172 patent. *Id.* at ¶ 41. CVP is a combination of the drugs cyclophosphamide, vincristine, and prednisone. Because the drug vincristine is also known as oncovin, CVP therapy is also sometimes referred to by the acronym "COP." CHOP is another chemotherapeutic regimen that uses the same three drugs as CVP but, in addition, uses a fourth drug called hydroxydaunorubicin — the "H" in CHOP. Chemotherapy drugs, including those used in CVP and CHOP therapies, are known to have a variety of toxic side effects. Thus, oncologists must strike an appropriate balance between activity and toxicity in order to effectively treat the disease with tolerable side-effects. Prior to the 102(b) date, CHOP was the treatment of first choice for more aggressive, higher-grade lymphomas, and moderate intensity therapies such as CVP were preferentially used to treat low grade lymphomas. *Id.* at ¶ 55; Ex. 1011 at abstract and 1243. This remains true today.

The primary goal of chemotherapy is to drive cancer into remission. But chemotherapy rarely kills all of the billions of malignant cells that were present at

the start of treatment. Thus, even patients who appear to be in complete remission usually have "minimal residual disease" in the form of a relatively small number of malignant cells that can only be detected with highly sensitive molecular diagnostic techniques, such as PCR. Ex. 1002 at ¶¶ 57-59. Relapse occurs when these cells start growing again, leading to a recurrence of the disease. *Id*. at ¶ 57. Relapse may trigger the start of another course of chemotherapy with its toxic side-effects, and enhance the possibility that the cancer cells will develop resistance to chemotherapy. *Id*. at ¶ 61.

It was widely understood for at least 10 years before the priority date of the '172 patent that the malignant B-cells of LG-NHL are very difficult to completely eliminate. For example, Al-Ismail noted in 1987 that:

> It is perhaps a misnomer to use the terms 'favourable histology' or 'good prognosis' for patients with low grade lymphoma as they are a group of incurable diseases. Although they are highly responsive to a variety of treatment programmes, their relapse rate remains high.

Ex. 1024 at 1382. As a result, treatment of LG-NHL was characterized by repeated cycles of induction, remission and relapse, followed some period later by death. Periods of remission would become shorter over time, while periods of relapse would become longer as remaining cancerous cells became resistant to subsequent, and increasingly more aggressive, courses of treatment. In end stages of LG-NHL, the cancer typically prevailed and the patient died. Accordingly, before the '172

patent's priority date, oncologists, were motivated to find ways to prolong the periods of remission when treating LG-NHL. Ex. 1002 at ¶¶ 60-61.

B. Maintenance therapy for LG-NHL

Since at least 1976, maintenance therapy has been used to treat the residual disease after chemotherapy, surgery, or radiation therapy. *See* Ex. 1012 at 63-64. The therapy that precedes maintenance therapy is sometimes referred to as "induction" therapy. Ex. 1002 at ¶ 40. Maintenance therapy for LG-NHL was first attempted using chemotherapeutic drugs, *See* Exs. 1012 and 1025, but this approach was relatively toxic and did not prolong survival. Greater success was obtained using the immunomodulatory agents, such as interferon, as maintenance therapy.

1. Maintenance therapy with interferon

Interferon-α ("IFN"), like rituximab, is a biological response modifier ("BRM") that has been used in combination with chemotherapy to treat LG-NHL. Ex. 1002 at ¶ 65. Interferon is a hormone made by white blood cells to stimulate the immune system. Multiple clinical trials have shown that interferon maintenance therapy following chemotherapy can prolong progression-free survival. Ex. 1002 at ¶¶ 66, 140. For example, Aviles published a study entitled "Interferon Alpha 2b as Maintenance Therapy in Low Grade Malignant Lymphoma Improves Duration of Remission and Survival" (Ex. 1056); Arranz found "significant differences in

[progression-free survival] that favored the patients who received CVP + IFN" (Ex. 1067 at abstract); and Solal-Céligny reported that "the addition of IFNα to a doxorubicin-containing regimen for patients with advanced-stage and clinically aggressive FL [follicular lymphoma] not only increased PFS [progression-free survival], as in most other similar trials, but also prolonged OS [overall survival]," Ex. 1034 at abstract.

2. The German Low-Grade Lymphoma Study Group trial as reported in 1994 and 1996—CVP followed by interferon maintenance therapy

In 1994, Hiddemann published an introduction to an ongoing German study in which patients with LG-NHL were treated with CVP induction therapy followed by INF maintenance therapy. Ex. 1068. After reviewing the results of previous IFN maintenance therapy trials, Hiddemann concluded that better results were obtained when IFN maintenance therapy was continued for as long as possible. Specifically, Hiddemann noticed that the best results known at that time were from a French study (Ex. 1034) where IFN maintenance was continued for 18 months. As a result, Hiddemann hypothesized that the length of the disease free interval depends on the duration of IFN maintenance therapy—*i.e.*, the longer the maintenance therapy continued, the longer the disease free interval. The German study was therefore designed to continue interferon maintenance therapy for as long as possible, "until relapse or untolerable toxicity." *Id*. at 35, col. 1. In 1996, Unterhalt

et. al. published a preliminary report from the same German study that stated that disease-free survival increased from 12 to 31 months in LG-NHL patients that were treated with IFN maintenance. Ex. 1006. Unterhalt is prior art under 35 U.S.C. §102(b).

C. Treating B-cell Lymphoma with Rituximab

Rituximab is a monoclonal antibody created by Idec Pharmaceuticals (now Biogen Idec). In 1997, rituximab was approved in the United States for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma. It is marketed in the United States under the brand name RITUXAN®. Ex. 1008. Early in its development, rituximab was also known as "IDEC-C2B8." Ex. 1001 at col. 2, lines 59-60.

Rituximab is a humanized monoclonal antibody that binds to CD20, a protein specifically expressed on the surface of B-cells. Ex. 1008. Monoclonal antibodies are proteins that bind to a specific antigen, such as CD20. A humanized monoclonal antibody is a chimeric protein in which the antigen-binding regions from a mouse monoclonal antibody are fused into a human antibody backbone. Humanized antibodies can activate the human immune system when they bind to their target antigen, and they are less likely than murine antibodies to be rejected as a foreign protein by the immune system of a human patient. Thus, rituximab binds to a protein that is only expressed on B-cells, including the cancerous B-cells of

LG-NHL, and it activates the patient's immune system to kill the B-cells. Ex. 1002 at ¶¶ 74-75.

1. 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." Ex. 1046.

Maloney described a phase I clinical trial using rituximab to treat NHL. The publication reported "a dose-dependent, rapid and specific depletion of the B cells in all patients." Ex. 1046 at 2460, col 2. All patients completed the planned antibody infusion with minimal infusion-related toxicity. *Id.* at 2460. The paper hypothesized that "extension of these studies to patients with minimal residual disease [*e.g.*, CR or complete remission], using antibody alone or in combination with conventional therapies, may provide the greatest benefit." *Id.* at 2465. Thus, the concept of rituximab maintenance therapy was disclosed to the public almost three years before the '172 patent's priority date. Ex. 1002 at ¶ 77.

2. The July 1997 FDA Biological Response Modifiers Advisory Committee Hearing

On July 25, 1997, the FDA's Biological Response Modifiers Advisory Committee held a public hearing with representatives from Idec Pharmaceuticals, including the '172 patent's named inventor, Dr. Grillo-López. Dr. Grillo-López presented data in support of Idec Pharmaceuticals' then-pending application to

market rituximab for relapsed or refractory LG-NHL patients. Ex. 1002 at ¶¶ 82-83. The transcript of the hearing (Ex. 1007, "FDA Transcript") states at page 7 that the hearing was an "Open Public Hearing." Given the public nature of the hearing, it would have been publicized by the FDA prior to the hearing. Additionally, the FDA transcript was available from the FDA prior to the 102(b) date and remains available on FDA's website. *Id.* at ¶ 82. Thus, this transcript is prior art under 35 U.S.C. §102(b).

Dr. Grillo-López explained the advantages of rituximab as a targeted treatment for LG-NHL:

> [Use of rituximab results in] very selective B-cell depletion. Mean serum immunoglobulin levels remain within normal limits. There is no apparent increase in the incidence of infections, and there is no apparent or significant impairment of clinical immunity due to B-cell depletion that occurs in these patients.

Ex. 1007 at 33:18-34:4.

Dr. Grillo-López disclosed that two patients had already been successfully treated with three courses of rituximab, and nearly 50 patients had been treated with two courses. *Id*. at 111:20 – 112:6. Since the patients studied by Dr. Grillo-López and colleagues were relapsed and refractory, they would have had prior chemotherapy and other induction treatments. Ex. 1002 at ¶ 84.

The FDA panel also heard a statement by Dr. Wendy Harpham, a practicing physician, who recounted her personal experience of having been diagnosed with LG-NHL and successfully treated with repeated doses of rituximab. Ex. 1007 at 9-15. Dr. Harpham explained that rituximab had allowed her to have a good quality of life while avoiding the toxicity associated with repeated courses of cytotoxic chemotherapy. *Id*. at 12, 14.

Dr. Bernard Parker, from the FDA, discussed the pharmacokinetics of rituximab. He explained that, because tumor cells essentially function as a sink that extracts rituximab from a patient's blood serum, the higher the tumor burden (*i.e.*, the greater the number of malignant B cells) the less rituximab remains in the serum. *Id*. at 78-79. Dr. Grillo-López agreed that higher serum levels correlate to higher activity: "serum levels of circulating free antibody do correlate with response." *Id* at 72:5-9. These pharmacokinetic properties suggested that rituximab would be more suitable as a maintenance therapy than as a first-line treatment because newly diagnosed patients typically have a high tumor burden that would sequester much of the rituximab and thereby reduce its effective serum concentration, whereas patients with minimal residual disease or a reduced tumor burden would sequester less rituximab and therefore have higher serum levels and a stronger response. Ex. 1002 at ¶¶ 88-90.

3. 1997 FDA-Approved RITUXAN® Product Insert

In 1997, the FDA approved RITUXAN®, the commercial formulation of rituximab, for the treatment of patients with relapsed or refractory low-grade 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. 1008.

According to the FDA label, the recommended dosage for rituximab was "375 mg/m^2 given as an IV infusion once weekly for four doses (days 1, 8, 15 and 22)." *Id*. at 2, col. 1. 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 1, col. 1. 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" and that "B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by twelve months following completion of treatment." *Id.*

4. 1998 McLaughlin et al. Publication

On August 7, 1998, McLaughlin et al. published a paper titled "Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent

Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program."[5] Ex. 1009. The study was published in the Journal of Clinical Oncology, a prestigious journal that would have been followed closely by those of ordinary skill. Ex. 1002 at ¶ 95. Dr. Grillo-Lopez, the named inventor on the '172 patent, is the second-named author on the McLaughlin publication. This publication is prior art under 35 U.S.C. § 102(b).

McLaughlin describes a clinical trial in which LG-NHL patients were first treated with chemotherapy (including necessarily CVP). Most of the patients had achieved a complete response (CR) or a partial response (PR); *i.e.*, they had responded to the chemotherapy. These patients were then subsequently administered the standard course of rituximab (i.e., four weekly doses of 375mg/m^2). Although the patients who received rituximab therapy had relapsed prior to its administration, they had lower tumor burdens at the time of their rituximab therapy. *Id*. Thus, these patients had lower tumor burdens just like patients who receive maintenance therapy following induction with chemotherapy.

[5] McLaughlin was one of the constituent parts of the '180 provisional application. As previously discussed, the challenged claim is not entitled to a priority date that is the filing date of the '180 provisional application. The earliest priority date to which the challenged claim may be entitled is the filing date of the '202 application—August 11, 1999.

McLaughlin also strongly encouraged use of rituximab as maintenance therapy, and suggested that 6 months would be an appropriate interval between courses of rituximab maintenance therapy. Ex. 1002 at ¶¶ 95-97. Specifically, McLaughlin reported that "[p]atients who had achieved a CR or PR with their last prior chemotherapy course had a nonsignificant but somewhat better response to the antibody than those who were resistant to chemotherapy (53% v. 36%, P=.06)." Ex. 1009 at 2827, col. 2. One of ordinary skill would have concluded from this statement that rituximab was more effective in patients with a lower tumor burden at the time of rituximab therapy, as would occur during maintenance therapy. Ex. 1002 at ¶ 95. Indeed, McLaughlin explicitly encourages the use of rituximab maintenance therapy in a CR (minimal residual disease or MRD) setting following chemotherapy induction when it states that "[w]ith its established efficacy in the setting of measurable disease, the use of this agent in a minimal or subclinical disease setting is a consideration." Ex. 1009 at 2831, col. 2. Additionally, McLaughlin shows that "the median B-cell count declined with [rituximab] treatment, to undetectable levels after the first dose for the majority" and "recovery of B cells started between 6 and 9 months, with recovery to normal between 9 and 12 months." *Id.* at 2829, col. 2. In other words, administration of rituximab maintained depletion of B-cells for 6 months. Ex. 1002 at ¶ 96.

Biogen Idec maintains a commercial website that provides information about RITUXAN®. Ex. 1048. Notably, Biogen Idec's RITUXAN® website acknowledges that McLaughlin provided the foundation for, and strongly encouraged, the use of rituximab maintenance therapy following CVP induction therapy to treat LG-NHL. *Id*. at 3. Specifically, Biogen Idec states on its website that "B-cell depletion observed in the McLaughlin trial ***formed the basis*** for the ECOG 1496 dosing strategy following first-line CVP induction in low-grade NHL." (emphasis added). *Id*. The ECOG 1496 trial, for which McLaughlin "formed the basis," was also directed to LG-NHL and describes the precise method of claim 1 of the '172 patent. Ex. 1003. The ECOG 1496 trial is discussed in greater detail below.

5. The ECOG 4494 and ECOG 1496 Clinical Trials

The Eastern Cooperative Oncology Group (ECOG) organized two clinical trials to test the efficacy of rituximab maintenance therapy in B-cell Lymphoma. The ECOG 4494 trial was activated on December 12, 1997, Ex. 1004, and the ECOG 1496 trial was activated on March 19, 1998, Ex. 1003. A copy of the ECOG website from May 19, 1998, announced to the public that protocols for both trials were "active" as of May 1998. Ex. 1022. The declaration of a protocol as "active" marked the beginning of the period when the ECOG could provide the protocol to member institutions. Ex. 1002 at ¶ 98. Importantly, it also marked the beginning of

when physicians at ECOG member institutions could: (i) freely discuss the protocol and distribute it to other physicians and patients; (ii) obtain informed consent from patients; and (iii) enroll patients as subjects in the clinical trial. *Id*.

ECOG is an organization of member institutions dedicated to clinical cancer research. As of May 1998, its membership included hundreds of institutions around the world. Ex. 1051. Protocols for the ECOG 1496 and ECOG 4494 trials (Exs. 1003 and 1004, respectively) were distributed to all members of the cooperative shortly after activation and before May 19, 1998, with no confidentiality restrictions. Ex. 1002 at ¶¶ 99-106. Those of ordinary skill in the art would have known that protocols for any ECOG trial, including the schema of the protocols (which schematically depict the methods used during the trial), could be readily obtained either from ECOG (for oncologists affiliated with an ECOG member institution) or through an ECOG-affiliated oncologist (for those oncologists who may not have been affiliated with an ECOG member institution). *Id*. Physicians also would have been able to readily obtain information about any ECOG trial, including the protocol schema used in the ECOG trial, from the PDQ database, which is operated by the National Cancer Institute. Ex. 1053. In sum, a person of ordinary skill in the art could have, by May 19, 1998, learned about the ECOG 1496 and ECOG 4494 clinical trials, *e.g.*, by simply searching the ECOG website for clinical trials pertaining to rituximab. In addition, the protocols for these trials,

and particularly their associated protocol schema, were available to any interested physician (including oncologists) by May 19, 1998. Ex. 1002 at ¶¶ 100-106, 112. Additionally, at least the protocol schema contained in ECOG 1496 and ECOG 4494 (Exs. 1003 and 1004) would have been disseminated to other interested physicians, including oncologists, on or shortly after the clinical trials' were activated and prior to the 102(b) date. *Id*. at ¶ 105. The published protocols (Exs. 1003 and 1004) for these trials are prior art under 35 U.S.C. § 102(b).

ECOG 1496 (Ex. 1003) discusses the treatment of patients with LG-NHL. It is the same protocol referenced in column 13, lines 8-16 of the '172 patent (Ex. 1001), and it includes all of the same steps and other features recited in claim 1 of the '172 patent. Ex. 1002 at ¶¶ 107-110. Specifically, LG-NHL patients received standard CVP induction therapy. Ex. 1003 at schema and at 6-7. Patients whose LG-NHL had not progressed following induction were randomized to either receive rituximab maintenance therapy or be observed. Those randomized to the rituximab maintenance therapy arm had therefore received both the CVP induction and rituximab maintenance therapy as recited in claim 1. *Id.* The results of the ECOG 1496 trial were published by Hochster in 2009. Ex. 1040.

The protocol for the ECOG 4494 trial (Ex. 1004) included intermediate grade NHL patients. Those patients received CHOP induction chemotherapy either alone or together with rituximab, followed by rituximab maintenance therapy. The

rituximab maintenance therapy was provided precisely as recited in claim 1 of the '172 patent—*i.e.*, four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months for 2 years. Ex. 1004 at schema,11. The ECOG 4494 trial was also described by McNeil in a February 1998 article published in the Journal of the National Cancer Institute. Ex. 1005. Specifically, the article states that the intermediate-grade NHL patients who had received CHOP induction chemotherapy would also receive rituximab maintenance therapy every 6 months for 2 years. *Id*. at 266, col. 3. It was understood well prior to February 1998—the date that the NCI Journal article was published—that the recommended dose for a single course of rituximab was 375 mg/m^2 administered weekly for four weeks. Ex. 1002 at ¶ 111; *see* Ex. 1008.

IX. THE CHALLENGED CLAIM IS UNPATENTABLE

A. Claim 1 is anticipated by ECOG 1496

ECOG 1496 (Ex. 1003) discloses all of the elements recited in claim 1 of the '172 patent. Specifically, (A) patients had "low-grade Non-Hodgkin's lymphoma" (*id*. at Title); (B) patients in Arm B received standard CVP induction therapy (*id*. at Schema); (C) patients whose LG-NHL had not progressed following induction were randomized to either rituximab maintenance therapy or observation (*id*. at 6); and (D) the rituximab maintenance therapy consisted of rituximab at "a dose of 375 mg/m^2 weekly x 4 every 6 months for a total of 2 years beginning 4 weeks

after last chemotherapy" (*id*. at 7). Therefore, claim 1 of the '172 patent is unpatentable under 35 U.S.C. § 102(b) because it is anticipated by ECOG 1496, which was published and widely available more than one year before the priority date of the claim. Ex. 1002 at ¶¶ 99-106, 108-109, 123.

B. Claim 1 of the '172 patent is obvious

1. Those of ordinary skill in the art were motivated to identify an effective and tolerable maintenance therapy for treating LG-NHL

The importance of prolonging remission in LG-NHL patients, and identifying an effective means of doing so, was widely acknowledged for many years before the priority date of the '172 patent. Ex. 1002 at ¶ 64. Low-grade NHL could be readily driven into remission by combination chemotherapy. *Id*. at ¶ 56. CVP had become a preferred induction chemotherapy because it was powerful enough to substantially reduce the LG-NHL tumor burden in most patients but had fewer toxic side effects than, for example, CHOP. *Id.* at ¶¶ 41, 55. However, even the most aggressive induction therapy left behind residual malignant B-cells that would inevitably start growing again, leading to relapse. *Id*. at ¶ 57. Recurrent LG-NHL could be treated once again by chemotherapy, but this was undesirable because relapse was accompanied by the return of debilitating disease symptoms, increased susceptibility to infection and the toxic side-effects of chemotherapy.

Furthermore, each successive remission was usually shorter than the last one in a relentless cycle of remission and relapse, eventually leading to death. *Id*. at ¶ 56.

Oncologists had long used maintenance therapy to treat the residual disease remaining after chemotherapy had driven LG-NHL into a complete or partial remission, for example. Ex. 1002 at ¶¶ 62-64. After limited success with maintenance chemotherapy, clinical researchers began investigating biologic therapeutics like IFN to activate the immune system to treat cancer. *Id*. at ¶¶ 65-66. IFN had undesirable side effects, but IFN maintenance therapy proved to be effective at substantially prolonging disease-free survival and even overall survival in patients whose LG-NHL had been previously treated with CVP induction therapy. *See id*. at ¶ 66; *see also* Exs. 1006, 1033, 1034, 1055, 1056, and 1067. Thus, the concept of maintenance therapy for LG-NHL patients had been firmly established well before the priority and 102(b) dates of the ’172 patent. Ex. 1002 at ¶¶ 119-120.

2. Rituximab was known to possess properties that would be beneficial for maintenance therapy

Through their experience with IFN and other treatments, oncologists had identified several properties that an ideal maintenance therapy should possess. Ex. 1002 at ¶¶ 70-72, 117-118. First, it must effectively control the residual disease. Second, it must be suitable for long-term administration to keep the cancer in remission for as long as possible. Third, it should operate through a different

mechanism than the chemotherapeutic drugs used for induction therapy to reduce the chances of developing drug resistant cancer cells. Fourth, it should be less toxic than IFN in order to improve the patient's quality of life during remission.

Rituximab was approved by the FDA as a front-line therapy for LG-NHL in 1997, prior to the 102(b) date. Ex. 1008. The clinical testing that had been done to support FDA approval showed that rituximab possessed all of the attributes of an ideal maintenance therapy. Ex. 1002 at ¶¶ 73-81. First, it effectively treated the underlying cause of LG-NHL by targeted killing of B-cells. Ex. 1046. Second, it was effective for long-term treatment as demonstrated, for example, by the successful treatment of patients with multiple courses of rituximab therapy. Ex. 1002 at ¶¶ 83-87. Third, rituximab operated through a different mechanism than CVP chemotherapy. Fourth, as demonstrated in various studies, rituximab had fewer toxic side effects than IFN. *See e.g.*, Ex. 1002 at ¶ 91; Ex. 1038.

Rituximab did not merely fit the profile for an effective maintenance drug; the prior art strongly suggested and encouraged that it be used as maintenance therapy to treat LG-NHL. Ex. 1002 at ¶¶ 116-117. As discussed in the prior art, rituximab is particularly effective to treat lower tumor burdens (such as exists in CR and PR following induction chemotherapy). *Id.* at ¶¶ 113-115. After the majority of tumor cells have been killed by CVP, rituximab can more effectively target the residual disease. *Id*. at ¶¶ 88-90, 95. McLaughlin's data, for example,

suggested that rituximab was more effective in patients with a lower tumor burden, Ex. 1009 at 2927, col.2 and Fig. 3, and multiple publications had explicitly encouraged the use of rituximab maintenance therapy to treat minimal residual disease. Ex. 1046 at 2465; Ex. 1038 at 3273, col. 2; Ex. 1009 at 2831, col. 2. As of August 11, 1999, rituximab was so obviously suitable for maintenance therapy that there were five ongoing clinical trials using rituximab maintenance for the treatment of NHL. Exs. 1040-1044; Ex. 1002 at ¶ 73.

Perhaps most telling, Dr. Grillo-López, the named inventor on the ’172 patent, admitted in a recently published retrospective article that many of his colleagues were skeptical about his plans in the early 1990’s to use rituximab as induction therapy combined with chemotherapy because they believed that “***antibodies have limited efficacy and should be used only after chemotherapy, to treat the remaining minimal residual disease.***” Ex. 1037 at 402, col. 1.

3. All the elements of claim 1 were known in the prior art, and one of ordinary skill in the art was motivated to combine them with a reasonable expectation of success

Every element of the ’172 patent claim was known before the priority and 102(b) dates. Furthermore, those of ordinary skill in the art were motivated to combine these elements because efforts to improve upon then-existing maintenance therapies (such as interferon maintenance therapy) were extensive and

well publicized, and every element had been previously used in the treatment of LG-NHL.

The use of rituximab maintenance therapy to treat LG-NHL was obvious because, when compared to other lymphomas, LG-NHL frequently relapsed; the cancerous B-cells were slow-growing and more difficult to eliminate using conventional chemotherapy. Ex. 1002 at ¶ 120. Thus, those of ordinary skill in the art were already using chemotherapy, such as CVP, followed by various forms of maintenance therapy to treat LG-NHL, including interferon maintenance therapy. *See, e.g.,* Ex. 1006. Moreover, although interferon maintenance therapy provided therapeutic benefits, such as an increase in progression-free and overall survivals, those of ordinary skill sought out a less toxic alternative that could be administered over a longer period of time. Ex. 1002 at ¶¶ 66, 117. Rituximab was known to be less toxic than interferon and had already demonstrated its ability to deplete cancerous B-cells in LG-NHL. Ex. 1039. Accordingly, before the priority and 102(b) dates, those of ordinary skill in the art recognized rituximab's utility as a maintenance therapy and encouraged others to use it as such. *See* Ex. 1002 at ¶ 115; *see also, e.g.,* Ex. 1046 at 2465; Ex. 1038 at 3273, col. 2; Ex. 1009 at 2831, col. 2.

CVP was, and still is, the preferred induction chemotherapy for LG-NHL. Ex. 1002 at ¶ 55; Ex. 1011. It would have been obvious to use CVP, the induction

therapy most suitable for LG-NHL, rather than CHOP, a more potent but also more toxic combination that was preferred for more aggressive forms of NHL. Ex. 1002 at ¶ 121. Rituximab maintenance therapy after CHOP induction therapy for the treatment of intermediate-grade or high-grade NHL was known in the prior art. Exs. 1004-1005. It would have been obvious to modify this protocol by using CVP instead of CHOP to treat LG-NHL. Ex. 1002 at ¶ 124.

The claimed rituximab dosage of four weekly administrations at 375 mg/m^2 had been used in multiple clinical trials and was the recommended dosage for treating LG-NHL, as provided in RITUXAN's® 1997 FDA-approved label. Ex. 1008. Thus, it would have been obvious to continue using the same dosage of the same drug to treat the same disease. Ex. 1002 at ¶ 93.

Administering rituximab maintenance therapy every six months for two years was exactly the same schedule described in ECOG 4494 (Ex. 1004) and McNeil (Ex. 1005), both of which describe rituximab maintenance therapy for more aggressive NHL. Even without these prior art references, the schedule would have been obvious because, for example, B-cell depletion after rituximab therapy was known to last for six months (Exs. 1009, 1002 at ¶ 118), experience with IFN maintenance had shown that maintenance therapy for LG-NHL was more effective when it was continued for as long as possible (Ex. 1068), and NHL patients had already been successfully treated with multiple courses of rituximab (Exs. 1007,

1002 at ¶¶ 92-94). Hainsworth independently devised an identical rituximab maintenance protocol, providing further confirmation that that the protocol was obvious. Ex. 1043 at 1612, col. 1.

Additionally, one of ordinary skill in the art would have had at least a reasonable expectation of success in combining all the known prior art elements to arrive at the claimed subject matter. Ex. 1002 at ¶¶ 113-121. CVP induction therapy followed by interferon maintenance therapy had already been shown to be effective for the treatment of LG-NHL. Ex. 1009. Replacing interferon maintenance therapy with rituximab maintenance therapy would have been reasonably expected to be successful given, among other reasons, rituximab's known lower toxicity profile (Exs. 1046 and 1038), its proven effectiveness in treating LG-NHL (Exs. 1038 and 1009), and that it had been effectively administered multiple times to numerous patients (Ex. 1007).

C. Proposed Combinations of Prior Art That Anticipate and Render Obvious Claim 1 of the '172 Patent

1. ECOG 1496 (Ex. 1003) Anticipates Claim 1

As described in section IX.A, ECOG 1496 describes the precise method of claim 1. Therefore, ECOG 1496 anticipates claim 1. Ex. 1002 at ¶ 123.

2. ECOG 4494 (Ex. 1004) Renders Obvious Claim 1

ECOG 4494 discloses the rituximab maintenance therapy method claimed in the '172 patent, "4 weekly doses repeated every 6 mos x 2 years", but it treats

intermediate-grade NHL instead of LG-NHL and uses CHOP instead of CVP for induction. Oncologists would have been motivated to use the rituximab maintenance therapy method of ECOG 4494 to treat LG-NHL because, for example, Maloney (Ex. 1046 at 2465; Ex. 1038 at 3273, col. 2); McLaughlin (Ex. 1009 at 2831, col. 2), and others had encouraged the use of rituximab maintenance therapy to treat the residual disease remaining after chemotherapy in LG-NHL patients. Ex. 1002 at ¶ 124. In addition, interferon maintenance therapy had been used in conjunction with CVP induction therapy to treat LG-NHL. Ex. 1006. Thus, one of ordinary skill in the art knew that maintenance therapy was an effective way to treat LG-NHL. Ex. 1002 at ¶ 125. Additionally, interferon maintenance therapy was tested in more aggressive NHL before LG-NHL trials were conducted, so there was precedent for adapting more aggressive NHL therapies for the treatment of LG-NHL. Exs. 1055-56, 1002 at ¶ 120. Furthermore, those of ordinary skill would have been motivated to substitute CVP for the CHOP used in ECOG 4494 because CVP had lower toxicity and was therefore a standard induction therapy for LG-NHL. Ex. 1011.

Since interferon had been successfully administered as maintenance therapy for LG-NHL, those of ordinary skill would have reasonably expected similar success with rituximab maintenance therapy, particularly in view of the fact that rituximab was known to have lower toxicity than interferon. Ex. 1002 at ¶ 73. Both

were known to be effective against LG-NHL, and to be immune response modifiers with a mechanism that is complementary to the mechanisms of chemotherapy drugs, including CVP. Ex. 1002 at ¶ 65.

Indeed, consistent with the conclusion that ECOG 4494 renders the '172 patent claim obvious is the notable fact that the ECOG 4494 and ECOG 1496 trials, which became active only a few months apart, used the exact same rituximab maintenance therapy dosing and schedule, despite having completely different people leading the trials, and that Hainsworth independently devised the identical rituximab maintenance protocol. *Ecolochem v S. Cal. Edison* 227 F.3d 1361, 1379 (Fed. Cir. 2000) ("The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art."); *see also* Ex. 1002 at ¶¶ 94,126.

3. ECOG 4494 (Ex. 1004) In Combination with Unterhalt 1996 (Ex. 1006) Renders Obvious Claim 1

Claim 1 is rendered obvious for all the same reasons discussed above in connection with ECOG 4494 alone, and for the additional reason that it further would have been obvious to modify the method discussed in ECOG 4494 to get the method of claim 1 given the teachings in Unterhalt. Ex. 1002 at ¶ 127. Specifically, Unterhalt successfully treated LG-NHL with CVP induction therapy followed by interferon maintenance therapy. Rituximab and interferon are both immune response modifiers with a mechanism that is complementary to the mechanisms of

chemotherapy drugs, including CVP. Rituximab, however, was known to have lower toxicity than interferon. Hence, Unterhalt provides further motivation to apply the rituximab maintenance therapy of ECOG 4494 to the treatment of LG-NHL after CVP induction therapy.

One of ordinary skill would have been motivated to modify ECOG 4494 (Ex. 1004) with what was discussed in Unterhalt (Ex. 1006) and would have reasonably expected to succeed in obtaining claim 1 of the ’172 patent in view of, for example: (i) the fact that both address NHL; (ii) other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL; (iii) CHOP had previously been used as induction therapy in LG-NHL; (iv) others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL; and (v) Unterhalt had treated LG-NHL using CVP induction therapy followed by BRM maintenance therapy and demonstrated a “significant prolongation of DFS [disease-free survival].” Ex. 1002 at ¶ 127.

4. ECOG 4494 (Ex. 1004) In Combination with the FDA Transcript (Ex. 1007) Renders Obvious Claim 1

Claim 1 is rendered obvious for all the same reasons discussed above in connection with ECOG 4494 alone, and for the additional reason that it further would have been obvious to modify the method discussed in ECOG 4494 to obtain the method of claim 1 of the ’172 patent given the discussion in the 1997 FDA Transcript. Ex. 1002 at ¶ 128. Specifically, the 1997 FDA Transcript discusses

treating LG-NHL with multiple courses of rituximab therapy, and describes at least one patient whose follicular LG-NHL was treated with CVP, which resulted in a CR of 11 months, followed by multiple courses of rituximab, each of which resulted in a PR lasting 20 months or more.

One of ordinary skill would have been motivated to modify the protocol of ECOG 4494 with what was discussed in the FDA Transcript and would have reasonably expected to succeed in obtaining claim 1 of the ’172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and the 1997 FDA Transcript encouraged the use of multiple courses of rituximab following CVP therapy to treat LG-NHL and discussed the benefits of using rituximab when tumor burden was reduced (*e.g.*, following CVP induction therapy). Ex. 1002 at ¶ 128.

5. McNeil (Ex. 1005) Renders Obvious Claim 1

As discussed above, McNeil reports on the ECOG 4494 trial. Like ECOG 4494, it discloses the use of CHOP induction therapy followed by rituximab maintenance therapy to treat intermediate-grade NHL. Further, like ECOG 4494, it also discloses that rituximab maintenance therapy is given every 6 months for two

years. Ex. 1005 at 266, col. 3. A person of ordinary skill in the art reading McNeil would understand that each course of the rituximab maintenance therapy to which the article is referring is the standard rituximab dosing regimen of four weekly doses of 375mg/m^2. Ex. 1002 at ¶ 129. Indeed, that is the precise regimen described in the 1997 FDA Label (Ex. 1008). For the same reasons discussed in connection with ECOG 4494, it would have been obvious to those of ordinary skill to use the protocol described in McNeil to treat LG-NHL, and it further would have been obvious to do so using standard CVP induction therapy, instead of CHOP, to treat LG-NHL.

6. McNeil (Ex. 1005) In Combination with the 1997 Rituxan® Label (Ex. 1008) Renders Obvious Claim 1

As discussed above, claim 1 is rendered obvious by McNeil. Claim 1 is further rendered obvious by the 1997 Rituxan® Label, which makes explicit what oncologists would understand from McNeil—namely, that each course of rituximab therapy is the standard rituximab dosing regimen of 4 weekly doses of 375mg/m^2. Ex. 1002 at ¶ 130. One of ordinary skill would have been motivated to modify McNeil with what was discussed in the 1997 Rituxan® Label and would have reasonably expected to succeed in obtaining claim 1 of the ’172 patent in view of, for example, the fact that the 1997 Rituxan® Label disclosed the FDA-approved standard dosing regimen of rituximab for the treatment of LG-NHL.

7. Either McNeil (Ex. 1005) Alone (or McNeil In Combination With the 1997 Rituxan® Label (Ex. 1008)) In Combination With Unterhalt (Ex. 1006) Renders Obvious Claim 1

As discussed above, both McNeil alone and McNeil in combination with the 1997 Rituxan® Label render obvious claim 1. As discussed in section 3 above with respect to ECOG 4494, claim 1 is further rendered obvious by Unterhalt, which discusses successfully treating LG-NHL with CVP induction therapy followed by IFN maintenance therapy. *See also* Ex. 1002 at ¶ 131. Unterhalt emphasizes what would have been apparent to one of ordinary skill from McNeil—specifically, that the method described in McNeil could be used for the treatment of LG-NHL and that CVP induction therapy could be used instead of CHOP induction therapy.

One of ordinary skill would have been motivated to modify McNeil with what was discussed in Unterhalt and would have reasonably expected to succeed in arriving at claim 1 of the ’172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and Unterhalt had treated LG-NHL using CVP induction therapy followed by BRM maintenance therapy and demonstrated a “significant prolongation of DFS [disease-free survival].” Ex. 1002 at ¶ 131.

8. McNeil (Ex. 1005) Alone (or McNeil In Combination with the 1997 Rituxan® Label (Ex. 1008)) In Combination With the 1997 FDA Transcript (Ex. 1007) Renders Obvious Claim 1

As discussed above, both McNeil alone and McNeil in combination with the 1997 Rituxan® Label render obvious claim 1. Claim 1 is further rendered obvious by the 1997 FDA Transcript, which discusses the use of CVP to treat a form of LG-NHL, followed by multiple courses of rituximab therapy. Ex. 1002 at ¶ 132.

One of ordinary skill would have been motivated to modify McNeil with what was discussed in the 1997 FDA Transcript and would have reasonably expected to succeed in obtaining claim 1 of the ’172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and the 1997 FDA Transcript encouraged the use of multiple courses of rituximab following CVP therapy to treat LG-NHL and discussed the benefits of using rituximab when tumor burden was reduced (*e.g.*, following CVP induction therapy). Ex. 1002 at ¶ 132.

9. McLaughlin (Ex. 1009) Renders Obvious Claim 1

McLaughlin describes a clinical trial in which LG-NHL patients were first treated with chemotherapy, including necessarily CVP, and subsequently treated

with 375mg/m^2 rituximab, administered once weekly for a total of four infusions. Ex. 1002 at ¶ 133.

As stated on Biogen Idec's RITUXAN® website, the "B-cell depletion observed in McLaughlin ***formed the basis*** for the ECOG 1496 dosing strategy following first-line CVP induction in low-grade NHL." (emphasis added). Ex. 1048. As discussed above, the ECOG 1496 trial tested the precise method claimed in claim 1 of the '172 patent. Thus, this statement by the patent owner, Biogen Idec, is a concession that claim 1 is obvious over McLaughlin. Ex. 1002 at ¶ 135.

Although the LG-NHL of the patients in the McLaughlin study had relapsed following chemotherapy, the patients had lower tumor burdens at the time of rituximab administration. Ex. 1002 at ¶ 95. Indeed, McLaughlin acknowledged that rituximab produced a better response in patients who had experienced a CR or PR following chemotherapy. Ex. 1009 at 2827. One of ordinary skill would have understood from this that rituximab was more effective when patients had lower tumor burdens following chemotherapy, which is precisely the case when rituximab maintenance therapy is administered. Ex. 1002 at ¶¶ 95, 133. These results caused McLaughlin to strongly encourage using rituximab in a maintenance therapy setting. *Id*. at 2831. Upon reading McLaughlin, one of ordinary skill in the art would have been encouraged to use rituximab as maintenance therapy for the treatment of LG-NHL. Ex. 1002 at ¶¶ 133-134.

CVP chemotherapy for LG-NHL would have been a logical choice as an induction therapy to use with rituximab maintenance therapy, particularly given that CVP induction therapy had previously been used to treat LG-NHL. Indeed, at least some of the patients treated in McLaughlin necessarily had been treated with CVP to achieve a CR or PR because CVP was the preferred combination chemotherapy to treat LG-NHL. Ex. 1011; Ex. 1002 at ¶ 133.

Those of ordinary skill reading McLaughlin also would have been motivated to administer multiple courses of rituximab maintenance therapy in order to prolong the period of remission for as long as possible. Ex. 1002 at ¶ 133. The length of treatment in trials using maintenance therapy drugs, such as interferon, was limited due to concerns regarding toxicity. In contrast, McLaughlin stated that "[t]he toxicity of the current program was notably mild, particularly with respect to myelosuppressive toxicities that are typical of standard chemotherapy or RIT [radioimmunotherapy]. Adverse events occurred mainly with the first infusion…By the second and subsequent infusions, the majority of patients experienced no further infusion-related toxicities." Ex. 1009 at 2831-31. Accordingly, it would have been obvious to one of ordinary skill to administer as many courses of rituximab maintenance therapy as possible to prolong the period of remission for as long as possible and, by doing so, to provide maintenance therapy for 2 years, or even longer.

Moreover, one of ordinary skill would have understood from McLaughlin that the courses of rituximab maintenance therapy should be separated by 6 months given that administration of a course of rituximab resulted in rapid depletion of B-cells and recovery of the B-cells did not occur until 6 months later. *Id*. at 2829 and Figure 3.

Given it was known that CVP induction therapy followed by maintenance therapy using interferon had successfully treated LG-NHL, and that rituximab had a mild toxicity profile, one of ordinary skill would have reasonably expected to successfully use rituximab maintenance therapy following CVP induction therapy to treat LG-NHL as encouraged by McLaughlin 1998. Ex. 1002 at ¶¶ 133-135.

10. McLaughlin 1998 (Ex. 1009) In Combination with McNeil (Ex. 1005) Renders Obvious Claim 1

As discussed above, McLaughlin renders obvious claim 1 of the ’172 patent. Claim 1 is further rendered obvious by McNeil, which discusses the treatment of intermediate-grade NHL by using CHOP induction therapy, followed by rituximab maintenance therapy every 6 months to provide maintenance therapy for two years. Ex. 1002 at ¶ 136. Given, for example, the strong encouragement in McLaughlin to use rituximab maintenance therapy in a LG-NHL setting, one of ordinary skill would have viewed the rituximab maintenance therapy regimen discussed in McNeil as a logical choice. This particularly would have been the case given that the CHOP induction therapy used in McNeil had previously been used to treat LG-

NHL (Ex. 1023 at 62), the maintenance therapy discussed in McNeil was consistent with the observation in McLaughlin that use of rituximab to treat LG-NHL resulted in B cell depletion that lasted at least 6 months (Ex. 1009 at 2829 and Figure 3), and maintenance therapies for the treatment of LG-NHL had previously been considered first in the context of treating higher grades of NHL, such as intermediate-grade NHL (Exs. 1055-6). Moreover, standard CVP chemotherapy for LG-NHL would have been a logical choice as induction therapy for use with rituximab maintenance therapy. Ex. 1011; Ex. 1002 at ¶ 133. In any event, at least some of the patients treated in McLaughlin were necessarily treated with CVP to achieve a CR or PR prior to administration of rituximab. Ex. 1002 at ¶ 133.

D. Claim Chart Comparing the Challenged Claim to the Prior Art

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising	ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003) • "Patients must have Stage III-IV (Ann Arbor classification) low-grade Non-Hodgkin's lymphoma" (p. 3) ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004) • "All patients must have a tissue diagnosis of non-Hodgkin's lymphoma, intermediate or high-grade histology …" (p. 5)

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	Unterhalt, Interferon maintenance, 1996 (Ex. 1006) • "[P]atients with advanced stage III and IV follicle center lymphoma and mantle cell lymphoma" FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007) • "I [Dr. Wendy Harpham] am a… seven-year survivor of small cleaved cell follicular non-Hodgkin's lymphoma." (p. 9:13-16) • "This patient was a 30-years old white male with follicular, small cleaved lymphoma diagnosed in '90." (p. 125:13-14) McNeil, NCI Journal, Feb. 1998 (Ex. 1005) • "Researchers in December launched a new randomized trial for elderly patients with intermediate-grade non-Hodgkin 's lymphoma (NHL)" (p. 266, col 1) 1997 Rituxan® Label (Ex. 1008) • "RITUXAN is indicated for the treatment of patients with relapsed or refractory low-grade or follicular CD20 positive B-cell non-Hodgkin's lymphoma." (p. 1, col. 2) McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009) • "Adult patients with relapsed low grade or follicular B-cell lymphoma" (p. 2826, col. 1)
administering to the patient chemotherapy consisting of CVP therapy to which the patient responds,	ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003) • "Patients randomized to this arm (standard therapy) will receive cyclophosphamide 1000 mg/m^2 (maximum 200 mg, administer in 500 cc D5W over 30 – 45 minutes), vincristine 1.4 mg/m^2 (maximum

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	2.0 mg, IV push through running IV) day 1 and prednisone 100 mg/m^2 orally days 1-5. Cycles will be repeated q21 days." (p. 7) • "Those completing the induction phase without frank progression …" (p. 6) ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004) • "Arm B – CHOP (p. 10)" • "Patients who are in complete remission by restaging after both four and six cycles of therapy …" (Schema) Unterhalt, Interferon maintenance, 1996 (Ex. 1006) • "responding to an initial cytoreductive therapy with a combination of Cyclophosphamide, Vincristine, Prednisone (COP)" FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007) • "He initially received chemotherapy with a CVP regimen, and had only a partial response lasting for 10 months. Upon progression of disease, he was treated with ABMT with cytoxan VP 16 and total body irradiation, and had a complete response which lasted for 18 months. He progressed and was treated with CVP, had a CR lasting 11 months." (p. 125:14-20) McNeil, NCI Journal, Feb. 1998 (Ex. 1005) • "[P]atients who responded [to CHOP]...." (p. 266, col 3) • "CHOP alternatives could also turn out [to] be less toxic chemotherapy regimens, another area where several NHL studies are underway in the elderly. One reason for poorer outcomes in older patients is thought to be that CHOP, like some other chemotherapy regimens, is more toxic in this age group." (p. 266, col 3)

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009) • "Prior therapy included chemotherapy in 97%, …" (p. 2826, col. 2) • "166 patients were enrolled", "Twenty-two patients had been resistant to all prior chemotherapy (had never achieved a CR or PR), while 45 were resistant to their most recent chemotherapy before study entry." (p. 2826, col. 2)
followed by rituximab maintenance therapy,	ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003) • "Those completing the induction phase without frank progression will be randomized in Step 2 to maintenance therapy with anti-CD20 vs. observation." (p. 6) • "Following induction chemotherapy as above, patients will be randomized to maintenance therapy with anti-CD20 vs. observation." (p. 10) ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004) • "Patients who are in complete remission by restaging after both four and six cycles of therapy will then be randomized to either anti-CD20 maintenance (Arm C) or to observation (Arm D)." (Schema) Unterhalt, Interferon maintenance, 1996 (Ex. 1006) • "IFN-α maintenance" FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007) • "He initially received chemotherapy with a CVP regimen, and had only a partial response lasting for 10 months. Upon progression of disease, he was treated with ABMT with cytoxan VP 16 and total body irradiation, and had a complete response which lasted

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	for 18 months. He progressed and was treated with CVP, had a CR lasting 11 months." (p. 125:14-20) • "Following this, he had progression of disease and was treated with IDEC-C2B8 back in December of '93. This patient had a very good partial response." (p. 125:21-24) • "Upon progression of disease, this patient who was wiser than we were, insisted that he get the antibody again." (p. 127:4-6) McNeil, NCI Journal, Feb. 1998 (Ex. 1005) • "After initial therapy, patients who responded will be again randomly assigned to receive the maintenance regimen – Rituxan" (p. 266, col 3) McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009) • "Prior therapy included chemotherapy in 97%, …" (p. 2826, col. 2) • "166 patients were enrolled", "Twenty-two patients had been resistant to all prior chemotherapy (had never achieved a CR or PR), while 45 were resistant to their most recent chemotherapy before study entry." (p. 2826, col. 2) • "[Patients] had to be at least 3 weeks beyond prior standard therapy including corticosteroids," (p. 2826, col. 1) • "The current report summarizes results of a multiinstitutional trial of a four-dose course of therapy with this chimeric anti-CD20 monoclonal antibody." (p. 2826, col. 1) • "Patients who had achieved a CR or PR with their last prior chemotherapy course had a nonsignificant but somewhat better response to the antibody than those who were resistant to chemotherapy (53% v 36%, P = .06)." (p. 2827, col. 2)

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	• "[w]ith its established efficacy in the setting of measurable disease, the use of this agent [rituximab] in a minimal or subclinical disease setting is a consideration." (p. 2831, col. 2)
wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years.	ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003) • "Anti-CD20 will be given at a dose of 375 mg/m^2 weekly x 4 every 6 months for a total of 2 years beginning 4 weeks after last chemotherapy." (Schema and p. 10) ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004) • "Anti-CD20 Maintenance: 4 weekly doses repeated every 6 mos x 2 years" (Schema) • "A cycle of maintenance therapy will consist of IDEC-C2B8, 375 mg/m^2 IV, given weekly for four consecutive weeks, if the maintenance week one IgG level is >500 mg/dl. This four-week cycle of therapy will be administered at six-month intervals for a total of four cycles. If the IgG level is ≤500 mg/dl for any given cycle of maintenance therapy, the IgG level should be followed monthly and further maintenance therapy withheld until the IgG level is > 500 mg/dl." (p. 11) Unterhalt, Interferon maintenance, 1996 (Ex. 1006) • "IFN-α was given without a fixed time limitation until relapse or untolerable [sic] toxicity" FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007) • "Treatment is well tolerated, and retreatment is feasible, and in fact, we have retreated 22 patients who received treatment twice, and 2 patients who have received treatment three times." (p. 35:8-11)

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	• "As far as I know, I [Wendy Harpham], am the first person ever to receive the IDEC Mab three times." (p. 12:15-17) • "Each of the last two courses of C2B8 brought me eight months with minimal toxicity. Repeated courses appear to be at least as effective for me as my first courses." (p. 13: 5-8) • "Upon progression of disease, this patient who was wiser than we were, insisted that he get the antibody again." (p. 127:4-6) McNeil, NCI Journal, Feb. 1998 (Ex. 1005) • "Rituxan every 6 months for 2 years - or observation" (p. 266, col 3) 1997 Rituxan® Label (Ex. 1008) • "The recommended dosage of RITUXAN is 375 mg/m^2 given as an IV infusion once weekly for four doses (days I, 8, 15, and 22)." (p. 2, col. 1) • "Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cell … Among the 166 patients in the pivotal study, circulating B-cells (measured as CD19+ cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. … B-cell recovery began at approximately six months following completion of treatment." (p. 2, col. 1) McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009) • "The antibody dose was 375 mg/m^2, administered intravenously once weekly for a total of four infusions (days 1, 8, 15, and 22) on an outpatient basis." (p. 2826, col. 1)

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	**Exemplary Disclosure in Prior Art**
	• Fig 3. • "the median B-cell count declined with treatment, to undetectable levels after the first dose for the majority … Recovery of B cells started between 6 and 9 months, with recovery to normal between 9 and 12 months." (p. 2829, col. 2) • "[t]he toxicity of the current program was notably mild, particularly with respect to myelosuppressive toxicities that are typical of standard chemotherapy or RIT. Adverse events occurred mainly with the first infusion…By the second and subsequent infusions, the majority of patients experienced no further infusion-related toxicities." (pp. 2830-31)

X. HOCHSTER FAILS 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 S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013). "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); *Hoffman La Roche, Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1334-35 (Fed. Cir. 2014) (finding that evidence of secondary considerations did not rebut *prima facie* showing of obviousness).

Claim 1 was ultimately allowed "in view of applicants' arguments regarding unexpected results." Ex. 1069 at 2. Relying on Hochster, which was published 10 years after the priority date of the challenged claim, applicants argued that the claimed method produced unexpected results, specifically "prolongation of PFS [progression free survival] for MR-treated [maintenance rituximab] patients with a median more than three times longer (4.3 v. 1.3 years) and a 60% reduction in progression risk (HR = 0.4; P < 10-9)." Ex. 1064 at 7. To the contrary, the prolonged progression-free survival reported by Hochster was entirely expected. Ex. 1002 at ¶¶ 119, 137-140.

First, Hochster itself emphasized that prolonged remission was expected when it concluded that "[o]ur study ***confirmed the hypothesis*** that rituximab would be an effective and safe maintenance after CVP chemotherapy." (emphasis added). Ex. 1040 at 1611, col. 1.

Furthermore, the applicant's unexpected results argument was limited to demonstrating that CVP induction followed by rituximab maintenance achieves unexpected results compared to ***CVP induction alone***. Ex. 1002 at ¶ 139. Applicant did not argue that the claimed method achieves unexpected results when compared to CVP induction ***followed by other forms of maintenance therapy*** that had been used to treat LG-NHL, e.g., IFN maintenance therapy. (emphasis added). *See* Ex. 1064 at 7-8.

Indeed, multiple studies published before the 102(b) date of the ’172 patent described successfully treating LG-NHL with IFN maintenance therapy to enhance progression free survival and overall survival. For example, Unterhalt treated LG-NHL with CVP followed by IFN maintenance and concluded that “these data clearly demonstrate a prolonged effect of IFN-α maintenance in low grade lymphoma which provides a significant prolongation of DFS [disease free survival] and the interval without the requirement of further cytostatic therapy in patients with advanced low grade NHL.” Ex. 1002 at ¶ 140. Similarly, Aviles reported that “with a median follow-up of 11 years (March 1997), disease progression has been observed in only 40% of our patients who received IFN maintenance therapy [for LG-NHL], compared to 93% in the control group [no IFN maintenance therapy]. Overall survival was statistically significantly different between groups at 11 years of follow-up: 60% of the patients who received IFN were alive compared to only 31% in the control group ($p < 0.001$).” Ex. 1033 at 155, col. 1. Furthermore, Solal-Celigny stated that “these results confirm that the addition of IFNα to a doxorubicin-containing regimen for patients with advanced-stage and clinically aggressive FL [low grade follicular lymphoma] not only increased PFS [progression-free survival], as in most other similar trials, but also prolonged OS [overall survival].” Ex. 1034 at abstract.

Even Hochster, after citing four studies that tested interferon maintenance for the treatment of LG-NHL, candidly acknowledged that rituximab maintenance was also expected to prolong progression-free survival, stating that "[t]hese experiences with continuation or maintenance therapy [with interferon] ***suggested***, however, that an active biologic agent with a favorable safety profile and high patient acceptability [rituximab] would improve clinical outcome in indolent lymphoma." (emphasis added). Ex. 1040 at 1607-8.

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 claim 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. 8,329,172
1002	Declaration of Michael L. Grossbard, M.D., in Support of the Petition for Inter Partes Review of U.S. Patent. No. 8,329,172, dated Dec. 5, 2014
1003	ECOG 1496
1004	ECOG 4494
1005	McNeil, *Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP*, Journal of the National Cancer Institute 90(4):266-267 (February 18, 1998)
1006	Unterhalt *et al*., *Significant Prolongation of Disease Free Survival in Advanced Low Grade Non Hodgkin's Lymphomas (nhl) by Interfereon Alpha Maintenance*, International Conference on Malignant Lymphoma (1996)
1007	Public Hearing Transcript, Biological Response Modifiers Advisory Committee, Center for Biological Evaluation and Research, Food and Drug Administration, nineteenth meeting (July 25, 1997), available at http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3311t2.pdf

Exhibit	Reference
1008	Rituxan® Product Label (1997)
1009	McLaughlin *et. al*., *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, J. Clinical Oncology 16:2825-2833 (August 7, 1998)
1010	Cheson *et al*., *Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas*, J. Clinical Oncology 17:1244-1253 (1999).
1011	Hiddemann, *Non-Hodgkin's Lymphomas—Current Status of Therapy and Future Perspectives*, European Journal of Cancer 31A:2141-2145 (1995)
1012	Portlock and Rosenberg, *Combination Chemotherapy with Cyclophosphamide, Vincristine, and Prednisone in Advanced Non-Hodgkin's Lymphomas*, Cancer 37:1275-1282 (1976)
1013	Definition of *Biological Therapy*, NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID =45617
1014	Definition of *Tumor Burden*, NCI Dictionary of Cancer Terms – National

Exhibit	Reference
	Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44627
1015	Definition of *Residual Disease*, NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=45869
1016	Definition of *Time to Progression*, NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44783
1017	Definition of *Disease-Free Survival*, NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44023
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