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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CELLTRION, INC.
Petitioner

v.

BIOGEN INC.
Patent Owner

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Case No. IPR2017-_____

Patent No. 8,557,244

Filing Date: July 28, 2000
Issue Date: October 15, 2013

Inventors: Christine White and Antonio Grillo-López

Title: TREATMENT OF AGGRESSIVE NON-HODGKINS LYMPHOMA WITH ANTI-CD20 ANTIBODY

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,557,244

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EXHIBIT LIST

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1001	U.S. Patent No. 8,557,244 ("the '244 patent")
1002	Excerpts from the certified file history of the '244 patent
1003	Expert Declaration of Dr. Izidore Lossos
1004	Expert Declaration of Dr. Walter Longo
1005	Link, B.K. *et al.*, *Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL*, Program/Proceedings Am. Soc. Clin. Oncol., 17:3a (Abstract 7) (1998) ("Link")
1006	McNeil, C., *Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP*, J. Nat'l Cancer Inst., 90(4):266-67 (Feb. 18, 1998) ("McNeil")
1007	Eastern Cooperative Oncology Group ("ECOG") E4494 Patient Consent Form (1997)
1008	Rituxan (Rituximab) label (Nov. 1997) ("1997 Rituxan Label")
1009	Sonneveld, P. *et al.*, *Comparison of Doxorubicin and Mitoxantrone in the Treatment of Elderly Patients with Advanced Diffuse Non-Hodgkin's Lymphoma Using CHOP Versus CNOP Chemotherapy*, J. Clin. Oncol., 13(10):2530-39 (Oct. 1995) ("Sonneveld")
1010	Public Hearing Transcript, Biological Response Modifiers Advisory Committee, Center for Biological Evaluation and Research, Food and Drug Administration, nineteenth meeting (July 25, 1997) ("FDA Transcript")
1011	Davis, T.A. *et al.*, *Rituximab: First Report of a Phase II (PII) Trial in NHL Patients (PTS) with Bulky Disease*, Blood, 92(10 Suppl. 1):414a (Abstract 1711) (Nov. 15, 1998) ("Davis")
1012	Davis, T.A. *et al.*, *Single-Agent Monoclonal Antibody Efficacy in Bulky Non-Hodgkin's Lymphoma: Results of a Phase II Trial of Rituximab*, J. Clin. Oncol., 17(6):1851-57 (June 1999) ("Davis 1999")
1013	Ford, B., *Rituxan (Rituximab)*, The CAL GAB, Quarterly Newsletter of the Cancer and Leukemia Group B, 7(1):4-5 (Spring 1998) ("CALGB 1998")

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1014	Coiffier, B. *et al.*, *A multicenter, randomized phase II study of rituximab (chimeric anti-CD20 mAb) at two dosages in patients with relapsed or refractory intermediate or high-grade NHL (IHG-NHL) or in elderly patients in first-line therapy*, Blood, 90(10):510a (Abstract 2271) (Nov. 15, 1997) ("Coiffier 1997")
1015	Coiffier, B., *et al.*, *Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients With Relapsing or Refractory Aggressive Lymphoma: A Multicenter Phase II Study*, Blood, 92(6):1927-1932 (Sept. 15, 1998) ("Coiffier 1998")
1016	Czuczman, M.S. *et al.*, *Chemoimmunotherapy of Low-Grade Lymphoma with the Anti-CD20 Antibody IDEC-C2B8 in Combination with CHOP Chemotherapy*, Cancer Invest., 14(Supp. 1):59-61 (Abstract 53) (1996) ("Czuczman 1996")
1017	Exhibit Number Not Used
1018	Gordon, L.I. *et al.*, *Comparison of a Second-Generation Combination Chemotherapeutic Regimen (m-BACOD) with a Standard Regimen (CHOP) for Advanced Diffuse Non-Hodgkin's Lymphoma*, New Engl. J. Med., 327(19):1342-1349 (Nov. 5, 1992) ("Gordon 1992")
1019	Fisher, R.I. *et al.*, *Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma*, New Engl. J. Med., 328(14):1002-1006 (Apr. 8, 1993) ("Fisher 1993")
1020	Stashenko, P. *et al.*, *Characterization of a Human B Lymphocyte-Specific Antigen*, J. Immunol., 125(4):1678-1685 (Oct.1980) ("Stashenko 1980")
1021	Anderson, K.C. *et al.*, *Expression of Human B Cell-Associated Antigens on Leukemias and Lymphomas: A Model of Human B Cell Differentiation*, Blood, 63(6):1424-1433 (June 1984) ("Anderson 1984")
1022	Exhibit Number Not Used

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1023	Foon, K.A. & Fisher, R.I., *Chapter 111: Lymphomas,* in Williams Hematology, Fifth Edition, 1076-1096 (Beutler, E. *et al.*, eds., 1995)
1024	Vose, J.M. *et al.*, *Phase II Study of Rituximab in Combination With CHOP Chemotherapy in Patients With Previously Untreated, Aggressive Non-Hodgkin's Lymphoma*, J. Clin. Oncol., 19(2):389-397 (Jan. 15, 2001)
1025	The Non-Hodgkin's Lymphoma Pathologic Classification Project, *National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin's Lymphomas: Summary and Description of a Working Formulation for Clinical Usage*, Cancer, 49(10):2112-2135 (May 15, 1982)
1026	Leget, G.A. *et al.*, *Use of rituximab, the new FDA-approved antibody,* Curr. Opin. Oncol., 10(6):548-551 (Nov. 1998)
1027	Harris, N.L. *et al.*, *A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group*, Blood, 84(5):1361-1392 (Sept. 1, 1994)
1028	Ford, S.M. and Donegan, S.E., *Immunotherapeutic Approaches to Treatment of B-Cell Neoplasms: Focus on Unconjugated Antibodies*, Highlights in Oncology Practice, 16(2):40-50 (1998)
1029	IDEC Pharmaceuticals Corporation, Form 10-K/A for the Fiscal Year ended December 31, 1997, filed with the U.S. Securities and Exchange Commission
1030	Exhibit Number Not Used
1031	Reff, M.E. *et al.*, *Depletion of B Cells In Vivo by a Chimeric Mouse Human Monoclonal Antibody to CD20*, Blood, 83(2):435-445 (Jan. 15, 1994) ("Reff 1994")
1032	Exhibit Number Not Used
1033	Exhibit Number Not Used

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1034	Anderson, D.R. *et al.*, *Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma*, Biochem. Soc. T., 25(2):705-708 (May 1997) ("Anderson 1997")
1035	Exhibit Number Not Used
1036	Exhibit Number Not Used
1037	Coiffier, B. *et al.*, *CHOP Chemotherapy Plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma*, N. Engl. J. Med., 346(4):235-242 (Jan. 24, 2002) ("Coiffier 2002")
1038	Shipp, M. *et al.*, *Section 3: Non-Hodgkin's Lymphomas*, in Cancer: Principles & Practice of Oncology, 5th Edition, 2165-2223 (DeVita, V.T., *et al.,* eds., 1997)
1039	FDA FOIA Response Letter (August 26, 2016)
1040	Exhibit Number Not Used
1041	Exhibit Number Not Used
1042	Exhibit Number Not Used
1043	Armitage, J.O. and Weisenberger, D.D., *New Approach to Classifying Non-Hodgkin's Lymphomas: Clinical Features of the Major Histologic Subtypes*, J. Clin. Oncol., 16(8):2780-2795 (Aug. 1998)
1044	Armitage, J.O., *Treatment of Non-Hodgkin's Lymphoma,* New Engl. J. Med., 328(14):1023-1030 (Apr. 8, 1993)
1045	Smith, M.R., *Rituximab (monoclonal anti-CD20 antibody): mechanism of action and resistance*, Oncogene, 22(47): 7359-7368 (Oct. 20, 2003)
1046	Eastern Cooperative Oncology Group ("ECOG") E4494 Protocol (1997)
1047	Exhibit Number Not Used
1048	Exhibit Number Not Used
1049	ECOG Protocols Active as of 05/19/98
1050	Exhibit Number Not Used

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1051	ECOG E4494 On Study Dates
1052	DeVita, V. T., Jr. *et al.*, *Chapter 44: Hodgkin's Disease and the Non-Hodgkin's Lymphomas*, in Cancer: Principles & Practice of Oncology, Second Edition (DeVita, Jr. *et al.*, eds., 1985)

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CLAIM LIST

Claims of U.S. Patent No. 8,557,244	
1	A method of treating a patient with diffuse large cell lymphoma, comprising administering an unlabeled chimeric anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is >60 years old and has bulky disease (tumor >10 cm in diameter).
2	The method of claim 1, wherein the chimeric antibody is rituximab.

I. INTRODUCTION

Celltrion, Inc. ("Celltrion" or "Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§311–319 and 37 C.F.R. §42 of claims 1 and 2 of U.S. Patent No. 8,557,244 ("the '244 patent"), owned by Biogen Inc. (individually, or with predecessors in interest, "Patent Owner" or "Applicant"). Review should be instituted because there is a reasonable likelihood that Celltrion will prevail in demonstrating that the claims of '244 patent are obvious, as set forth below.

The '244 patent has two claims, both of which are challenged here. Claim 1 recites a method of treating a patient with diffuse large cell lymphoma ("DLCL"), which is a subset of Non-Hodgkin's Lymphoma ("NHL"). The method involves administering a combination of an unlabeled chimeric anti-CD20 antibody and CHOP,[1] wherein the patient is greater than 60 years old and has bulky disease, where the tumor is greater than 10 cm in diameter. Claim 2 depends from claim 1 and recites rituximab as the chimeric anti-CD20 antibody.

Prior to the advent of rituximab, CHOP was a standard treatment for patients with DLCL, including those over 60 years old and those with bulky disease (characterized by at least one particularly large tumor). The challenged claims call

[1] CHOP is a standard chemotherapy consisting of cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone.

for combining this standard treatment with an antibody, such as rituximab, that targets CD20, an antigen found exclusively on B-cells. Rituximab had been the subject of extensive study for several years before Patent Owner applied for the '244 patent. Before the '244 patent's earliest priority date of August 11, 1999, and even before the critical date one year prior, it was already known that (1) rituximab was effective in treating low-grade and intermediate-/high-grade NHL, including DLCL (Ex. 1010 at 019(18:16-21); Ex. 1008 at 001; Ex. 1014 at 002; Ex. 1015 at 003), and (2) the combination of rituximab and CHOP was effective in treating DLCL patients in general (Ex. 1005 at 002 (Abstract 7)). Given the established safety and efficacy of rituximab, both alone and in combination with CHOP, use of the combination therapy to treat the claimed patient population would have been obvious to one skilled in the art.

In fact, a person skilled in the art would have understood the claimed treatment was already in practice, as it was publicly known that patients over 60 years old with DLCL were being treated with the combination of rituximab and CHOP in a large Phase III study. (Ex. 1006 at 003; Ex. 1013 at 003; Ex. 1007 at 001; Ex. 1046 at 010.) Because aggressive NHLs such as DLCL are often accompanied by bulky disease, it would have been understood by those skilled in the art that bulky disease patients were likely being treated in that Phase III study.

It was further known that rituximab was effective in treating patients with low-grade NHL accompanied by bulky disease. (Ex. 1010 at 045-46 (44:23-45:2); Ex. 1011 at 002 (Abstract 1711); Ex. 1008 at 001.) This data would have provided more motivation for one skilled in the art to treat the claimed patient population. The '244 specification itself states that the published data from the low-grade bulky disease study "suggests that . . . rituximab therapy will also be useful for more aggressive intermediate- or high-grade NHL accompanied by bulky disease." (Ex. 1001 at 7:40-45.) Indeed, aside from the generally known fact that DLCL is often accompanied by bulky disease, the ***only*** support in the '244 patent specification for the claimed treatment of bulky DLCL is the prior art data showing rituximab's efficacy in treating bulky ***low-grade*** NHL.

Given the prior art disclosures of all claim elements and the clear motivation to combine them, there is a reasonable likelihood that the claims of the '244 patent are obvious. Petitioner respectfully requests institution of *inter partes* review of claims 1 and 2.

II. MANDATORY NOTICES (37 C.F.R. §42.8(A)(1))

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Celltrion; Celltrion Healthcare Co., Ltd.; and Teva Pharmaceuticals International GmbH are the real parties-in-interest.

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

Simultaneously with the filing of the instant petition, Petitioner has filed petitions for *inter partes* review of U.S. Patent Nos. 8,329,172 and 9,296,821.

Patent Owner is the owner of the following related U.S. applications and patents: The '244 patent claims priority from application number 09/628,187 filed on July 28, 2000, which claims priority from provisional application number 60/148,286, filed on August 11, 1999. PCT/US00/19563 (published) filed on 08-02-2000; 14/045,375 (patented) filed on 10-03-2013; and 14/310,167 (pending) filed on 06-20-2014 all claim the benefit of 09/628,187.

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

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D. Service Information

Petitioner may be served at the address provided in Section II.C, above, and consents to electronic service at zCelltrion-PTAB-IPR@cooley.com.

E. Power Of Attorney (37 C.F.R. §42.10(b))

Power of attorney is being filed concurrently with this petition.

III. PAYMENT OF FEES (37 C.F.R. §42.103)

This Petition requests review of claims 1 and 2 of the '244 patent and is accompanied by a payment of $23,000, which comprises a $9,000 request fee and $14,000 post-institution fee. 37 C.F.R. §42.15(a). This Petition meets the fee requirements of 35 U.S.C. §312(a)(1).

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW (37 C.F.R. §§42.104, 42.108)

A. Grounds For Standing (37 C.F.R. §42.104(a))

Petitioner certifies that the '244 patent is eligible for *inter partes* review, and that the Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified in the present Petition.

B. Identification Of Challenge (37 C.F.R. §42.104(b)) And Statement Of Precise Relief Requested

Petitioner requests *inter partes* review of claims 1 and 2 of the '244 patent on the grounds set forth in the following table and requests that these claims be deemed invalid. The '244 patent is to be reviewed under pre-AIA §103. This Petition, supported by the accompanying declarations of Dr. Izidore Lossos and Dr. Walter Longo, demonstrates that there is a reasonable likelihood that Petitioner will prevail with respect to challenged claims 1 and 2.

Ground	'244 Patent Claims	Basis for Unpatentability
Ground 1	1 and 2	Obvious under 35 U.S.C. §103 over the combination of Link, McNeil, and the FDA Transcript

Ground 2	1 and 2	Obvious under 35 U.S.C. §103 over the combination of Link, McNeil, and the 1997 Rituxan Label
Ground 3	1 and 2	Obvious under 35 U.S.C. §103 over the combination of the E4494 Patient Consent Form and the FDA Transcript
Ground 4	1 and 2	Obvious under 35 U.S.C. §103 over the combination of Sonneveld and Link

As discussed in more detail in Section IX below, Link, McNeil, the FDA Transcript, the E4494 Patient Consent Form, the 1997 Rituxan Label, and Sonneveld are all §102(b) prior art to the '244 patent, because each reference was published or otherwise made publicly available more than one year before the earliest effective filing date of the '244 patent.

V. TECHNICAL BACKGROUND

A. DLCL Is An Aggressive Subtype Of Non-Hodgkin's Lymphoma

NHL is a diverse group of malignant lymphomas that typically arise from the lymphoid cells of the immune system. (Ex. 1023 at 026-27; Ex. 1052 at 026-27.) NHL can be divided into T-cell and the more common B-cell lymphoma. (Ex. 1023 at 023, 026; Ex. 1003 ¶36.)

Numerous classification systems exist for NHL, as greater understanding about the various forms of the disease has led to further refinement of the taxonomy. (Ex. 1043 at 002; Ex. 1003 ¶37.) By the mid-1990s, several classification systems were in use, including the International Working Formulation ("IWF"), established in 1982, and the Revised European American

Lymphoma ("REAL") classification, established in 1994. (Ex. 1025 at 012; Ex. 1027 at 003; Ex. 1003 ¶37.) The '244 patent specification refers to both of these classification systems. (Ex. 1001 at 2:36-3:4; Ex. 1003 ¶37.)

The IWF divides NHL into low-, intermediate-, or high-grade. (Ex. 1038 at 021; Ex. 1003 ¶38.) The REAL divides NHL classes into indolent or aggressive lymphoma designations, as well as specific individual lymphoma types. (Ex. 1003 ¶38; *see* Ex. 1027.) In the 1990s, low-grade (indolent) NHL was characterized by slow development with prolonged median survival, but was generally considered incurable. (Ex. 1028 at 004; Ex. 1044 at 003; Ex. 1003 ¶38.) Intermediate-grade and high-grade (aggressive) NHL were characterized by rapid tumor growth, but with the potential for cure. (Ex. 1028 at 004; Ex. 1044 at 003; Ex. 1003 ¶38.)

Diffuse large cell lymphoma ("DLCL") is the most frequent type of NHL, and accounts for approximately 30% of new cases of lymphoma each year. (Ex. 1043 at 004; Ex. 1003 ¶39.) More than half of patients with DLCL are over 60 years of age at diagnosis. (Ex. 1043 at 004; Ex. 1003 ¶39.) DLCL is aggressive, but potentially curable with aggressive therapy. (Ex. 1027 at 016; Ex. 1003 ¶39.) Under the REAL classification, the category of DLCL encompasses IWF types F, G, and H (diffuse mixed, diffuse large cell, and immunoblastic large cell, respectively). (Ex. 1027 at 006; Ex. 1003 ¶39.)

Patients with NHL may also present with large (or bulky) tumors. NHL patients with at least one particularly large tumor are considered to have bulky disease. (Ex. 1012 at 006; Ex. 1003 ¶40.) Bulky disease can occur in both low-grade and aggressive NHL patients. (Ex. 1012 at 002; Ex. 1009 at 005; Ex. 1003 ¶40.) In 1998, it was estimated that about 30% of patients with diffuse large B-cell lymphoma had bulky tumors with a diameter of at least 10 cm. (Ex. 1043 at 004; Ex. 1003 ¶40.)

B. CHOP Was A Standard Of Care For DLCL Prior To Rituximab

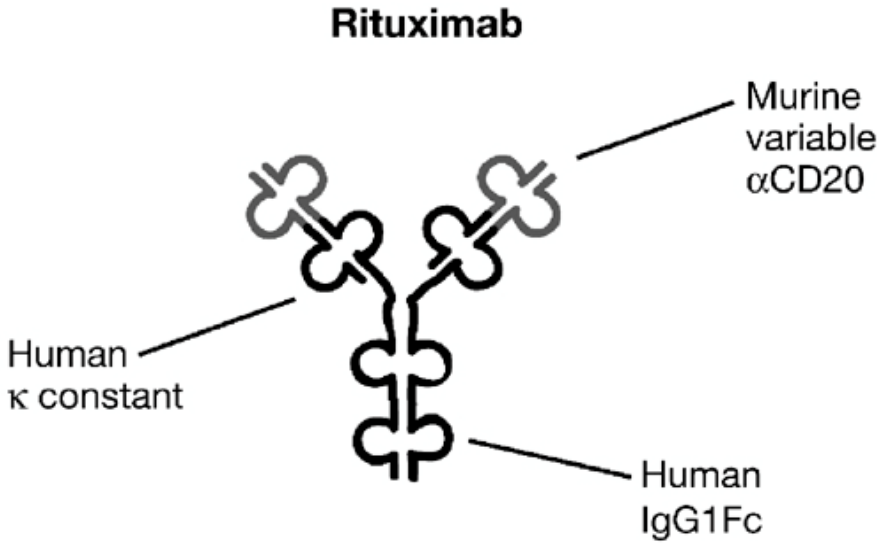
Combination CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) was developed in the 1970s, and was considered a standard therapy for both younger and older patients with DLCL in the 1990s. (Ex. 1019 at 003; Ex. 1003 ¶41.) CHOP was also a standard therapy for high-risk DLCL patients, including those with bulky disease. (Ex. 1009 at 003; Ex. 1003 ¶41.) Even with standard CHOP therapy, long-term remission occurred in only about 54% of DLCL patients. (Ex. 1009 at 009; Ex. 1003 ¶41.) Thus, more than half of patients relapsed with the best therapy possible in the early 1990s. (Ex. 1018 at 005-06; Ex. 1019 at 002-04, Figure 1; Ex. 1003 ¶41.) The advent of rituximab in the mid-1990s radically changed treatment of NHL. (Ex. 1003 ¶41.)

C. CD20 Is A Protein Expressed On The Surface Of B-Cells

The CD20 antigen is a hydrophobic transmembrane protein found on pre-B cells and mature B lymphocytes. (Ex. 1034 at 003; Ex. 1003 ¶43.) CD20, previously described as "human B lymphocyte-specific antigen," is restricted to B cells and is present on more than 90% of B-cell lymphomas. (Ex. 1020 at 002; Ex. 1021 at 004, 006, 007; Ex. 1003 ¶43.)

D. Rituximab Is A Chimeric Anti-CD20 Antibody

Rituximab (IDEC-C2B8) is a chimeric (human-mouse) monoclonal antibody directed against CD20. (Ex. 1031 at 003; Ex. 1003 ¶44.) It contains the human IgG1 and κ constant regions with murine variable regions. (Ex. 1031 at 003; Ex. 1003 ¶44.)



(Ex. 1045 at 004, Figure 1.)

Rituximab binds with high affinity and selectivity to normal and malignant B cells expressing the CD20 antigen. (Ex. 1034 at 003; Ex. 1003 ¶45.) Rituximab is thought to induce direct apoptosis and mediate complement-dependent cell lysis. (Ex. 1015 at 003; Ex. 1003 ¶45.) This kills both normal and malignant B cells. (Ex. 1015 at 003; Ex. 1003 ¶45.) Because of its ability to kill B cells selectively, rituximab was developed for cancers characterized by excessive B cell proliferation, such as B-cell NHL. (Ex. 1003 ¶45.)

E. By August 1998, Published Clinical Trial Information Established Rituximab As An Effective Therapy For NHL, Including DLCL

By August 11, 1998, the critical date of the '244 patent, numerous clinical studies had been conducted using rituximab for treatment of various B-cell lymphomas. (Ex. 1003 ¶46.) These studies generated a wealth of published information about the safety and efficacy of rituximab, alone or in combination with CHOP, for the treatment of both low-grade and aggressive NHL, and for the treatment of bulky disease. (*Id.*)

1. Publications reported that rituximab was effective treatment for low-grade B-cell NHL and intermediate/high-grade NHL

Rituximab was approved by the FDA in November 1997 for use as a single agent to treat refractory or relapsed low-grade B-cell NHL. (Ex. 1008 at 001; Ex. 1003 ¶47.) Based on the finding that "[r]ituximab has been shown to be

effective as a single agent in relapsed low-grade NHL," researchers also studied its efficacy and safety in patients with intermediate- or high-grade NHL. (Ex. 1014 at 002 (Abstract 2271); Ex. 1003 ¶47.) The 1997 Coiffier abstract reports the results of a clinical study of rituximab monotherapy involving patients with a median age of 64.5 years, and concludes that "[t]he two dosing regimen [sic] of Rituximab evaluated in this study were both safe and effective in patients with relapsed or refractory IHG [intermediate- or high-grade]-NHL, or in elderly [patients] in 1st line therapy. Further evaluation in phase III studies is warranted." (Ex. 1014 at 002; Ex. 1003 ¶47.) The article reporting the full results of that study urges combining rituximab and chemotherapy to treat DLCL patients: "Rituximab has significant activity in DLCL . . . patients and should be tested in combination with chemotherapy in such patients." (Ex. 1015 at 003; Ex. 1003 ¶47.)

2. Publications taught to combine rituximab with CHOP to treat intermediate/high-grade NHL, including DLCL

By 1997, researchers were already investigating rituximab in combination with CHOP for the treatment of various forms of NHL. IDEC Pharmaceuticals Corporation (corporate predecessor to Patent Owner Biogen) reported in a December 1997 10-K filing with the SEC:

> Rituxan is indicated for single agent use in relapsed or refractory, low grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma . . . . *Ongoing or completed Phase II studies suggest that*

> *Rituxan may also be useful in combination with chemotherapy in low grade or follicular lymphomas, and as a single agent, or in combination with various chemotherapies, in the treatment of other forms of non-Hodgkin's lymphoma*.
>
> . . .
>
> In an effort to identify expanded applications for Rituxan, [IDEC] in conjunction with Genentech, has authorized over 35 Rituxan post-marketing trials to date. Several of these trials will explore the use of Rituxan in a variety of investigational B-cell non-Hodgkin's lymphoma clinical settings including: *(i) combination therapy with widely used chemotherapy regimens for both low grade and intermediate/high grade disease;* . . . .
>
> . . . [IDEC] and Genentech have committed to providing [rituximab] to a small group of trials to be undertaken by National Cancer Institute ("NCI") funded cooperative study groups. *At least two of these trials will be large Phase III studies designed to explore the utility of Rituxan in combination with standard chemotherapy regimens*.

(Ex. 1029 at 012-13 (emphasis added); Ex. 1003 ¶48.)

By April 1998, patients with DLCL were treated with rituximab-CHOP combination therapy in a clinical trial, and the encouraging results were published. (Ex. 1005 at 002 (Abstract 7); Ex. 1003 ¶50.) The Link abstract discloses results from a study administering rituximab-CHOP combination therapy to patients with intermediate- or high-grade NHL, at least two-thirds of whom had DLCL.

(Ex. 1005 at 002; Ex. 1003 ¶50.) Link showed an overall response rate of 96%, and concluded that: "[t]his regimen represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone *and may offer higher response rates*." (Ex. 1005 at 002 (emphasis added.)

At about the same time, the Eastern Cooperative Oncology Group ("ECOG") was conducting a larger trial, designated "E4494," to investigate the effectiveness of the rituximab-CHOP combination therapy in elderly (age 60+) DLCL patients. (Ex. 1003 ¶51; *see* Ex. 1007; Ex. 1046; Ex. 1013; Ex. 1006.) E4494 would include 630 patients with DLCL. (Ex. 1046 at 033; Ex. 1003 ¶51.) DLCL patients with bulky disease were not excluded from the study. (Ex. 1046 at 033; Ex. 1003 ¶51.) About 30% of DLCL patients have bulky disease. (Ex. 1043 at 004; Ex. 1003 ¶51.) The E4494 study was publicized (Ex. 1004 ¶¶37-54; *see, e.g.*, Ex. 1006; Ex. 1013), and the E4494 Protocol and Patient Consent Form were freely accessible to potential patients and physicians, including interested oncologists and hematologists, as of December 12, 1997. (Ex. 1004 ¶¶43, 47, 54.)

In providing the rationale for the study, the E4494 Protocol reviews several studies involving CHOP and/or rituximab in patients with a variety of NHLs. (Ex. 1046 at 005-09; Ex. 1003 ¶64.) The E4494 Protocol addresses the need for

such studies in older patients, particularly since "[t]here is an increasing fraction of older patients in many countries." (Ex. 1046 at 005; Ex. 1003 ¶64.)

3. Publications reported that rituximab was effective treatment for bulky disease

During a July 1997 presentation to the FDA that was published in transcript form on August 8, 1997, Dr. Antonio Grillo-López, an inventor of the '244 patent, repeatedly referred to the effectiveness of rituximab against bulky disease. (Ex. 1010 at 045-46 (44:19-45:2), 128-30 (127:22-129:12); Ex. 1003 ¶52.) As Dr. Grillo-López explained to the FDA: "[W]e do believe that patients with bulky disease, although there is a trend for lower response rate, there is a clinically important response rate in these patients . . . ." (Ex. 1010 at 130 (129:7-9); Ex. 1003 ¶52.)

In November 1998, Davis published an abstract reporting that rituximab had activity against bulky tumors greater than 10 cm in diameter. (Ex. 1011 at 002; Ex. 1003 ¶53.) Davis discusses a Phase II trial in which 31 patients with a "median age [of] 55" were treated with rituximab, where the patients had "bulky LG/F [low grade/follicular] NHL ([defined as] ≥1 lesion ≥10 cm) . . . ." (Ex. 1011 at 002.) Davis reports an overall response rate of "43% (12/28)," and concludes that rituximab treatment "is safe and effective in patients with bulky LG/F NHL

and does not limit subsequent Rx options." (*Id*.) The complete results of this trial were published in June 1999. (Ex. 1012; Ex. 1003 ¶53.)

Patent Owner reported results from the trial described by Davis 1998 in the 1997 drug label for its proprietary rituximab product, Rituxan®: "Twenty-nine patients with relapsed or refractory, bulky (single lesion of >10 cm in diameter), low grade NHL received 375 mg/m^2 of RITUXAN as four weekly infusions . . . . Ten of 21 patients evaluable for response have obtained a complete or partial remission." (Ex. 1008 at 001; Ex. 1003 ¶53.)

Notably, the '244 specification refers to Davis 1998 as showing that rituximab therapy resulted in responses in patients with "relapsed or refractory, bulky low-grade NHL (single lesion of >10 cm in diameter)." (Ex. 1001 at 7:27-39; Ex. 1003 ¶54.) The '244 patent specification then states what the Davis 1998 abstract teaches: "*This suggests* that . . . rituximab therapy will also be useful for more aggressive intermediate- or high-grade NHLs accompanied by bulky disease." (Ex. 1001 at 7:40-45 (emphasis added); Ex. 1003 ¶54.) As discussed below, Applicant repeatedly relied on this disclosure in the Davis 1998 abstract as written description support for claims directed to bulky disease. That disclosure was available in the prior art, at least in the 1997 Rituxan drug label.

VI. THE '244 PATENT AND ITS PROSECUTION HISTORY

A. The '244 Patent

The '244 patent (Ex. 1001) is entitled "Treatment of Aggressive Non-Hodgkin's Lymphoma with Anti-CD20 Antibody." It describes methods of treating aggressive NHL using an anti-CD20 antibody, such as rituximab, in combination with chemotherapy. Its two claims are listed in the Claim List above.

B. The Prosecution History Of The '244 Patent

The '244 patent issued on October 15, 2013 from U.S. Application No. 09/628,187 (the "'187 application"), filed on July 28, 2000. The '187 application claims priority to U.S. Provisional Application No. 60/148,286 filed on August 11, 1999.

More than 12 years passed from the time the '187 application was filed until the '244 patent issued. During this time, proposed claims of the '187 application were repeatedly rejected, amended and replaced with new claims. The prosecution history shows that each time Applicant introduced claims referring to treatment of bulky disease in intermediate-/high-grade (*i.e.*, aggressive) NHL, it relied on the same passages from the specification for written description support. Specifically, Applicant relied on (1) statements that aggressive NHL is often accompanied by bulky disease, (2) the Davis data from patients with *low-grade*, bulky disease, and (3) the ongoing E4494 study. As discussed in Section IX below, all of this

information was publicly available and known to those skilled in the art prior to the August 11, 1998 critical date.

Applicant cited to the three specification disclosures enumerated above on several occasions to support newly introduced claims reciting "bulky disease." When Applicant presented 22 new claims on June 11, 2002, two of the new claims included the "bulky disease" element. (Ex. 1002 at 082-83, claims 44 and 55.) Applicant cited various sections of the specification for support for the 22 new claims, but the only disclosures regarding bulky disease in those cited sections are statements of general knowledge of those skilled in the art that aggressive NHLs "are often characterized by large extranodal bulky tumors" or "are generally characterized by . . . bulky disease . . . . " (Ex. 1002 at 079-81; Ex. 1001 at 1:32-34, 3:5-8.)

Applicant subsequently introduced new claims with the "bulky disease" element in its December 7, 2009 Amendment and Reply. (Ex. 1002 at 310-13.) To support claims 77 and 87, which were directed to treatment of diffuse large B-cell lymphoma "accompanied by bulky disease," Applicant relied on original claim 3 and the specification at page 14.[2] (*Id*. at 314.) The only disclosure regarding

[2] Original claim 3 depends from original claims 1 and 2:

Claim 1: A method for treating or alleviating the symptoms of intermediate- or

bulky disease on page 14 is that "[r]ituximab is quite active in high bulk disease" and the mention that the Davis study of *low-grade* NHL patients with bulky disease suggests that "[r]ituximab therapy will also be useful for more aggressive intermediate- or high-grade NHLs accompanied by bulky disease." (*Id.* at 018 (corresponding to Ex. 1001 at 7:27-45).)

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high-grade non-Hodgkins [*sic*] lymphoma comprising administering to a patient a therapeutically effective amount of an anti-CD20 antibody or a therapeutically effective fragment thereof.

Claim 2: The method of claim 1, wherein said non-Hodgkins [*sic*] lymphoma is selected from the group of classifications consisting of follicular large cell (FL), diffuse small cleaved cell (DSC), diffuse mixed small and large cell (DM), diffuse large cleaved cell (DL-C), diffused noncleaved large cell (DL), immunoblastic large cell (IBL), small noncleaved cell – Burkitt's (SNC-B), small noncleaved cell – non-Burkitt's (SNC), mantle cell lymphoma and AIDS related lymphoma.

Claim 3: The method of claim 2, wherein said non-Hodgkin's lymphoma is accompanied by bulky disease.

(Ex. 1002 at 021.)

Following another rejection, Applicant canceled all claims and added two new claims—the claims now at issue. (Ex. 1002 at 348, claims 102 and 103.) To support new claims 102 and 103, Applicant cited to the original "disclosure at page 14, line 12 – page 15, line 35, and in particular at page 15, lines 14-22 of the specification." (*Id*. at 353.) Again, the cited portions of the specification refer to the same discussion of the published Davis data from low-grade NHL patients and the conclusion that rituximab would be useful for patients with aggressive NHL accompanied by bulky disease. (Ex. 1002 at 018-19 (corresponding to Ex. 1001 at 7:27-8:28).) In addition, the specific cited disclosure at page 15, lines 14-22 is a description of the E4494 clinical trial. (Ex. 1002 at 019 (corresponding to Ex. 1001 at 8:9-17).)

After one more rejection, Applicant presented the same two claims and argued that the data in Coiffier 1998 taught away from the claimed method. (Ex. 1002 at 366.) The Examiner accepted that argument and allowed the claims. (Ex. 1002 at 372-73.) In doing so, the Examiner failed to consider the art as a whole by misinterpreting Coiffier 1998 itself and by specifically failing to consider (1) the publicly available E4494 Protocol and Patient Consent Form (Ex. 1007; Ex. 1046; Ex. 1004 ¶¶43, 54) and published descriptions of the E4494 study, such as McNeil (Ex. 1006), (2) the publicly available FDA Transcript, published August 8, 1997 (Ex. 1010; Ex. 1039), or (3) Sonneveld (1995) (Ex. 1009).

VII. PERSON OF ORDINARY SKILL IN THE ART

As of the August 11, 1999 priority date of the '244 patent (or the August 11, 1998 critical date), a person of ordinary skill in the art ("POSA") was a practicing physician specializing in hematology or oncology, with at least three years of experience in treating patients with NHL. (Ex. 1003 ¶21.)

VIII. CLAIM CONSTRUCTION UNDER 37 C.F.R. §42.104(B)(3)

A claim subject to *inter partes* review must be given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. §42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275-76 (Fed. Cir. 2015), *aff'd sub nom. Cuozzo Speed Techs., LLC v. Lee* , 579 U.S. --, 136 S. Ct. 2131, 2136 (2016). Accordingly, the construction proposed in this Petition represents the broadest reasonable interpretation that a POSA would assign. For claim terms not addressed below, Petitioner has applied the plain and ordinary meaning of the term.

A. "A method of treating a patient" Does Not Require Any Degree Of Therapeutic Efficacy

"A method of treating a patient" should be construed as "[a] method of administering therapy to a patient." That is, construction of this phrase should not add any level of treatment success or therapeutic efficacy.

The challenged claims neither include nor imply any level of success or efficacy, and there is no support in the specification for a construction that adds a

level of success or efficacy. Nowhere does the specification disclose any results from the claimed method of treatment, let alone disclose any way of determining whether such results would constitute success or therapeutic efficacy. The lack of support for any therapeutic efficacy in the specification by itself means that the claims should not be read to require such an effect.

Furthermore, the patent does not support a requirement of therapeutic efficacy for the additional reason that Patent Owner/Applicant deliberately omitted any therapeutic efficacy requirement from the challenged claims. During prosecution of the '244 patent, Applicant's proposed claims to a "method for treating a patient" were consistently limited by the phrase, "administering to the patient a therapeutically effective amount . . . ."[3] This limitation was included in every proposed independent claim, beginning with the initial application and continuing for nearly ten years thereafter. (Ex. 1002 at 176 (June 27, 2005

[3] *See, e.g.*, Claim 87: "A method for treating a patient with diffuse large B-cell, CD20-positive non-Hodgkin's lymphoma accompanied by bulky disease, comprising administering to the patient a therapeutically effective amount of a chimeric, humanized, or human anti-CD20 antibody or therapeutically effective antigen-binding fragment thereof . . . ." (Ex. 1002 at 312 (December 7, 2009 Applicant's Amendment and Reply).)

Applicant's Reply); 226, 228 (November 13, 2006 Applicant's Supplemental Amendment); 263 (August 21, 2008 Applicant's Reply); 272 (December 23, 2008 Applicant's Reply); 284 (May 1, 2009 Applicant's Amendment and Reply); 300 (May 29, 2009 Applicant's Amendment and Reply); 310-12 (December 7, 2009 Applicant's Amendment and Reply); 329-31 (May 18, 2010 Applicant's Response to Restriction Requirement).) In fact, Applicant used this limitation to distinguish its then-pending claims over the prior art. Applicant argued that, in contrast to prior art allegedly describing an administration of antibody that lacked therapeutic effectiveness, then-pending claim 66 "requires that the patient not only be treated with the anti-CD20 antibody (or fragment), but the antibody (or fragment) must be administered such that it is 'therapeutically effective.'" (*Id.* at 288-89 (May 1, 2009 Applicant's Amendment and Reply).)

The only time Applicant did not include the "therapeutically effective amount" limitation was when it canceled all pending claims and proposed the two claims that were eventually allowed. (*Id.* at 348 (May 31, 2011 Applicant's Amendment and Response).) The Board should not read any degree of efficacy into the claim when the Applicant chose to omit such language.

B. "diffuse large cell lymphoma" Includes IWF And REAL Classifications Of The Disease

"Diffuse large cell lymphoma" should be construed as "diffuse large cell lymphoma, including diffuse large B-cell lymphoma under the REAL classification and diffuse large cell lymphomas previously defined as Grades F, G, and H under the IWF," which is what a POSA would have understood "diffuse large cell lymphoma" to mean. (Ex. 1003 ¶¶31, 34.)

Petitioner anticipates that Patent Owner and Petitioner may disagree regarding the construction of the term "diffuse large cell lymphoma." However, the distinction between the Parties' constructions of this term may be immaterial. Petitioner expects Patent Owner to assert that DLCL is equivalent to IWF grade G NHL. Petitioner believes this term should be construed to refer to any diffuse large cell lymphoma, as recognized by those skilled in the art at the time. (Ex. 1003 ¶34.) Despite this anticipated disagreement, Petitioner's invalidity grounds remain viable under a construction of "diffuse large cell lymphoma" as being equivalent to IWF grade G NHL. In particular, Sonneveld and Link both identify treatment of patients with IWF grade G NHL, and the E4494 Protocol clarifies that patients with IWF grade G NHL were included in E4494. (Ex. 1005 at 002; Ex. 1009 at 005; Ex. 1046 at 009; Ex. 1003 ¶35.) Accordingly, Petitioner does not believe this term requires construction.

IX. THE PRIOR ART

As discussed above in Section V, the prior art was replete with reports of clinical studies demonstrating the safety and efficacy of rituximab, alone or in combination with CHOP. These studies reported the treatment of various forms of NHL, including aggressive NHL, such as DLCL. These studies also investigated different patient populations, including those over 60 years of age and those with bulky disease.

Petitioner relies on a subset of these prior art references, described below:

A. Link (Ex. 1005)

Link is an abstract entitled "Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL." (Ex. 1005 at 002 (Abstract 7).) Link describes a study investigating the safety and efficacy of rituximab-CHOP combination therapy in previously untreated patients with intermediate or high grade B-NHL (IWF grades D-H). (*Id.*; Ex. 1003 ¶58.) Link was published in the Program/Proceedings of the American Society of Clinical Oncology, Thirty-Fourth Annual Meeting, Vol. 17, p. 3a., and publicly available no later than the April 28, 1998 "received on" date affixed to the face of the

document.[4] (Ex. 1005 at 001-02.) Link was thus published and publicly available as of the August 1998 critical date, and is 102(b) prior art.

B. McNeil (Ex. 1006)

McNeil is an article entitled "Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP" published in the Journal of the National Cancer Institute in Vol. 90, No. 4, on February 18, 1998. (Ex. 1006 at 001-03.) It discusses the ongoing E4494 clinical trial investigating the combination of rituximab and CHOP in 630 elderly (60+ years old) patients with intermediate-grade lymphoma. (*Id.*; Ex. 1003 ¶60.) McNeil qualifies as prior art under 35 U.S.C. §102(b).

C. FDA Transcript (Ex. 1010)

The FDA Transcript is a transcript of the July 25, 1997 public proceedings before the FDA's Biological Response Modifiers Advisory Committee. (Ex. 1010 at 001; Ex. 1003 ¶68.) This reference contains a presentation by one of the inventors of the '244 patent, Dr. Antonio Grillo-López, to the FDA and a subsequent discussion regarding potential approval of rituximab. (Ex. 1010 at 004; Ex. 1003 ¶68.) Dr. Grillo-López made numerous disclosures regarding the

[4] During prosecution, the examiner used a publication date of April 21, 1998. (Ex. 1002 at 305 (June 5, 2009 Office Action).) Patent Owner never challenged that publication date.

treatment of bulky disease during these proceedings. The Examiner did not consider this reference in allowing the claims of the '244 patent.

The FDA Transcript was made available to the public on August 8, 1997, as confirmed by a letter from Dynna Bigby from the Division of Dockets Management (DDM) at the FDA. (Ex. 1039.) As the letter details, the August 8, 1997 stamp on page 2 of the FDA Transcript indicates that "the Division of Dockets Management (DDM) would have received the transcript on that date." (*Id*. at 001.) The Bigby letter further states that "[i]n 1997, once the DDM received a document, it made that document publicly available via the DDM Public Reading Room. Following August 8, 1997, any member of the public could have requested and received a copy of the transcript in question by filling out a reading room request form." (*Id*.) Thus, this transcript was publicly available more than one year before the earliest filing to which the '244 patent claims priority and qualifies as prior art under 35 U.S.C. §102(b).

D. 1997 Rituxan Label (Ex. 1008)

The 1997 Rituxan Label was included in the packaging of Rituxan, which was approved by the FDA on November 26, 1997. (Ex. 1008; Ex. 1029 at 002.) The 1997 Rituxan Label discloses data regarding the clinical study of patients with

bulky disease (tumor >10 cm),[5] noting that "[t]en of 21 patients evaluable for response have obtained a complete or partial remission." (Ex. 1008 at 001; Ex. 1003 ¶73.)

The 1997 Rituxan Label is dated "November 1997." (Ex. 1008 at 002.) It qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before August 11, 1999, the earliest filing to which the '244 patent claims priority.

E. The E4494 Patient Consent Form (Ex. 1007)

As described below, the E4494 Patient Consent Form qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available as of December 12, 1997.

1. The E4494 Patient Consent Form teaches administering rituximab plus CHOP combination therapy to 60+ year old patients with DLCL

E4494 Patient Consent Form is entitled "Phase III Trial of CHOP versus CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients 60 years or Older with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell Histology Non-Hodgkin's Lymphoma." (Ex. 1007 at 001; Ex. 1003 ¶62.) E4494 clinical trial was coordinated by ECOG, and designed, in relevant

[5] This is the same clinical trial disclosed in Davis 1998. (Ex. 1003 ¶73.)

part, to compare CHOP treatment with or without rituximab in elderly patients with diffuse mixed, diffuse large cell, and immunoblastic large cell NHL.[6] (Ex. 1046 at 009; Ex. 1007 at 001 (Title); Ex. 1003 ¶63.) Patients in the study were all 60+ years old. (Ex. 1046 at 010; Ex. 1007 at 001 (Title); Ex. 1003 ¶63.) The Examiner did not consider the E4494 Patient Consent Form or the E4494 Protocol in allowing the claims of the '244 patent.

2. The E4494 Patient Consent Form is prior art under 35 U.S.C. §102(b)

Dr. Walter Longo, a medical oncologist at the University of Wisconsin, Madison, who was a sub-investigator in the E4494 clinical trial, verifies in his declaration that the E4494 Patient Consent Form and the E4494 Protocol were freely available to potential patients and interested clinicians without any confidentiality restrictions as of December 1997. (Ex. 1004 ¶¶3, 4.)

A printed "publication" is a publication that is "'sufficiently accessible to the public interested in the art.'" *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (citation omitted). A reference is deemed a "printed publication," therefore, "'upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled

[6] These are the three subtypes of DLCL under the REAL classification. (Ex. 1027 at 006; Ex. 1003 ¶63 n. 3.)

in the subject matter or art, exercising reasonable diligence, can locate it.'" *In re Wyer,* 655 F.2d 221, 226 (C.C.P.A. 1981) (citation omitted); *see also Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1379-80 (Fed. Cir. Nov. 5, 2012) (finding public accessibility where the reference was well known to the community interested in the art); *see also Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1379 (Fed. Cir. 2006) (finding public accessibility when an indexed "research aid" would have directed interested researchers to the potentially invalidating reference). Once accessibility is shown, it is unnecessary to show that anyone actually inspected the reference. *Lister*, 583 F.3d at 1314.

Dr. Longo was a sub-investigator in the E4494 clinical trial and enrolled patients in that trial through his clinical institution, the University of Wisconsin Clinical Cancer Center (now re-named the Carbone Clinical Cancer Center) (hereinafter "UWCCC"). (Ex. 1004 ¶¶18, 30, 33.) Dr. Longo first received copies of the E4494 Protocol and Patient Consent Form from the UWCCC data coordinators, who did not instruct him to keep any portion of the documents confidential. (Ex. 1004 ¶32.)

Dr. Longo states that the E4494 Patient Consent Form (Ex. 1007) was distributed to potential patients with no expectation of confidentiality. (Ex. 1004 ¶40.) He personally distributed the consent form to approximately ten prospective patients, every prospective patient who inquired about the E4494 trial. (*Id.*) He

expected that prospective patients would take the consent form home and discuss the pros and cons of the clinical study with their own physicians, other oncologists who might provide second opinions, family, friends, or anyone else before deciding whether to participate. (*Id.*)

Information about E4494 was also publicly available by way of the E4494 Protocol. (*Id.* ¶54.) The UWCCC published a list of open trials, including E4494, and posted the list in clinician work spaces. (*Id.* ¶22.) ECOG affiliates would also distribute letters listing all active ECOG trials to any physician requesting such information. (*Id*. ¶47.) Starting in December 1997, the E4494 Protocol would have been included in this distribution. (*Id.*) There was no expectation that the E4494 Protocol was confidential or could not be shared with other interested clinicians. (*Id.* ¶50.) Indeed, the UWCCC would routinely disclose the E4494 Protocol to any inquiring physician, so that the physician could be fully informed about the potential risks and benefits of the E4494 trial before referring patients to the institution. (*Id.* ¶48.)

Dr. Longo further testifies that any interested physician could have learned about the E4494 trial by, for example, visiting the list of active protocols on the ECOG website. (*Id.* ¶47; Ex. 1049 at 004.) Like the "research aid" in *Bruckelmyer*, this list of active protocols was indexed by subject matter under the heading "Lymphoma Committee." *See, e.g.,* 445 F.3d at 1379. (Ex. 1004 ¶47;

Ex. 1049 at 004.) The indexed list provides sufficient detail—namely, the protocol number—to lead an interested party directly to both the E4494 Protocol and Patient Consent Form by contacting an ECOG institution and inquiring about the trial. (Ex. 1004 ¶¶47-48.) These documents were freely disseminated as a matter of course to ensure that physicians and patients were fully informed of the potential risks and benefits of enrollment. (*Id.* ¶¶37, 48.)

Dr. Longo concludes that the E4494 Patient Consent Form was known to the community interested in the subject matter of the reference—namely, physicians and patients interested in treatments for elderly patients with diffuse mixed, diffuse large cell, and immunoblastic large cell NHL—as of at least December 12, 1997. *Voter Verified*, 698 F.3d at 1379-80. For these reasons, the E4494 Patient Consent Form was publicly available as of December 1997 and qualifies as §102(b) anticipatory prior art.

F. Sonneveld (Ex. 1009)

Sonneveld is an article entitled "Comparison of Doxorubicin and Mitoxantrone in the Treatment of Elderly Patients With Advanced Diffuse Non-Hodgkin's Lymphoma Using CHOP Versus CNOP Chemotherapy," published in the Journal of Clinical Oncology, Vol. 13, No. 10 (October), 1995, pp. 2530-2539. (Ex. 1009 at 003.) Sonneveld describes a study of CHOP therapy versus another chemotherapy for the treatment of elderly (age ≥ 60) patients with "diffuse mixed

or large-cell NHL**,** including immunoblastic lymphoma and excluding lymphoblastic lymphoma (intermediate-/high-grade malignancy, groups D through H according to the Working Formulation)." (Ex. 1009 at 004; Ex. 1003 ¶66.) The Examiner did not consider Sonneveld in allowing the claims of the '244 patent.

Sonneveld qualifies as prior art under 35 U.S.C. §102(b) because it was publicly available as of October 1995, more than one year before the earliest filing to which the '244 patent claims priority. (Ex. 1009 at 001; Ex. 1003 ¶67.) Sonneveld therefore qualifies as prior art under 35 U.S.C. §102(b).

G. Additional Prior Art Confirming The General Knowledge Of The POSA

In addition to the specific references discussed in detail above, Dr. Lossos addresses additional prior art confirming the general knowledge of the POSA as of August 11, 1999 and one year earlier. (Ex. 1003 ¶75.) These disclosures are discussed above in Section V.

X. THERE IS A REASONABLE LIKELIHOOD THAT THE CLAIMS OF THE '244 PATENT ARE OBVIOUS

The question of obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). "The combination of familiar elements according to known methods is likely to be obvious when it does

no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Claims reciting a process, such as a method of treatment, are not patentable if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (internal citation omitted). The standard does not require absolute predictability, and "[a determination of] obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."). *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-00172, Paper No. 9 at 16 (P.T.A.B. May 17, 2016), the Board noted, "all that is required to show obviousness is a reasonable expectation of success, not conclusive proof of superior efficacy." *Id.* citing *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007); *Pfizer*, 480 F.3d at 1364.

Similarly, in *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, the Board found claims directed to specific dosing regimen were obvious. The Board noted that the experimentation required to achieve the claimed regimen was "'nothing more than the routine' application of a well-known problem solving

strategy . . . 'the work of a skilled [artisan], not of an inventor.'" No. IPR2013-00534, Paper No. 81 at 14 (P.T.A.B. Feb. 23, 2015) (citing *Pfizer*, 480 F.3d at 1368). Finally, the "motivation to optimize the therapy disclosed in [the prior art] flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Id*. (citation omitted).

Here, the claims of the '244 patent combine the use of a well-known antibody (rituximab) with a well-known chemotherapy regimen (CHOP), and apply this method to elderly patients suffering from DLCL and bulky disease—conditions for which both rituximab and CHOP had previously been shown to be effective. The '244 patent simply represents routine combination of well-known elements amply described in the prior art.

A. Ground 1: Claims 1 And 2 Are Obvious Under §103 Over The Combination Of Link, McNeil, And The FDA Transcript

The claims of the '244 patent would have been obvious over Link (Ex. 1005), in view of McNeil (Ex. 1006) and the FDA Transcript (Ex. 1010), because a POSA would have had a motivation and expectation of successfully combining their disclosures to achieve the claimed inventions. The Examiner did not consider either McNeil or the FDA Transcript in allowing these claims.

Link describes a study investigating the safety and efficacy of rituximab-CHOP combination therapy in previously untreated patients with intermediate or

high grade B-NHL (IWF grades D-H). (Ex. 1005 at 002.) Patients enrolled in this trial received rituximab 375 mg/m^2 on day 1 of each 21 day cycle followed 48 hours later by CHOP. (*Id.*) Thirty-one patients (median age 49) were treated, and at least 21 patients (those identified as having IWF grade "G" pathology) had DLCL. (*Id.*) The overall response rate was 96% in the 30 evaluable patients: 19 patients achieved complete response (63%), 10 patients achieved partial response (33%), and 1 patient showed progression. (*Id.*) The investigators concluded that: "This regimen represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone and may offer higher response rates." (*Id.*) Therefore, Link teaches treating DLCL with a combination of CHOP and rituximab. (Ex. 1003 ¶¶58, 78-80.)

McNeil discusses the ongoing E4494 clinical trial investigating the combination of rituximab and CHOP in 630 elderly (60+ years old) patients with intermediate-grade lymphoma. (Ex. 1006 at 003.) McNeil addresses two motivations for using the rituximab-CHOP combination to treat elderly patients suffering from intermediate-grade lymphoma. First, from a patient health perspective, McNeil states: "Another impetus is the fact that treatment for intermediate-grade lymphoma—common among elderly NHL patients—is markedly less successful in older patients. CHOP cures only about half as many elderly patients as younger patients . . . ." (*Id.*) Second, McNeil emphasizes the

need for a treatment, stating: "It is not unreasonable to expect more than a doubling of the absolute numbers of patients with lymphoma who are over the age of 65 years during the next 20 to 25 years." (*Id*.) McNeil therefore teaches the use of rituximab and CHOP in combination to treat elderly patients with intermediate-grade NHL. (Ex. 1003 ¶¶60, 79.)

The FDA Transcript is a transcript of the July 25, 1997 public proceedings before the FDA's Biological Response Modifiers Advisory Committee, including a presentation by Dr. Grillo-López. (Ex. 1010 at 001.) Dr. Grillo-López made numerous disclosures regarding the treatment of bulky disease with rituximab during these proceedings. Regarding the efficacy of rituximab treatment for patients with bulky disease (tumor >10 cm), Dr. Grillo-López stated: "Suffice it to say that we do have some preliminary data from the separate study that we conducted including patients with lesions greater than 10 cm and that preliminary data . . . shows a 48% response rate." (Ex. 1010 at 045-46 (44:23-45:2); Ex. 1003 ¶¶68, 69, 83.)[7]

[7] This is the same clinical trial disclosed in Davis (Ex. 1011) discussed below; the 48% response rate is derived from preliminary data showing 10 out of 21 patients responding. (Ex. 1003 ¶83 n. 5.)

Dr. Grillo-López discussed another study that included patients with bulky disease, where bulky disease was defined as tumors larger than 7 cm. Dr. Grillo-López stated: "So in the Phase III pivotal trial, the bulky disease patients were 21 of 166 patients. These 21 had lesions greater than 7 cm, and 8 of these 21 patients responded, for a response rate in the 21 patients of 38 percent." (Ex. 1010 at 129 (128:6-10); Ex. 1003 ¶¶70, 83.) Dr. Grillo-López noted that, although that study had an exclusion criteria for patients with tumors larger than 10 cm, the patient population nonetheless included patients with such tumors: "[W]e did have patients in that study with lesions whose maximum diameter was as large as 15 cm." (Ex. 1010 at 128-29 (127:25-128:2); Ex. 1003 ¶83.)

Finally, regarding the totality of the data on treatment of bulky disease with rituximab, Dr. Grillo-López stated: "[W]e do believe that patients with bulky disease, although there is a trend for lower response rate, there is a clinically important response rate in these patients, that is 38 percent in the pivotal trial, and in this study [specific to bulky disease patients] it looks like it is going to be in the 40, 45 percent range or thereabouts." (Ex. 1010 at 130 (129:7-12); Ex. 1003 ¶71, 84.)

Thus, Link teaches treating DLCL patients with an average age of 49 by administering a combination of CHOP and rituximab. McNeil teaches treating patients aged 60+ years old with intermediate-grade NHL, of which DLCL is the

most common form, using a combination of CHOP and rituximab. And the FDA Transcript teaches treating bulky disease with rituximab. As explained below, it would have been obvious to a POSA to combine these references to arrive at claims 1 and 2 of the '244 patent. (Ex. 1003 ¶¶78-86.)

1. Link, McNeil, and the FDA Transcript disclose all elements of Claims 1 and 2

a. "A method of treating a patient with diffuse large cell lymphoma, comprising"

Both Link and McNeil disclose the treatment of patients with DLCL. Link discloses treatment of patients in a Phase II clinical study in which "[p]atients were eligible . . . if they had previously untreated intermediate or high grade B-NHL (IWF D-H) with measurable disease." (Ex. 1005 at 002.) A POSA would have known that DLCL includes NHL in IWF categories F, G, and H. (Ex. 1038 at 046; Ex. 1003 ¶78.) Link further discloses that, out of 31 patients, "[p]athology included IWF 'D'-6, ***'G'-21***, 'H'-2 . . . ." (Ex. 1005 at 002 (emphasis added); Ex. 1003 ¶78.) Therefore, even under a narrow construction of "diffuse large cell lymphoma" as only IWF grade G, two-thirds of the patients in Link qualify. (Ex. 1003 ¶78.)

McNeil discloses treatment of patients in a Phase III "randomized trial for elderly patients with intermediate-grade non-Hodgkin's lymphoma . . . ." (Ex. 1006 at 003; Ex. 1003 ¶79.) A POSA would have known that DLCL is the

most common form of intermediate-grade lymphoma, and would have understood that the treated patients likely included those with DLCL. (Ex. 1003 ¶79.)

b. "administering an unlabeled chimeric anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient"

Link and McNeil both teach administering a combination of CHOP and rituximab, which is a chimeric anti-CD20 antibody. Link discloses a "Phase II pilot study of the safety and efficacy of rituximab in combination with CHOP chemotherapy in patients with previously untreated intermediate- or high-grade NHL." (Ex. 1005 at 002; Ex. 1003 ¶80.) Link discloses that "Rituxan™ (rituximab, IDEC-C2B8) is a chimeric murine/human monoclonal antibody that targets the CD20 antigen . . . ." (Ex. 1005 at 002.) The study described in Link investigated the safety and efficacy of rituximab-CHOP combination therapy in previously untreated patients with intermediate- or high-grade B-NHL (IWF grades D-H), including patients with DLCL. (*Id*.) Likewise, McNeil discloses that "[t]he Phase III trial will compare CHOP alone to CHOP plus the new monoclonal antibody, IDEC-C2B8 (Rituxan®)." (Ex. 1006 at 003; Ex. 1003 ¶80.)

c. "wherein the patient is >60 years old"

McNeil is specifically directed to the treatment of patients over age 60. McNeil discloses that "[t]he new trial, organized by the Eastern Cooperative

Oncology Group (ECOG), will recruit 630 patients age 60 and over . . . ." (Ex. 1006 at 003; Ex. 1003 ¶81.)

Additionally, Link discloses a "[m]edian age [of] 49" for the 31 patients treated. (Ex. 1005 at 002; Ex. 1003 ¶81.) The average patient age of 49 suggests that some patients may have been over 60. (Ex. 1003 ¶81.)

d. "and has bulky disease (tumor >10 cm in diameter)"

The FDA Transcript explicitly teaches the efficacy of rituximab to treat bulky disease, and a POSA would have understood that Link and McNeil likely included patients with bulky disease.

The FDA Transcript repeatedly discloses positive results of administering rituximab to treat patients with bulky disease. (Ex. 1010 at 045-46 (44:19-45:2), 128-30 (127:22-129:12); Ex. 1003 ¶83.) One of the inventors of the '244 patent, Dr. Grillo-López, states: "[W]e do have some preliminary data from the separate study that we conducted including patients with lesions greater than 10 cm, and that preliminary data . . . shows a 48% response rate." (Ex. 1010 at 045-46 (44:23-45:2); Ex. 1003 ¶83.)[8] Dr. Grillo-López also discusses another study that included

[8] This is the same clinical trial disclosed in Davis (Ex. 1011); the 48% response rate is derived from preliminary data showing 10 out of 21 evaluable patients responding, as compared to the 12 responders out of 28 evaluable patients

patients with bulky disease (defined in that study as tumors larger than 7 cm). Despite an exclusion criterion for patients with tumors larger than 10 cm, the patient population nonetheless included patients with tumors as large as 15 cm. (Ex. 1010 at 128-29 (127:25-128:2); Ex. 1003 ¶83.) Dr. Grillo-López discloses that the 21 bulky disease patients in the study had a response rate of 38 percent. (Ex. 1010 at 129 (128:6-10); Ex. 1003 ¶83.) Finally, Dr. Grillo-López concluded that the totality of the data on treatment of bulky disease with rituximab demonstrated "a clinically important response rate." (Ex. 1010 at 130 (129:7-12); Ex. 1003 ¶84.)

Furthermore, neither Link nor McNeil indicate any exclusion of patients with bulky disease from the studies. A POSA would have understood that DLCL is characterized by bulky disease in about 30% of DLCL patients. (Ex. 1043 at 004; Ex. 1003 ¶85.) In the absence of any indication to the contrary, a POSA would consider it highly likely that numerous patients in the studies disclosed in Link and McNeil had bulky disease because both Link and McNeil studied patients with DLCL. (Ex. 1003 ¶85.)

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disclosed in Davis. (Ex. 1003 ¶83 n. 5.)

e. "The method of claim 1, wherein the chimeric antibody is rituximab"

Claim 2 differs from claim 1 only in that claim 2 specifies rituximab as the chimeric anti-CD20 antibody. Link, McNeil, and the FDA Transcript are all directed specifically to the use of rituximab. (Ex. 1003 ¶86; Ex. 1005 at 002; Ex. 1006 at 003; Ex. 1010 at 045-46 (44:19-45:2), 128-30 (127:22-129:12).)

2. Motivation To Combine

A POSA would have been motivated to combine the teachings of Link, McNeil, and the FDA Transcript to optimize therapy for elderly patients with DLCL and bulky disease. (Ex. 1003 ¶87.) The desire of scientists and researchers to optimize therapy by improving what is already known as disclosed in the combined references "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

A POSA would have been motivated by Link's disclosure of the efficacy of the combination of CHOP and rituximab in DLCL patients to administer CHOP and rituximab in combination to elderly patients with DLCL and bulky disease. Link discloses treatment of DLCL patients with the combination of rituximab and CHOP, and concludes that the combination "represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with

conventional CHOP therapy alone and may offer higher response rates." (Ex. 1005 at 002; Ex. 1003 ¶87.) In light of these positive results, a POSA would have been motivated to implement the claimed treatment method, particularly given the understanding, discussed above, that patients over 60 years old and those with bulky disease were likely among those treated in Link. (Ex. 1003 ¶87.)

Additionally, a POSA would have been motivated to combine Link with McNeil to arrive at the claimed method, because McNeil discloses that a large study of rituximab-CHOP combination therapy in patients age 60 and older was underway. (Ex. 1006 at 003; Ex. 1003 ¶87.) As discussed above, a POSA would have understood that many of these patients were likely to have both DLCL and bulky disease. (Ex. 1003 ¶87.) A POSA would have therefore appreciated that rituximab and CHOP could be administered in combination to elderly patients with DLCL and bulky disease. (*Id.*)

Furthermore, a POSA would have known that CHOP was a standard treatment for patients with DLCL, regardless of age and presence of bulky disease. (Ex. 1009 at 003; Ex. 1003 ¶88.) McNeil confirmed this understanding, describing CHOP as "the standard chemotherapy for this form of NHL." (Ex. 1006 at 003; Ex. 1003 ¶88.) McNeil also provides additional motivation (both treatment-focused and practical) for combining rituximab with CHOP in an elderly patient population, noting that 1) "for intermediate-grade lymphoma—common among

elderly NHL patients— . . . . CHOP [alone] cures only about half as many elderly patients as younger patients," and 2) "'[i]t is not unreasonable to expect more than a doubling of the absolute numbers of patients with lymphoma who are over the age of 65 years during the next 20 to 25 years.'" (Ex. 1006 at 003 (citation omitted); Ex. 1003 at ¶88.)

The disclosures in the FDA Transcript would have provided even more motivation to combine the references by explicitly and repeatedly touting rituximab's success in treating patients with bulky disease. (Ex. 1010 at 045-46 (44:19-45:2), 128-30 (127:22-129:12); Ex. 1003 ¶89.)

Thus, a POSA seeking to optimize treatment for elderly patients with DLCL and bulky disease would be motivated to combine CHOP—a standard chemotherapy regimen for DLCL—with rituximab—a therapy with success at treating bulky disease. (Ex. 1003 ¶89; Ex. 1010 at 045-46 (44:19-45:2), 128-30 (127:22-129:12); Ex. 1006 at 003.)

3. Reasonable Expectation Of Success

A POSA would have had a reasonable expectation of successfully achieving the claimed methods based on Link, McNeil, and the FDA Transcript. As an initial matter, as described in Section VIII.A above, the claims require no minimum level of therapeutic efficacy or treatment success; they simply require the administration of the rituximab-CHOP combination to the claimed patient population.

Regardless, a POSA would have had a reasonable expectation that the combination of rituximab and CHOP would be at least as efficacious as CHOP alone. (Ex. 1003 ¶90.)

First, a POSA would have known Link's conclusion that the combination therapy "may offer higher response rates." (Ex. 1005 at 002; Ex. 1003 ¶91.) Second, a POSA would have known that a 630-patient Phase III trial involving the claimed method, E4494, was already underway, suggesting that the multi-center cooperative organizing the trial (ECOG) had a reasonable expectation of success. (Ex. 1006 at 003; Ex. 1003 ¶91.)[9] E4494 also targets patients over 60 years of age. (Ex. 1006 at 003; Ex. 1003 ¶91.) Third, a POSA would have known that CHOP

[9] The Manual of Patent Examining Procedure's provisions relating to the effect of ongoing human clinical trials in the context of §112 further support this suggestion. "[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." MPEP (2015) §2107.03 at IV. Likewise, a POSA would have presumed that the treatment method investigated by the large ECOG clinical trial described in McNeil was reasonably likely to have therapeutic utility. (Ex. 1003 ¶ 91.)

was already a standard treatment for the claimed patient population (Ex. 1009 at 003; Ex. 1003 ¶91), and that there was "known synergy" between rituximab and CHOP. (Ex. 1016 at 003 (Abstract 53); Ex. 1003 ¶91.) Link itself notes the "synergistic cytotoxicity between rituximab and chemotherapy." (Ex. 1005 at 002; Ex. 1003 ¶91.) Link further discloses that the combination therapy was "tolerable . . . with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone," so any synergy between rituximab and CHOP would likely increase response rates. (Ex. 1005 at 002.)

Finally, the data disclosed in the FDA Transcript regarding rituximab treatment of low-grade NHL accompanied by bulky disease would have increased a POSA's expectation of success. As Patent Owner itself concluded, that same data "suggests that . . . rituximab therapy will also be useful for more aggressive intermediate- or high-grade NHLs accompanied by bulky disease." (Ex. 1001 at 7:27-45.) A POSA reviewing the data in the FDA Transcript would have likewise concluded that rituximab, particularly when combined with CHOP, would be useful for treating bulky tumors in patients with DLCL. (Ex. 1003 ¶92.)

Thus, a POSA would have had a reasonable expectation that the combination of rituximab and CHOP would be safe and efficacious for elderly patients with DLCL and bulky disease. (Ex. 1003 ¶¶90-92.)

B. Ground 2: Claims 1 And 2 Are Obvious Under §103 Over The Combination Of Link, McNeil, And The 1997 Rituxan Label

The claims of the '244 patent would have been obvious over Link (Ex. 1005), in view of McNeil (Ex. 1006) and the 1997 Rituxan Label (Ex. 1008), because a POSA would have had a motivation and expectation of successfully combining their disclosures to achieve the claimed inventions. (Ex. 1003 ¶¶93-96.)

As discussed in Ground 1, Link describes a study investigating the safety and efficacy of rituximab-CHOP combination therapy in previously untreated patients with intermediate- or high-grade B-NHL (IWF grades D-H). (Ex. 1005 at 002.) McNeil discusses the ongoing E4494 clinical trial investigating the combination of rituximab and CHOP in 630 elderly (60+ years old) patients with intermediate-grade lymphoma. (Ex. 1006 at 003.)

The 1997 Rituxan Label discloses positive results from the same clinical trial of patients with bulky disease that was discussed in the FDA Transcript (Ex. 1010) and Davis (Ex. 1011). Specifically, the 1997 Rituxan Label states: "Twenty-nine patients with relapsed or refractory, bulky (single lesion of > 10 cm in diameter), low grade NHL received 375 mg/m^2 of RITUXAN as four weekly

infusions. . . . Ten of 21 patients evaluable for response have obtained a complete or partial remission."[10] (Ex. 1008 at 001; Ex. 1003 ¶94.)

Thus, Link teaches treating DLCL patients with an average age of 49 by administering a combination of CHOP and rituximab. McNeil teaches treating patients age 60+ years old with intermediate-grade NHL, of which DLCL is the most common form, using a combination of CHOP and rituximab. The 1997 Rituxan Label teaches the efficacy of treating bulky disease with rituximab. Because the 1997 Rituxan Label reports the same study data as the FDA Transcript, it would have been obvious to a POSA to combine these references to arrive at claims 1 and 2 of the '244 patent for the same reasons articulated in Ground 1 above. (Ex. 1003 ¶¶95-96.)

For the same reasons articulated in Ground 1 above, a POSA would have been motivated to combine Link with McNeil to arrive at the claimed method. (Ex. 1003 ¶95.) As with the FDA Transcript in Ground 1, the disclosures in the 1997 Rituxan Label would have provided even more motivation to combine the

[10] The reported results are preliminary data showing 10 responders out of 21 evaluable patients, as compared to the 12 responders out of 28 evaluable patients disclosed in Davis. (Ex. 1011 at 002; Ex. 1003 ¶94 n. 6.)

references by demonstrating rituximab's success in treating patients with bulky disease. (Ex. 1008 at 001; Ex. 1003 ¶95.)

Also for the reasons articulated in Ground 1 above, a POSA would have had a reasonable expectation of success in treating DLCL patients with bulky tumors and achieving some level of therapeutic efficacy based on the teachings of Link and McNeil. (Ex. 1003 ¶96.) The data disclosed in the 1997 Rituxan Label regarding rituximab treatment of low-grade NHL accompanied by bulky disease would have further increased a POSA's expectation of success for the reasons stated in Ground 1 regarding the same data reported in the FDA Transcript. (Ex. 1008 at 001; Ex. 1003 ¶96.)

Ground 2 is a non-redundant ground over Ground 1 because, to the extent Patent Owner challenges the public availability of the FDA Transcript, the 1997 Rituxan Label remains as §102(b) prior art.

C. Ground 3: Claims 1 And 2 Are Obvious Under §103 Over The Combination Of The E4494 Patient Consent Form And The FDA Transcript

The claims of the '244 patent would have been obvious over the E4494 Patient Consent Form (Ex. 1007) and the FDA Transcript (Ex. 1010), because a POSA would have had a motivation and expectation of successfully combining their disclosures to achieve the claimed inventions. The Examiner did not consider

either the E4494 Patient Consent Form or the FDA Transcript in allowing these claims.

The E4494 Patient Consent Form discloses details of the E4494 clinical trial, which was also discussed in McNeil. (Ex. 1006). Specifically, the E4494 Patient Consent Form discloses a "Phase III Trial of CHOP versus CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients 60 Years or Older with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell Histology Non-Hodgkin's Lymphoma." (Ex. 1007 at 001; Ex. 1003 ¶98.) The title of the E4494 study teaches the administration of rituximab (also known as IDEC-C2B8) in combination with CHOP in patients over age 60 with DLCL. (Ex. 1007 at 001; Ex. 1003 ¶98.) Neither the E4494 Patient Consent Form nor the associated E4494 Protocol excludes DLCL patients with bulky disease, and a POSA would have known that DLCL is often characterized by bulky disease. (Ex. 1007; Ex. 1046; Ex. 1003 ¶¶97, 98.)

As described in Ground 1, the FDA Transcript includes numerous statements made by Dr. Grillo-López regarding the efficacy of treating bulky disease with rituximab.

Ground 3 is a non-redundant ground over Ground 1 because, to the extent Patent Owner challenges the public availability of the E4494 Patient Consent Form, McNeil remains as §102(b) prior art.

1. Motivation To Combine

A POSA would have been motivated to combine the teachings of the E4494 Patient Consent Form and the FDA Transcript to treat DLCL patients over 60 years of age, who have bulky tumors, with the combination of CHOP and rituximab. Scientists have a motivation to optimize therapy by improving upon what is disclosed in the combined references, which "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d at 1330).

The E4494 Patient Consent Form and the associated E4494 Protocol provide the blueprint for administering CHOP plus rituximab to a DLCL patient who is more than 60 years of age. (Ex. 1003 ¶99.) A POSA would have understood that, because bulky disease patients were not excluded in the E4494 Protocol, such patients would be included in the E4494 trial. (*Id.*) Dr. Grillo-López's report of a 48% response rate in patients with lesions greater than 10 cm (Ex. 1010 at 045-46 (44:23-45:2)) would have further motivated a POSA to administer the rituximab-CHOP combination taught by the E4494 trial to DLCL patients with bulky disease. (Ex. 1003 ¶99.)

2. Reasonable Expectation Of Success

A POSA would have had a reasonable expectation of successfully achieving the claimed methods based on the E4494 Patient Consent Form and the FDA

Transcript. As an initial matter, as described in Section VIII.A above, the claims require no minimum level of therapeutic efficacy or treatment success; they simply require the administration of the rituximab-CHOP combination to the claimed patient population. Regardless, a POSA would have had a reasonable expectation that the combination of rituximab and CHOP would be efficacious in elderly patients with DLCL and bulky disease.

A POSA would have had a reasonable expectation that the DLCL patients in the E4494 trial who had bulky disease would respond to treatment with CHOP and rituximab. (Ex. 1003 ¶100.) Applicants themselves acknowledge in the '244 specification that rituximab is "quite active in high bulk disease" in "bulky low-grade NHL patients," and conclude that this "suggests that with the appropriate dosages depending on the extent of disease . . . rituximab therapy will also be useful for more aggressive intermediate- or high-grade NHLs accompanied by bulky disease." (Ex. 1001 at 7:28-45.) This is precisely how a POSA would have understood the FDA Transcript's disclosure regarding the effect of rituximab on bulky tumors. (Ex. 1003 ¶100.)

Based on the expectation that rituximab would treat bulky tumors, a POSA reading the E4494 Patient Consent Form's teaching of administering a rituximab-CHOP combination to DLCL patients over age 60 would have reasonably expected that the rituximab-CHOP combination would also benefit DLCL patients over age

60 with bulky disease. This expectation would be supported by a POSA's appreciation that CHOP was a standard chemotherapy that was already in use to treat this patient population, such that adding rituximab as taught by the FDA Transcript would result in positive responses. (*Id.*)

D. Ground 4: Claims 1 And 2 Are Obvious Under §103 Over The Combination Of Sonneveld And Link

The claims of the '244 patent would have been obvious over Sonneveld (Ex. 1009), in view of Link (Ex. 1005 at 002), because a POSA would have had a motivation and expectation of successfully combining their disclosures to achieve the claimed inventions. The Examiner did not consider Sonneveld in allowing these claims.

Sonneveld describes a study of CHOP therapy versus another chemotherapy for the treatment of patients over 60 years old with "diffuse mixed or large-cell NHL**,** including immunoblastic lymphoma and excluding lymphoblastic lymphoma . . . ." (Ex. 1009 at 004; Ex. 1003 ¶66.) This patient group corresponds to IWF groups D through H. (Ex. 1009 at 004, 005 (Table 1).) Sonneveld notes that "[s]tandard chemotherapy in stage III/IV [advanced] lymphoma is considered to be cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP)," and Table 1 in Sonneveld shows that 44% of patients receiving CHOP treatment in the Sonneveld trial had bulky disease, defined as tumor mass ≥ 10 cm. (Ex. 1009 at

003-05; Ex. 1003 ¶66.) The study found that "CHOP is well tolerated in elderly patients with advanced intermediate- or high-grade NHL . . . . CHOP should be recommended for elderly patients with high-risk NHL." (Ex. 1009 at 003; Ex. 1003 ¶66.)

As discussed in Ground 1, Link describes a study investigating the safety and efficacy of rituximab-CHOP combination therapy in previously untreated patients with intermediate- or high-grade B-NHL (IWF grades D-H). (Ex. 1005 at 002.)

Thus, Sonneveld teaches CHOP as a recommended therapy for patients over age 60 with DLCL, including patients with bulky disease. Link teaches treating DLCL patients with an average age of 49 by administering a combination of CHOP and rituximab. As explained below, it would have been obvious to a POSA to combine these references to arrive at claims 1 and 2 of the '244 patent.

1. Sonneveld and Link disclose all elements of Claims 1 and 2

a. "A method of treating a patient with diffuse large cell lymphoma, comprising"

Both Sonneveld and Link teach treatments for patients with DLCL. Sonneveld discloses treatment of patients in a Phase III clinical trial in which "[e]ligibility criteria included age ≥ 60 years and a confirmed histologic diagnosis of diffuse mixed or large-cell NHL**,** including immunoblastic lymphoma and

excluding lymphoblastic lymphoma (intermediate-/high-grade malignancy, groups D through H according to the Working Formulation)." (Ex. 1009 at 004; Ex. 1003 ¶101.) Link discloses treatment of patients in a Phase II clinical study in which "[p]atients were eligible . . . if they had previously untreated intermediate or high grade B-NHL (IWF D-H) with measurable disease" (Ex. 1005 at 002; Ex. 1003 ¶101.)

Furthermore, even under a narrow construction of "diffuse large cell lymphoma" as only IWF grade G, many of the patients in Sonneveld and Link are patients with DLCL. (Ex. 1003 ¶102.) Sonneveld discloses that 27 (38%) of the patients receiving CHOP therapy had IWF grade G histology. (Ex. 1009 at 005 (Table 1); Ex. 1003 ¶102.) Link further discloses that, out of 31 patients, "[p]athology included IWF 'D'-6, ***'G'-21***, 'H'-2 . . . ." (Ex. 1005 at 002 (emphasis added); Ex. 1003 ¶102.)

b. "administering an unlabeled chimeric anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient"

Link discloses administering rituximab, which is a specific chimeric anti-CD20 antibody, to DLCL patients. Specifically, the title of Link is a "Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy . . . ." (Ex. 1005 at 002; Ex. 1003 ¶103.)

c. "wherein the patient is >60 years old"

Sonneveld teaches that CHOP is a recommended chemotherapy for DLCL patients over 60 years old. Sonneveld discloses that "[e]ligibility criteria included age ≥ 60 years . . . ." (Ex. 1009 at 004; Ex. 1003 ¶104.) Sonneveld further found that "CHOP is well tolerated in elderly patients with advanced intermediate- or high-grade NHL . . . . CHOP should be recommended for elderly patients with high-risk NHL." (Ex. 1009 at 003; Ex. 1003 ¶104.)

Additionally, Link discloses a "[m]edian age [of] 49" for the 31 patients treated. (Ex. 1005 at 002; Ex. 1003 ¶104.) The average patient age of 49 suggests that some patients may have been over 60. (Ex. 1003 ¶104.)

d. "and has bulky disease (tumor >10 cm in diameter)"

Sonneveld explicitly teaches the efficacy of CHOP to treat bulky disease, and a POSA would have understood that Link likely included patients with bulky disease because approximately 30% of DLCL patients have bulky disease. (Ex. 1043 at 004; Ex. 1003 ¶¶105, 106.)

Sonneveld discloses that "[e]ligibility criteria included . . . bulky disease . . . defined as a biopsy-proven tumor mass ≥ 10 cm." (Ex. 1009 at 004; Ex. 1003 ¶105.) Indeed, 44% of patients who received CHOP treatment in Sonneveld's trial had bulky disease. (Ex. 1009 at 005 (Table 1); Ex. 1003 ¶105.)

Furthermore, Link does not indicate any exclusion of patients with bulky disease. (Ex. 1003 ¶106.) A POSA would have understood that DLCL is often characterized by bulky disease and thus that some patients in the Link study had bulky disease. (*Id*.)

e. "The method of claim 1, wherein the chimeric antibody is rituximab"

Claim 2 differs from claim 1 only in that claim 2 specifies rituximab as the chimeric anti-CD20 antibody. Link is directed specifically to the use of rituximab. (Ex. 1005 at 002; Ex. 1003 ¶107.)

2. Motivation To Combine

A POSA would have been motivated to combine the teachings of Sonneveld and Link to optimize therapy for elderly patients with DLCL and bulky disease. (Ex. 1003 ¶108.) The desire of scientists and researchers to optimize therapy by improving what is already known as disclosed in the combined references "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d at 1330).

Sonneveld teaches the efficacy of CHOP in DLCL patients over age 60, including patients with bulky disease. After studying patients with advanced, high-risk NHL, including those with bulky disease (tumor mass ≥ 10 cm), Sonneveld concludes that "CHOP is well tolerated in elderly patients with advanced

intermediate- or high-grade NHL . . . . CHOP should be recommended for elderly patients with high-risk NHL." (Ex. 1009 at 003-05; Ex. 1003 ¶108.) Based on a wealth of data showing the effectiveness of rituximab alone in treating NHLs of many types, including diffuse large cell lymphoma, a POSA would have been motivated to add rituximab to the standard treatment. (Ex. 1003 ¶109.) Link in particular discloses the efficacy of combining CHOP and rituximab in DLCL patients. Link concludes: "This regimen represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone *and may offer higher response rates*." (Ex. 1005 at 002 (emphasis added); Ex. 1003 ¶109.) This motivation to add rituximab to the standard therapy of CHOP for elderly DLCL patients would have been bolstered by the understanding, discussed above, that patients over 60 years old and those with bulky disease were likely among those treated in the Link study. (Ex. 1003 ¶109.)

Alternately, a POSA reviewing Link would understand that Link likely included elderly patients and patients with bulky disease. Thus, a POSA would be motivated by Sonneveld's explicit teaching regarding CHOP's efficacy for elderly DLCL patients to administer the combination therapy described by Link to Sonneveld's patient population of DLCL patients over age 60, including patients with bulky disease. (*Id.* ¶110.)

3. Reasonable Expectation Of Success

A POSA would have had a reasonable expectation of successfully achieving the claimed methods based on Sonneveld and Link. (Ex. 1003 ¶111.) As discussed in Section VIII.A above, the claims require no minimum level of therapeutic efficacy or treatment success; they simply require the administration of the rituximab-CHOP combination to the claimed patient population. Regardless, a POSA would have had a reasonable expectation that the combination of rituximab and CHOP would be efficacious in elderly patients with DLCL and bulky disease.

Given Sonneveld's teaching that CHOP was the recommended standard treatment for elderly DLCL patients, the effectiveness of rituximab alone in treating a variety of NHLs (including DLCL), and Link's demonstration of the positive results obtained by combining CHOP with rituximab in the general population of patients with DLCL (likely including elderly patients and those with bulky disease), a POSA would have had a reasonable expectation that the combination would also be successful for the claimed patient population. (Ex. 1009; Ex. 1005 at 002; Ex. 1003 ¶111.)

A POSA would have known Link's conclusion that the combination therapy "may offer higher response rates." (Ex. 1005 at 002; Ex. 1003 ¶112.) Link notes in particular the "synergistic cytotoxicity between rituximab and chemotherapy." (Ex. 1005 at 002.) Link discloses that the combination therapy was "tolerable . . .

with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone," so any synergy between rituximab and CHOP would likely increase response rates. (*Id*.)

Therefore, a POSA reviewing Sonneveld and Link would have a reasonable expectation that the combination of CHOP and rituximab would be safe and efficacious for DLCL patients over age 60, including patients with bulky disease. (Ex. 1003 ¶¶111-12.)

E. No Secondary Indicia Of Non-Obviousness Exist

Applicant made arguments during prosecution of the '244 patent that (1) the rituximab-CHOP combination unexpectedly produced synergistic results in treating patients with aggressive NHL, and (2) the prior art taught away from the claimed method. These arguments do not negate the obviousness of the claims.

1. No Unexpected Results

During prosecution of the '244 patent, Applicant argued that the rituximab-CHOP combination "yielded long lasting therapeutic benefits in the absence of increased toxicity. . . . *The greater-than-additive effect of anti-CD20 therapy in combination with chemotherapy was unexpected and could not have been predicted prior to performance of the methods of the present disclosure*." (Ex. 1002 at 104 (August 5, 2003 Applicant's Reply) (underlining in original; italics added).)

As an initial matter, any "therapeutic benefits" and "greater-than-additive effect of anti-CD20 therapy in combination with chemotherapy" are irrelevant to the claims of the '244 patent, which do not require any particular level of therapeutic benefits or effectiveness. (*See* Section VIII above.) This is in contrast to the claims proposed by Applicant during nearly the entirety of prosecution of the '244 patent, which were consistently limited by the phrase, "administering to the patient a therapeutically effective amount." (*Id*.) The "therapeutically effective amount" limitation is absent from the claims of the '244 patent, which only require administration of rituximab and CHOP. Accordingly, the Applicant's argument of unexpected success because of a therapeutic effect had no nexus to the claim limitations.

In any event, Applicant's alleged surprising therapeutic success cites two references that do not discuss response rates for DLCL patients with bulky disease. Applicant relied on (1) the Link data (later published again in Vose 2001 (Ex. 1024)) and (2) the Coiffier 2002 data (reporting results of the European counterpart to the E4494 study). (Ex. 1002 at 097-98 (White Declaration accompanying August 5, 2003 Applicant's Reply).) But neither of these publications mentions any therapeutic result in treating the claimed patient population, DLCL patients

with bulky disease. (Ex. 1003 ¶117; *see* Ex. 1024; Ex. 1037.)[11] These claims of unexpected results are thus off the mark, particularly in light of the full scope of prior art discussed previously.

2. No Teaching Away

Coiffier 1998 is an article that reports the results of a Phase II study to evaluate the efficacy and tolerability of rituximab in patients with aggressive NHL, more than half of whom "had diffuse large B-cell lymphoma (DLCL) according to the REAL Classification . . . ." (Ex. 1015 at 004; Ex. 1003 ¶118.) Coiffier 1998 found that DLCL patients "experienced a significant clinical activity with low toxicity" (Ex. 1015 at 003), and explicitly teaches that rituximab "should be evaluated in combination with standard chemotherapy in patients with aggressive B-cell lymphoma." (Ex. 1015 at 008; Ex. 1003 ¶118.)

Contrary to that teaching, Applicant argued during prosecution that the results of this study taught away from the claimed method. Specifically, regarding

[11] Vose 2001 notes how many patients had bulky disease and provides response rates, but does not discuss whether these patients had DLCL. (Ex. 1024 at 006-07; Ex. 1003 ¶117 n. 7.) Coiffier 2002 notes how many patients had bulky disease, but does not indicate the response rate for these patients. (Ex. 1037 at 005 (Table 1); Ex. 1003 ¶117 n. 7.)

the data presented in Table 3 of the Coiffier 1998 article, Applicant argued:

> [N]one of the patients who had tumor lesions ≥ 10 cm in size responded to treatment with rituximab. Based on this observation, Coiffier *et al.* not only does not create a reasonable expectation that a combination treatment with an anti-CD20 antibody, such as rituximab, and CHOP would be effective in treating patients with diffuse large cell lymphoma of ≥ [10] [sic] in size (bulky disease), it actually teaching [sic] away from the treatment method claimed in the present application.

(Ex. 1002 at 366 (August 20, 2012 Applicant's Remarks).) As previously discussed, the Examiner accepted this argument and withdrew her rejection of the claims. (*Id*. at 372 (November 7, 2012 Office Action).)

The Examiner erred in allowing the claims for several reasons. First, for the five patients with bulky disease, no other information about these patients is disclosed, such as whether the five patients with bulky disease were DLCL patients or patients with other NHL subtypes. (Ex. 1015 at 005.) This insufficient information about the five patients with bulky disease makes it impossible to determine whether other factors may have contributed to the lack of response. (*Id*.)

Additionally, Coiffier 1998 reported a study of rituximab as a ***single agent***. One skilled in the art would expect to treat aggressive NHLs, such as DLCL, with a combination of treatments, and would understand that combining rituximab with

a standard CHOP chemotherapy would be reasonably likely to lead to better results in patients with bulky disease. (Ex. 1003 ¶122.)

More significantly, the Examiner erred by failing to consider the art as a whole in accepting Applicant's argument. "[O]bviousness must be determined in light of all the facts, and there is no rule that a single reference that teaches away will mandate a finding of nonobviousness." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). "Rather, the prior art must be considered as a whole for what it teaches." *Id*. at 1166. In *Merck & Cie v. Gnosis S.p.A.*, for example, the Federal Circuit considered several arguments that certain prior art taught away from the claimed invention, and concluded that the "isolated prior art disclosures" cited by patentee do not teach away when "[v]iewing the prior art as a whole." 808 F.3d 829, 833-836 (Fed. Cir. 2015).

The art as a whole contradicts Applicant's teaching away argument. First, a POSA would have been aware of E4494, a large Phase III study. (Ex. 1004 ¶¶3, 4, 27; Ex. 1003 ¶123.) The fact that this study was underway leads to a presumption that the treatment method being studied was reasonably likely to have therapeutic utility. *See* MPEP §2107.03 at IV. The E4494 study included patients with bulky disease and did not suggest that such patients would not respond to treatment. (Ex. 1004 ¶1; Ex. 1007 at 001; Ex. 1046 at 042.)

Furthermore, a POSA would have been aware of the 1997 Rituxan Label, reporting the favorable results obtained from the Davis study of rituximab in patients with low-grade, bulky NHL. (Ex. 1011; Ex. 1008; Ex. 1003 ¶124.) A POSA would have recognized, as Patent Owner did, that "there is a clinically important response rate in these patients" (Ex. 1010 at 130 (129:7-12)), and would have had a reasonable expectation that rituximab, when combined with CHOP, would also be effective in treating bulky disease in more aggressive NHLs. (Ex. 1003 ¶¶124, 125.)

XI. CONCLUSION

Petitioner respectfully requests institution of *inter partes* review of claims 1 and 2 of the '244 patent, and a finding that the claims are unpatentable, based on the grounds presented in this Petition.

Dated: March 15, 2017

Respectfully submitted,

By: */s / Michelle S. Rhyu*

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37 C.F.R. § 42.24(d) CERTIFICATION

The undersigned hereby certifies that this submission, excluding the parts of this petition that are exempted by 37 C.F.R. § 42.24(a) (including the tables of contents and authority, mandatory notices, claim listings, certificate of word count, exhibit list, and certificate of service), contains 13,902 words, as determined using the standard word counting feature of the Microsoft Word program.

Dated: March 15, 2017

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CERTIFICATION OF SERVICE

I, Michelle S. Rhyu, hereby certify that pursuant to 37 C.F.R. Sections 42.6 and 42.105, a complete copy of the attached **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,557,244,** including all exhibits (**Nos. 1001-1052)** and related documents, are being served on the 15th day of March, 2017, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, via Federal Express upon the Patent Owner at the following correspondence address of record with the USPTO:

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