UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and FRESENIUS KABI SWISSBIOSIM GmbH
Petitioners,
v.

CHUGAI SEIYAKU KABUSHIKI KAISHA
Patent Owner.

IPR 2021-01025

Patent No. 10,744,201

Title: METHOD FOR TREATING RHEUMATOID ARTHRITIS WITH A HUMAN IL-6 RECEPTOR ANTIBODY AND METHOTREXATE

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,744,201

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LIST OF EXHIBITS

PETITIONERS EXHIBIT NO.	DESCRIPTION
Ex. 1001	U.S. Patent No. 10,744,201 ("'201 patent")
Ex. 1002	Declaration of Thomas M. Zizic, M.D. ("Zizic Decl.")
Ex. 1003	*Reserved*
Ex. 1004	File History for U.S. Patent No. 10,744,201 ("'201 Patent File History")
Ex. 1005	Kazuyuki Yoshizaki et al., *Therapy of Rheumatoid Arthritis by Blocking IL-6 Signal Transduction with a Humanized Anti-IL-6 Receptor Antibody*, Springer Seminars in Immunopathology 20:247-59 (1998) ("Yoshizaki")
Ex. 1006	Certificate of Translation (pg. 1), Translation (pgs. 2-6), & Original (pgs. 7-10): Norihiro Nishimoto, *Anti-IL-6 Receptor Antibodies, Usefulness and Issues in Rheumatoid Arthritis*, ChiryoGaku 36(12):1264-67 (2002) ("Nishimoto")
Ex. 1007	Eric L. Matteson, *Concise Review for Clinicians, Current Treatment Strategies for Rheumatoid Arthritis*, Mayo Clinic Proceedings 75:69-74 (2000) ("Matteson")
Ex. 1008	Michael E. Weinblatt et al., *Adalimumab, a Fully Human Anti-Tumor Necrosis Factor α Monoclonal Antibody, for the Treatment of Rheumatoid Arthritis in Patients Taking Concomitant Methotrexate*, Arthritis & Rheumatism 48(1):35-34 (Jan. 2003) ("Weinblatt 2003")

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Ex. 1009	Food and Drug Administration, Center for Drug Evaluation and Research, *Guidance for Industry, Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)* (1999) ("1999 FDA Guidance")
Ex. 1010	American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, *Guidelines for the Management of Rheumatoid Arthritis 2002 update*, Arthritis Rheum. 46:328-346 (2002) ("2002 Guidelines")
Ex. 1011	Rebholz et al., *An Assessment of Emerging Patterns of Etanercept Use in the Treatment of Rheumatoid Arthritis*, Journal of Managed Care Pharmacy, Vol. 7, No. 1 (Jan/Feb. 2001) ("Rebholz")
Ex. 1012	*ENBREL® (etanercept)*, Physicians' Desk Reference (54th ed. 2000) ("2000 PDR – Enbrel")
Ex. 1013	*REMICADE® (infliximab)*, Physicians' Desk Reference (55th ed. 2001) ("2001 PDR – Remicade")
Ex. 1014	Certificate of Translation (pg. 1), Translation (pgs. 2-8), & Original (pgs. 10-16): Koichi Amano & Tsutomu Takeuchi, *RA Anti-Cytokine Therapy*, Pharma Medica, The Review of Medicine and Pharmacology 19(7):73-78 (2001) ("Amano")
Ex. 1015	Ravinder N. Maini et al., *Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis*, Arthritis & Rheumatism 41(9):1552-63 (1998) ("Maini 1998")

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Ex. 1016	Norihiro Nishimoto et al., *Safety and Efficacy of Repetitive Treatment with Humanized Anti-Interleukin-6 Receptor Antibody (MRA) in Rheumatoid Arthritis (RA)*, Arthritis & Rheumatism 44(9 Supplement):S84 (2001) ("Nishimoto Abstract A")
Ex. 1017	Norihiro Nishimoto et al., *A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Humanized Anti-interleukin-6 (IL-6) Receptor Monoclonal Antibody (MRA) in Rheumatoid Arthritis (RA)*, Arthritis & Rheumatism 46(9 Supplement):S559 (2002) ("Nishimoto Abstract B")
Ex. 1018	*Reserved*
Ex. 1019	Certificate of Translation (pg. 1), Translation (pgs. 2-8), & Original (pg. 10-16): Keisuke Hagihara et al., *Recent Advances in Pharmacotherapy: Anti-IL-6 Therapy*, Nippon Rinsho 60(12):2401-07 (2002) ("Hagihara")
Ex. 1020	*METHOTREXATE SODIUM TABLETS*, Physicians' Desk Reference (54th ed. 2000) ("2000 PDR – Methotrexate")
Ex. 1021	*METHOTREXATE Tablets*, Physicians' Desk Reference (45th ed. 1991) ("1991 PDR – Methotrexate")
Ex. 1022	American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, G*uidelines for the Management of Rheumatoid Arthritis*, Arthritis & Rheumatism 39(5):713-22 (1996) ("ACR 1996")

PETITIONERS EXHIBIT NO.	DESCRIPTION
Ex. 1023	*METHOTREXATE Tablets*, Physicians' Desk Reference (46th ed. 1992) ("1992 PDR - Methotrexate")
Ex. 1024	Joan M. Bathon et al., *A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis*, The New England Journal of Medicine 343(22):1586-93 (2000) ("Bathon")
Ex. 1025	Joachim R. Kalden, *Expanding Role of Biologic Agents in Rheumatoid Arthritis*, The Journal of Rheumatology 66:27-37 (2002) ("Kalden")
Ex. 1026	Curriculum Vitae of Thomas M. Zizic, M.D.
Ex. 1027	E. H. S. Choy et al., *Therapeutic Benefit of Blocking Interleukin-6 Activity with an Anti-Interleukin-6 Receptor Monoclonal Antibody in Rheumatoid Arthritis*, Arthritis & Rheumatism 46(12):3143-50 (2002) ("Choy")
Ex. 1028	G. Tridente, *Tocilizumab*, Adverse Events with Biomedicines 369-82 (2014) ("Tridente")
Ex. 1029	M. Cutolo et al., *Anti-Inflammatory Mechanisms of Methotrexate in Rheumatoid Arthritis*, Annals of Rheumatic Diseases 60:729-35 (2001) ("Cutolo")
Ex. 1030	Michael E. Weinblatt et al., *Long-Term Prospective Study of Methotrexate in the Treatment of Rheumatoid Arthritis*, Arthritis & Rheumatism 35(2):129-37 (1992) ("Weinblatt 1992")
Ex. 1031	*Reserved*
Ex. 1032	*Reserved*

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Ex. 1033	*Humira (adalimumab) Package Insert* (Dec. 2002) ("2002 Humira FDA Label")
Ex. 1034	Abbott Laboratories SEC Form 8-K, dated April 9, 2003 ("Abbott 8K")
Ex. 1035	*FDA Approves New Therapy for Rheumatoid Arthritis*, Dec. 31, 2002, www.fda.gov/bbs/topics/ANSWERS/2002/ANS01186.html with Affidavit of Duncan Hall (Internet Archive) ("FDA Talk Paper")
Ex. 1036	Larry W. Moreland, M.D., *Tumor Necrosis Factor Inhibitors: New Options for Treating Rheumatoid Arthritis*, IMAJ 3:686-90 (Sept. 2001) ("Moreland")
Ex. 1037	David Wendling et al., *Treatment of Severe Rheumatoid Arthritis by Anti-Interleukin 6 Monoclonal Antibody*, J Rheumatol 20:259-62 (1993) ("Wendling")
Ex. 1038	Highlights of Prescribing Information for ACTEMRA® (tocilizumab), Revised 05/2020 ("Actemra Label")
Ex. 1039	R.N. Maini, et al., *Double-Blind Randomized Controlled Clinical Trial of the Interleukin-6 Receptor Antagonist, Tocilizumab, in European Patients With Rheumatoid Arthritis Who Had an Incomplete Response to Methotrexate*, Arthritis & Rheumatism 54(9): 2817-29 (2006) ("Maini 2006")

PETITIONERS EXHIBIT NO.	DESCRIPTION
Ex. 1040	Maxime Dougados et al., *Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY)*, Annals of Rheumatic Diseases 72:43-50 (2012) ("Dougados")
Ex. 1041	Young-Won Chin, *Methods for treating IL-6-related diseases (US20150105554A1): a patent evaluation*, Expert Opinion on Therapeutic Patents, 25:9, 1065-1068 (205) ("Chin")
Ex. 1042	O'Dell et al., *Treatment of Rheumatoid Arthritis with Methotrexate and Hydroxychloroquine, Methotrexate and Sulfasalazine, or a Combination of the Three Medications*, Arthritis & Rheumatism, Vol. 46, No. 5 (May 2002) ("O'Dell")

I. INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH, pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, *et seq.*,[1] petition for *Inter Partes* Review ("IPR") of claims 1-15 of U.S. Patent No. 10,744,201 ("the '201 patent," Ex. 1001). Petitioners' request is supported by the Expert Declaration of Thomas M. Zizic, M.D. (Ex. 1002) ("Zizic Decl."), and the other exhibits submitted herewith.

The claims of the '201 patent are directed to a method of achieving, or increasing the likelihood of achieving, an ACR70 response[2] in a rheumatoid arthritis ("RA") patient by administering a combination of MRA[3] and methotrexate. More specifically, the claims require intravenously administering an

[1] Unless otherwise stated, all statutory and regulatory citations herein are to 35 U.S.C. or 37 C.F.R. All exhibits cited herein have been stamped with page numbers. Page number citations are to the stamped page numbers, not the original page numbers.

[2] As explained below, an ACR70 response is a measurement of efficacy for a rheumatoid arthritis treatment. Ex. 1001 at 17:11-26.

[3] MRA is also known as rhPM-1 and tocilizumab. Ex. 1002, ¶33.

8 mg/kg dose of MRA every four weeks and orally administering a dose of methotrexate between 10 and 25 mg every week to achieve the claimed response.

By April 28, 2003, the earliest claimed priority date of the '201 patent, both methotrexate (administered as a once weekly oral dose of 7.5 mg to 25 mg) and MRA (administered every four weeks at an intravenous dose of 8 mg/kg) were known to be safe and effective for treating RA, and the prior art disclosed combining these two drugs in precisely the manner required by the claims. The remaining limitations[4] are merely the natural result of following the claimed methods, and therefore cannot impart patentability to the claims. *King Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010). Accordingly, the claims are anticipated.

The claims are also obvious. The prior art provided ample motivation to carry out the claimed methods to treat RA with a reasonable expectation of success. Patent Owner's allegations during prosecution of unexpected results of the claimed regimen are unfounded. The evidence shows that the claimed methods are not superior to the prior art, much less unexpectedly so.

[4] For purposes of this IPR only, Petitioners agree that the preambles of the claims of the '201 patent are limiting.

The Board should institute review because there is at least a reasonable likelihood that Petitioners will prevail. § 314(a). Moreover, there are no persuasive grounds for denying institution under § 314(a) or § 325(d). This is Petitioners' first petition challenging any claim of the '201 patent, and the petition raises arguments that have not previously been presented to the Office.

II. GROUNDS FOR STANDING

Pursuant to § 42.104(a), Petitioners certify that the '201 patent is available for IPR and that Petitioners are not barred or estopped from requesting IPR on the grounds raised in this petition. Moreover, neither Petitioners nor their privies or the real parties-in-interest have filed or been served with any complaint alleging infringement or invalidity of the '201 patent, and therefore are not subject to any bar under § 315(a) or (b).

III. MANDATORY NOTICES

A. Real Parties-In-Interest (§ 42.8(b)(1))

The real parties-in-interest are Fresenius Kabi USA, LLC, Fresenius Kabi SwissBioSim GmbH, Fresenius Kabi AG, Fresenius Kabi Pharmaceuticals Holding, Inc., Fresenius Kabi Deutschland GmbH and Fresenius SE & Co. KGaA.

B. Related Matters (§ 42.8(b)(2))

The '201 patent is not currently the subject of any litigation or post-grant proceedings. Petitioners are concurrently filing a petition seeking *inter partes* review of U.S. Patent No. 7,521,052, to which the '201 patent claims priority.

C. Identification of Counsel (§ 42.8(b)(3))

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D. Service Information (§ 42.8(b)(4))

This Petition is being served by Federal Express Next Business Day Delivery to the correspondence address of record for the '201 patent: Foley & Lardner LLP, 3000 K Street N.W., Suite 600, Washington, DC 20007-5109.

E. Power of Attorney (§ 42.10(b))

The Petitioners' Power of Attorney forms will be filed concurrently herewith in accordance with 37 C.F.R. § 42.10(b).

IV. FEE PAYMENT (§ 42.15(a))

The required fee set forth in § 42.15(a) is paid pursuant to § 42.103, and the Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

V. TECHNICAL BACKGROUND

Rheumatoid arthritis is a chronic, systemic autoimmune inflammatory disorder that can affect many tissues and organs, but principally attacks the joints. The response of patients to such treatments was generally defined in terms of the American College of Rheumatology ("ACR") improvement criteria, *e.g.*, ACR70. Ex. 1009 (1999 FDA Guidance) at 6-7. Satisfaction of the ACR20 criteria requires a 20% improvement in tender and swollen joint counts, as well as a 20% improvement in three of the following five criteria: pain assessment by patient, global assessment of disease activity by patient, global assessment of disease activity by physician, assessment of physical function by patient, and levels of an acute phase reactant. Ex. 1009 (1999 FDA Guidance) at 3. ACR20 is analogous to ACR70, except the improvement threshold is 20% instead of 70%. *Id*. at 6 n.2.

By April 28, 2004, RA patients were commonly treated with methotrexate, considered the "anchor therapy" and "treatment of choice" because of its favorable

efficacy and toxicity profile, low cost and established track record. Ex. 1007 (Matteson) at 2; Ex. 1008 (Weinblatt 2003) at 2; Ex. 1010 at 10; Ex. 1002, ¶42. MTX was approved by the FDA for the treatment of RA in 1988, and was typically administered orally at a dose of between 7.5 mg and 25 mg per week, beginning with an initial dose of 7.5 mg/week and titrated upwards to as much as 20-30 mg per week. Ex. 1007 (Matteson) at 2-3; Ex. 1020 (2000 PDR - Methotrexate) at 7; Ex. 1010 (2002 Guidelines) at 4 ("[u]sual maintenance dose] of methotrexate is 7.5-20 mg/week"); Ex. 1002, ¶40.

Numerous clinical studies had confirmed the safety and efficacy of this regimen, capable of achieving ACR20 and ACR70 responses in RA patients. *See*, *e.g.*, Ex. 1024 (Bathon) at 5. However, many RA patients were not sufficiently responsive to methotrexate, and so it was typically combined with other RA drugs. *See, e.g.*, Ex. 1008 (Weinblatt 2003) at 2 ("many patients continue to have some degree of disease activity despite receiving therapeutic doses of MTX").

It was also known by April 2003 that the cytokine interleukin-6 (IL-6) plays a crucial role in the pathogenesis of RA, and that MRA (an anti-IL-6 receptor antibody) inhibits the binding of IL-6 to its receptors, thus reducing pro-inflammatory activity. Ex. 1017 (Nishimoto Abstract B) at 2. In view of this mechanism of action, several clinical trials were carried out to evaluate dosage regimens of MRA, and on the basis of these studies, the prior art recommended a

dose of 8 mg/kg administered intravenously every 4 weeks for the treatment of RA. Ex. 1006 (Nishimoto) at 3-4. This regimen "was well tolerated and significantly reduced the disease activity in patients with RA," providing an ACR20 response of 78.2% (compared to 11.3% for placebo) and an ACR70 response of 16.4% (compared to 0.0% for placebo) within twelve weeks. Ex. 1017 (Nishimoto Abstract B) at 2.

The prior art also taught that RA drugs should be administered in combination—in particular, in combination with methotrexate—for maximum effect. For example, the prior art taught that methotrexate was the "anchor therapy" for RA, and "[t]o improve disease control, therapies that contain combinations of DMARDs [disease-modifying antirheumatic drug] are often used." Ex. 1007 (Matteson) at 4. The FDA similarly acknowledged that "since methotrexate therapy is used to treat many RA patients, it is inevitable that new agents will be used in combination with methotrexate in clinical practice unless a contraindication exists." Ex. 1099 (1999 FDA Guidance) at 21. Such combinations were used, in large part, because patients often had an inadequate response to methotrexate alone. Ex. 1008 (Weinblatt 2003) at 2.

This strategy of combining new RA drugs with methotrexate was followed by numerous researchers, and indeed had been demonstrated to be safe and effective for treating RA. By April 28, 2003, three biologic drugs—adalimumab,

infliximab, and etanercept—had been approved for the treatment of RA, and all three were approved by FDA in combination with methotrexate. Ex. 1012 (2000 PDR – Enbrel) at 4; Ex. 1011 (Rebholz) at 1; Ex. 1013 (2001 PDR - Remicade) at 4; Ex. 1035 (Moreland) at 3; Ex. 1033 (2002 Humira FDA Label) at 7, 14, 16; Ex. 1034 (Abbott 8K) at 5; Ex. 1035 (FDA Talk Paper) at 5.

All three of these drugs are cytokine inhibitors, specifically, anti-TNF agents. The prior art taught that other anti-cytokine agents, including anti-IL-6 receptor antibodies, should similarly be administered in combination with methotrexate. Ex. 1014 (Amano) at 8 ("anti-cytokine therapy such as anti-TNF therapy and anti-IL-6 receptor antibody is expected to be used in combination with MTX"). This was no mere suggestion; skilled artisans had, in fact, applied these teachings to MRA. Early studies showed that MRA was safe and effective in combination with MTX for treating RA patients. Ex. 1005 (Yoshizaki) at 11 ("A 67 year-old woman with severe RA given … MTX … received 50 mg [MRA] twice a week or once a week combined with the conventional treatment. The clinical and laboratory abnormalities improved after the [MRA] therapy."). Following several additional studies that established 8 mg/kg every four weeks as its optimal intravenous dosing regimen, the prior art disclosed ongoing clinical trials wherein MRA and methotrexate were administered in combination to treat RA. Ex. 1006 (Nishimoto) at 5; Ex. 1019 (Hagihara) at 7.

VI. THE '201 PATENT

The '201 patent, entitled "Method for Treating Rheumatoid Arthritis with a Human IL-6 Receptor Antibody and Methotrexate," issued on August 18, 2020.

A. Challenged Claims

Petitioners challenge all of the claims of the '201 patent. The '201 patent includes 15 claims, of which claims 1, 6, and 11 are independent. The independent claims are reproduced below:

> 1. A method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone, comprising administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously, and (ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg.
>
> 6. A method for achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient, comprising administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously, and (ii) methotrexate (MTX), wherein the MTX is orally administered once per week at a dose in a range of 10 to 25 mg, wherein the patient would not have achieved an ACR70 response with administration of MRA alone or methotrexate (MTX) alone.
>
> 11. A method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient, comprising administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R

> monoclonal antibody MRA is administered intravenously, and (ii) methotrexate (MTX), wherein the MTX is orally administered once per week at a dose in a range of 10 to 25 mg, and wherein administration of (i) and (ii) in a tested population of rheumatoid arthritis patients resulted in an American College of Rheumatology (ACR) 70 response in a larger percentage of patients than the sum of percentages for administration of (i) alone and (ii) alone.

Thus, all of the independent claims require administering the ***exact same*** treatment regimen to a RA patient: (i) 8 mg/kg of MRA intravenously every four weeks; and (ii) 10 to 25 mg methotrexate orally every week. The independent claims differ only in the stated result, as set forth in the preamble and/or "wherein" clauses.

Claims 2, 7, and 12 depend from claims 1, 6, and 11, respectively, and require that the patient had a prior inadequate response or disease flare on methotrexate alone.

Claims 3, 8, and 13 depend from claims 1, 6, and 11, respectively, and require that the patient has no anti-MRA antibodies following administration of the combined regimen.

Claims 4, 9, and 14 depend from claims 1, 6, and 11, respectively, and require that the patient does not exhibit hypersensitivity following administration of the combined regimen.

Claims 5, 10, and 15 depend from claims 1, 6, and 11, respectively, and require that the MRA is administered four times at four week intervals.

B. Prosecution History

The '201 patent issued from U.S. Patent Application No. 15/919,429 ("the '429 application"), filed on March 13, 2018. The '429 application claims priority to PCT Application No. 10/554,407, filed on April 28, 2004, and an application filed in Great Britain, No. O3096195, filed on April 28, 2003.

During prosecution of the '429 application, following a preliminary amendment and response to a restriction requirement, only one independent claim remained pending. That independent claim, claim 16, recited as follows:

> 16. A method for treating rheumatoid arthritis in a patient, comprising administering to a patient a combination of (i) 4 mg/kg or 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks and (ii) methotrexate (MTX).

Ex. 1004 at 131 (Jan. 31, 2020 Amendment). The Examiner rejected the then-pending claims as obvious over, *inter alia*, "Nishimoto (2002")[5] and Maini 1998.

[5] It is unclear upon which Nishimoto reference the Examiner based the rejection. Three different Nishimoto references published in 2002 had been disclosed on an IDS (Ex. 1004 at 65), and the Examiner did not specify which of these was "Nishimoto (2002)." Notably, however, according to the IDS, only a partial English translation was provided for Nishimoto (Ex. 1006) relied upon here. *Id.*

Id. at 153-156 (April 7, 2020 Office Action). According to the Examiner, "Nishimoto (2002)" disclosed a method of treating RA by intravenously administering either 4 mg/kg or 8 mg/kg MRA every four weeks, but was "silent with respect to administering MTX and MRA and the dosage of MTX administered." *Id*. at 153 (April 7, 2020 Office Action). The Examiner asserted that Maini 1998 disclosed administering 7.5 mg methotrexate orally once per week in

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(listed on the IDS as reference A285). Furthermore, the Examiner's description of "Nishimoto (2002)" is inconsistent with Nishimoto (Ex. 1006). For example, the Examiner indicates that "Nishimoto (2002)" disclosed administering MRA at a dose of 4 mg/kg every four weeks, while Nishimoto (Ex. 1006) discloses administering 4 mg/kg every two weeks. *Compare* Ex. 1004 ('201 Patent File History) at 153 (April 7, 2020 Office Action) *with* Ex. 1006 (Nishimoto) at 4-5. Also, the Examiner stated that "Nishimoto (2002)" "is silent with respect to administering MTX with MRA," while Nishimoto (Ex. 1006) expressly discloses "a phase II study of coadministration with methotrexate." *Compare* Ex. 1004 ('201 Patent File History) at 153 (April 7, 2020 Office Action) *with* Ex. 1006 (Nishimoto) at 4-5. Accordingly, it appears the Examiner did not rely upon Nishimoto as a ground for rejection (or, at a minimum, was not aware of its most pertinent disclosures).

combination with an anti-TNF antibody, and that a person of ordinary skill in the art would have modified the method taught by "Nishimoto et al. and administer with MTX antibody, once per week as taught by Maini, because Maini teaches that synergistic action could be obtained by combining the antibody and MTX." *Id*. at 153-154.

The Examiner also rejected the then-pending claims as obvious over Okuda and Maini 1998. Ex. 1004 at 156-160 (April 7, 2020 Office Action). According to the Examiner, Okuda disclosed administering MRA intravenously at a dose of 2 mg/kg, 4 mg/kg, or 8 mg/kg every two weeks in combination with methotrexate, but did not disclose the dosage or duration of methotrexate treatment. *Id*. at 156. The Examiner asserted that a POSA would have combined the method disclosed by Okuda with the 7.5 mg/week methotrexate dosing taught by Maini 1998, thereby arriving at the claimed method. *Id*.

The Applicants responded by cancelling the pending claims and replacing them with those that would ultimately issue as the '201 patent. *Id*. at 764-765. The new claims limited the dosage regimen to 8 mg/kg MRA administered intravenously every four weeks, and 10 to 25 mg methotrexate administered orally every week. *Id*. In response to the obviousness rejections, the Applicants asserted that "[t]he claimed method is based on the unexpected discovery that administering to a rheumatoid arthritis patient [the claimed combination] improved the likelihood

of achieving an American College of Rheumatology (ACR) 70 response compared to MTX treatment alone." *Id*. at 769.

To support this allegation, the Applicants relied upon the data presented in Table 1 of the '201 patent for the Phase II trial described in Example 1. *Id*. at 770. The clinical trial assessed various doses of MRA alone and in combination with 10 to 25 mg methotrexate as compared to methotrexate alone. Ex. 1001 at 16:37-17:10. The patients in the trial each had an inadequate response to, or disease flare while taking, a weekly dose of at least 10 mg methotrexate. *Id*. at 16:54-60. The patients were assigned to one of seven groups: (1) 10 to 25 mg methotrexate orally every week; (2) 2 mg/kg MRA intravenously every four weeks; (3) 4 mg/kg MRA intravenously every four weeks; (4) 8 mg/kg MRA intravenously every four weeks; (5) 10 to 25 mg methotrexate orally every week plus 2 mg/kg MRA intravenously every four weeks; (6) 10 to 25 mg methotrexate orally every week plus 4 mg/kg MRA intravenously every four weeks; or (7) 10 to 25 mg methotrexate orally every week plus 8 mg/kg MRA intravenously every four weeks. *Id*. at 16:63-17:2. After 12 weeks of administering the regimens, ACR improvement criteria were assessed, as shown in the following table:

TABLE 1

	2 mg/kg MRA	4 mg/kg MRA	8 mg/kg MRA	MTX
ACR 20	30.8%	61.1%	62.7%	40.8%
ACR 50	5.8%	27.8%	41.2%	28.6%
ACR 70	1.9%	5.6%	15.7%	16.3%

	2 mg/kg MRA + MTX	4 mg/kg MRA + MTX	8 mg/kg MRA + MTX
ACR 20	64.0%	63.3%	73.5%
ACR 50	32.0%	36.7%	53.1%
ACR 70	14.0%	12.2%	36.7%

Id. at 17:28-39. The data presented in Table 1 indicates that 16.3% of the patients receiving methotrexate alone exhibited an ACR70 response, while 36.7% of patients receiving both 8 mg/kg MRA and methotrexate exhibited an ACR70 response. The Applicants alleged that this increased response for the combination of 8 mg/kg MRA and methotrexate was unexpected in view of the results for the 2 mg/kg and 4 mg/kg groups, which did not exhibit a greater percentage of ACR70 responders when combined with methotrexate. Ex. 1004 at 769-770.

The Applicants further alleged that the response to the combined regimen was "synergistic" because the 36.7% of patients having an ACR70 response was more than the sum of the percentage of patients having an ACR70 response to the individual 8 mg/kg MRA (15.7%) and methotrexate (16.3%) regimens. *Id*. at 770.

The Examiner allowed the claims, concluding that none of the prior art references taught or suggested the purported unexpected result that administering the claimed combination of 8 mg/kg MRA intravenously every four weeks and 10

to 25 mg methotrexate orally every week would increase the likelihood of an ACR70 response compared to methotrexate alone. Ex. 1004 at 2093-2094. While the Examiner specifically referenced the comparison of ACR70 responses for the 8 mg/kg MRA plus methotrexate group (36.7%) and the methotrexate alone group (16.3%), the Examiner did not respond to Applicant's allegation of a "synergistic" effect. *Id*.

VII. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art ("POSA") to whom the '201 patent is directed would have been an individual with an M.D. specializing in the treatment of autoimmune disorders and having several years of experience treating patients with such disorders, including rheumatoid arthritis, or having several years of experience researching treatments for autoimmune disorders, including rheumatoid arthritis. *See* Ex. 1002, ¶30. A POSA would have easily understood the prior art references referred to herein and would have had the capacity to draw inferences from them.

VIII. CLAIM CONSTRUCTION

In an IPR, the terms of challenged claims are construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," just as they are in district court. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303,

1313-14 (Fed. Cir. 2005) (*en banc*). For the purpose of this proceeding, Petitioners state that all terms of the '201 patent claims should be given their ordinary and customary meaning to a POSA as of the invention date of the '201 patent, which Petitioners assume for purposes of this IPR only to be April 28, 2003.[6]

IX. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claims 1-15 of the '201 patent under §§ 102 and 103 for the reasons explained in this petition, which are summarized in the following table:

Ground No	Claims and Basis
1	Claims 1-15 are anticipated by Nishimoto
2	Claims 1-15 are obvious over Nishimoto and Weinblatt 2003

A. Ground 1: Claims 1-15 Are Anticipated By Nishimoto

Nishimoto is an article titled "Anti-IL-6 Receptor Antibodies, Usefulness and Issues in Rheumatoid Arthritis," published in Therapeutics (Chiryo-Gaku), Vo.

[6] Petitioners adopt this position for purposes of this IPR only and reserve the right to change or modify their position in future litigation, for example in response to expert opinions, statements by the patent owner, or court rulings. Petitioners do not waive any argument concerning indefiniteness or invalidity under 35 U.S.C. § 112.

36(12), pgs. 1264-67 in December 2002. Ex. 1006. Nishimoto is a printed publication, and prior art to the '052 patent under pre-AIA § 102(b). Ex. 1006; Ex. 1002, ¶73.

While Nishimoto was disclosed to the Examiner during prosecution of the '201 patent, it was not the subject of any rejection. Furthermore, Nishimoto contains critical disclosures not present in the references relied upon by the Examiner. For example, Nishimoto discloses (1) the combined administration of MRA and MTX to treat RA;[7] and (2) the claimed intravenous MRA dosing regimen of 8 mg/kg every four weeks.[8] Ex. 1006 (Nishimoto) at 4-5. The Examiner overlooked these teachings and failed to make a rejection over Nishimoto, and thus, the arguments presented herein have not previously been considered by the patent office. *Sony Interactive Entertainment LLC v. Bot M8, LLC*, No. IPR2020-00726, 2020 WL

[7] By contrast, the Examiner pointedly noted that the "Nishimoto 2002" reference relied upon during prosecution was "silent with respect to administering MTX with MRA." Ex. 1004 at 153.

[8] According to the Examiner, the "Okuda" reference relied upon during prosecution disclosed administering MTX in combination with MRA, but disclosed administering MRA every two weeks, not every four weeks as required by the claims. Ex. 1004 at 156.

5924211, at *5 (P.T.A.B. Oct. 6, 2020) (instituting IPR where "the Examiner overlooked these specific teachings of [a prior art reference]").

1. Independent Claims 1, 6, and 11 are Anticipated by Nishimoto

Independent claims 1, 6, and 11 of the '201 patent each require administering a combination of 8 mg/kg intravenous MRA every four weeks and 10 to 25 mg oral MTX every week to an RA patient. These are the only active steps required by these claims.

Nishimoto discloses that, on the basis of earlier clinical trial results, the recommended dosage regimen of MRA for treating RA is 8 mg/kg administered intravenously every four weeks, and discloses an ongoing clinical study in which MRA is co-administered with methotrexate for the treatment of RA. Ex. 1006 (Nishimoto) at 5. *Id*. Therefore, Nishomoto discloses a clinical study of MRA in combination with MTX, involving administering MRA according to the recommended regimen, *i.e.*, 8 mg/kg administered intravenously every four weeks. Ex. 1002, ¶124.

Nishimoto does not expressly disclose the dosing parameters for methotrexate in the clinical study of MRA in combination with methotrexate. However, a POSA would have known that methotrexate was typically administered at an oral dose of between 7.5 mg and 25 mg once weekly to treat RA, since this was the range of doses known to be useful for treating RA patients

with methotrexate. *See, e.g.*, Ex. 1002, ¶¶126-128; Ex. 1007 (Matteson 2000) at 2-3 (reporting that "the DMARDs currently in use are listed in Table 1," which identifies methotrexate at a "single dose of 7.5-25 mg orally"); Ex. 1020 (2002 FDA Label) at 7 (recommending a starting dose schedule of methotrexate of "[s]ingle oral doses of 7.5 mg once weekly" and "adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg"); Ex. 1010 (2002 Guidelines) at 4. A POSA would have further known that doses within this same range were used for clinical trials involving methotrexate in combination with other RA drugs. Ex. 1002, ¶127; Ex. 1008 (Weinblatt 2003) at 4 (orally administering an average of 16.8 mg – range 10 to 25 mg – once weekly in combination with adalimumab); Ex. 1024 (Bathon) at 1-2 (orally administering an average of 19 mg – range of 7.5 to 20 mg – methotrexate once weekly in combination with etanercept). A POSA would also have known that the dosage would be titrated up from 7.5 mg to at least 10 mg if a patient was not responsive to the low dose. Ex. 1002, ¶128; Ex. 1020 (2002 PDR – Methotrexate) at 7. A POSA would therefore have understood that the reference in Nishimoto to "a phase II study of coadministration with methotrexate" necessarily means that some patients would be treated with a dosage from 10 mg to 25 mg of methotrexate. Accordingly, a POSA would have understood that Nishimoto discloses administering methotrexate orally at a dose between 7.5 and 25 mg, and that some

patients would receive between 10 and 25 mg. Ex. 1002, ¶¶126-128; *see In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) ("The Board was correct in characterizing the dispositive question regarding anticipation as whether one skilled in the art would reasonably understand or infer from the Becker document's teaching that Becker's primary bag was plasticized with DEHP."); *see also id*. ("[E]xtrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference.").

Even if a POSA would have understood the disclosure in Nishimoto to only disclose the broader range of 7.5 to 25 mg methotrexate dosage, rather than the claimed range of 10 to 25 mg, that is of no moment. A patentee must "establish[] the criticality of a claimed range to the claimed invention in order to avoid anticipation by a prior art reference disclosing a broader, overlapping range." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 870 (Fed. Cir. 2015). In this case, there is no indication that the claimed range is critical to the operability of the method, nor any suggestion that the method is more effective when methotrexate is dosed at an amount between 10 and 25 mg than between 7.5 and 10 mg, all of which are within the prior art range. In other words, there is no considerable difference between the prior art range and the claimed range; accordingly, Nishimoto's disclosure of a range of 7.5 to 25 mg methotrexate teaches and enables the claimed 10 to 25 mg methotrexate dose. *ClearValue, Inc.*

v. Pearl River Polymers, Inc., 668 F.3d 1340, 1344-45 (Fed. Cir. 2012) (broader prior art range anticipates claimed range where "there is no allegation of criticality or any evidence demonstrating any difference across the range"). Thus, Nishimoto discloses administering a combination of 8 mg/kg MRA intravenously every four weeks and between 10 and 25 mg MTX orally every week to an RA patient.

In addition to these active method steps, each of the claims require a particular result. For claim 1, the method increases the likelihood of achieving an ACR70 response as compared to treatment with MTX alone. For claim 6, the method achieves an ACR70 response in a patient that would not have achieved an ACR70 response with administration of either MRA or MTX alone. For claim 11, the method increases the likelihood of achieving an ACR70 response such that a greater percentage of patients receiving the combined regimen achieves an ACR70 response than the sum of percentages for administration of MRA and MTX alone. These results are inherently disclosed by Nishimoto.

"To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *King Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010). In *King Pharm.*, the Federal Circuit concluded that a claimed bioavailability result was inherent in practicing the prior art because the patent at issue disclosed nothing more than the exact steps disclosed in the prior art:

> According to the [patent at issue], the natural result of taking metaxalone with food is an increase in the bioavailability of the drug. The prior art discloses taking metaxalone with food, but not the natural result of this process.
>
> As taught by the [patent at issue], the only steps required to increase metaxalone's bioavailability are (1) ingesting metaxalone (2) with food. These steps are undeniably disclosed by the prior art. An increase in metaxalone's bioavailability is, therefore, an inherent aspect of the prior art. In other words, the increase in metaxalone's bioavailability is the natural result flowing from the prior art's explicitly explicated limitations.

King Pharm., 616 F.3d at 1276; (quotations omitted); *see also Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001) ("A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations."); *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("[T]he claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by [the prior art]. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.").

The '201 patent does not explain how to achieve the claimed results beyond the simple act of administering the claimed regimen of intravenous MRA at a dose

of 8 mg/kg every four weeks and oral MTX at a weekly dose of 10 to 25 mg to an RA patient, the very same regimen disclosed in Nishimoto. Ex. 1001 at Example 1. Indeed, during prosecution, the Applicants stated that the "claimed methods recite limitations supported by Example 1 of the specification" (Ex. 1004 at 768), but Example 1 does not provide any information on specific steps to achieve the claimed result other than administer the claimed treatment regimen. Ex. 1002, ¶123. Therefore, like the bioavailability limitation deemed inherent by the Federal Circuit in *King Pharm.*, the functional result limitations of claims 1, 6, and 11 merely reflect the "natural result" of administering the claimed regimen, and are inherently disclosed by Nishimoto's disclosure of the same regimen. Accordingly, Nishimoto discloses and enables each and every limitation of claims 1, 6, and 11, and therefore anticipates those claims.

a. Claim 1

(1) "[a] method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone"

The '201 patent discloses that a greater percentage of patients receiving 8 mg/kg MRA every four weeks in combination with methotrexate achieved an ACR70 response as compared to those receiving methotrexate alone. Ex. 1001 at 17:28-39. Nothing in the patent suggests that achieving this increased likelihood

of response requires anything beyond administering the same regimen disclosed by the prior art; the only steps the '201 patent teaches are required to obtain the claimed result are administering MRA and methotrexate in the same amounts and frequencies disclosed in Nishimoto. Ex. 1002, ¶¶122-123. Accordingly, increasing the likelihood of achieving an ACR70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone is inherently disclosed by Nishimoto. *See*, *e.g.*, *King Pharm.*, 616 F.3d at 1276.

(2) "administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously"

Nishimoto discloses administering to an RA patient a combination of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA and MTX, wherein the MRA is administered intravenously at a dose of 8 mg/kg every four weeks. *See supra* pgs. 19-22; Ex. 1002, ¶¶121-125.

(3) "(ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg"

Nishimoto discloses administering to an RA patient a combination of MRA and MTX, wherein the MTX is orally administered once per week at a dose in a range of 10 to 25 mg. *See supra* pgs. 19-22; Ex. 1002, ¶¶126-128.

b. Claim 6

(1) "[a] method for achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient … wherein the patient would not have achieved an ACR70 response with administration of MRA alone or methotrexate (MTX) alone"

The '201 patent discloses that a greater percentage of patients receiving 8 mg/kg MRA every four weeks in combination with methotrexate achieved an ACR70 response as compared to those receiving either MRA or methotrexate alone. Ex. 1001 at 17:28-39. As with claim 1, the only steps the '201 patent teaches are required to obtain the result recited in claim 6 are administering MRA and methotrexate in the same amounts and frequencies disclosed in Nishimoto. Ex. 1002, ¶¶129-130. Accordingly, achieving an ACR70 response in a rheumatoid arthritis patient wherein the patient would not have achieved such a response with MRA or MTX alone is inherently disclosed by Nishimoto. *See King Pharm.*, 616 F.3d at 1275-76.

(2) "administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously"

Nishimoto discloses administering to an RA patient a combination of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA and MTX,

wherein the MRA is administered intravenously at a dose of 8 mg/kg every four weeks. *See supra* pgs. 19-22; Ex. 1002, ¶¶121-125.

(3) "(ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg"

Nishimoto discloses administering to an RA patient a combination of MRA and MTX, wherein the MTX is orally administered once per week at a dose in a range of 10 to 25 mg. *See supra* pgs. 19-22; Ex. 1002, ¶¶126-128.

c. Claim 11

(1) "[a] method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient … wherein administration of (i) and (ii) in a tested population of rheumatoid arthritis patients resulted in an American College of Rheumatology (ACR) 70 response in a larger percentage of patients than the sum of percentages for administration of (i) alone and (ii) alone"

The '201 patent discloses that a greater percentage of patients receiving 8 mg/kg MRA every four weeks in combination with methotrexate achieved an ACR70 response as compared to the sum of those receiving either MRA or methotrexate alone. Ex. 1001 at 17:28-39. Nothing in the patent suggests that achieving this result requires anything beyond administering the same regimen disclosed by the prior art. As with claims 1 and 6, the only steps the '201 patent teaches are required to obtain the result recited in claim 11 are administering MRA and methotrexate in the same amounts and frequencies disclosed in Nishimoto.

Ex. 1002, ¶¶133-134. Accordingly, increasing the likelihood of achieving an ACR70 response by administering the claimed combination of MRA and MTX such that a larger percentage of patients achieve an ACR70 response in a tested population of RA patients than the sum of percentages for MRA and MTX alone is inherently disclosed by Nishimoto.[9] *See*, *e.g.*, *King Pharm.*, 616 F.3d at 1275-76.

(2) "administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously"

Nishimoto discloses administering to an RA patient a combination of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA and MTX,

[9] As discussed in section IX.C, *infra*, the data presented in the '201 patent does not, in fact, establish that administering MRA intravenously at a dose of 8 mg/kg every four weeks and MTX orally at a dose of 10 to 25 mg every week to RA patients results in a larger percentage of patients having an ACR 70 response than the sum of percentages for MRA and MTX alone. However, to the extent the patented method allows for this result, so too does the prior art. *See King Pharm.*, 616 F.3d at 1276 ("To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does.").

wherein the MRA is administered intravenously at a dose of 8 mg/kg every four weeks. *See supra* pgs. 19-22; Ex. 1002, ¶¶121-125.

(3) "(ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg"

Nishimoto discloses administering to an RA patient a combination of MRA and MTX, wherein the MTX is orally administered once per week at a dose in a range of 10 to 25 mg. *See supra* pgs. 19-22; Ex. 1002, ¶¶126-128.

2. Dependent Claims 2-5, 7-10, and 12-15 are Anticipated by Nishimoto

a. Claims 2, 7, and 12

Claims 2, 7, and 12 depend from claims 1, 6, and 11, respectively, and further require that "the patient, prior to treatment had an inadequate response or disease flare on methotrexate (MTX) treatment alone." Nishimoto discloses that MRA is administered to patients who are resistant to MTX—the clinical study from which the recommended MRA dosing regimen was derived was conducted in patients who were resistant to DMARD therapy. Ex. 1006 (Nishimoto) at 5 (citing to Nishimoto Abstract B in footnote 18); Ex. 1017 (Nishimoto Abstract B) at 2. A POSA would have understood that the MRA/MTX phase II clinical study disclosed by Nishimoto likewise involved patients who had an inadequate response or disease flare on methotrexate (MTX) treatment alone. Ex. 1002, ¶¶137-138. Claims 2, 7, and 12 are therefore anticipated by Nishimoto.

b. Claims 3, 8, and 13

Claims 3, 8, and 13 depend from claims 1, 6, and 11, respectively, and further require that "the patient has no anti-MRA antibodies following administering the combination of anti-IL-6R antibody MRA and MTX." As with the claimed ACR70 response, the lack of appearance of anti-MRA antibodies is the natural result of administering the claimed regimen. Ex. 1001 at 19:10-17. Indeed, Nishimoto discloses that the appearance of antibodies to MRA is "very rare." Ex. 1006 (Nishimoto) at 5. Accordingly, claims 3, 8, and 13 are anticipated by Nishimoto. Ex. 1002, ¶¶139-140.

c. Claims 4, 9, and 14

Claims 4, 9, and 14 depend from claims 1, 6, and 11, respectively, and further require that "the patient does not experience hypersensitivity following administering the combination of anti-IL-6R antibody MRA and MTX." The lack of hypersensitivity is the natural result of administering the claimed regimen, and claims 4, 9, and 14 are therefore anticipated by Nishimoto. Ex. 1001 at 18:42-57 (reporting no hypersensitivity reactions in patients given the combination of MRA and MTX); Ex. 1002, ¶¶141-142.

d. Claims 5, 10, and 15

Claims 5, 10, and 15 depend from claims 1, 6, and 11, respectively, and further require that "the anti-IL-6R antibody MRA is administered four times at four week intervals." As discussed above, a POSA would have understood that the

combined MRA/MTX clinical study disclosed by Nishimoto would have involved the 8 mg/kg recommended regimen derived from Nishimoto Abstract B, which is administered at four week intervals. *See supra* pgs. 19, 29. Although Nishimoto does not expressly disclose that the MRA is administered four times, a POSA would have known that the clinical study from which this regimen was derived administered MRA over a twelve week period, for a total of four administrations. Ex. 1017 (Nishimoto Abstract B) at 2. A POSA would have therefore understood that the ongoing clinical study of MRA in combination with MTX would likewise include four administrations of MRA. Ex. 1002, ¶¶143-144. Claims 5, 10, and 15 are therefore anticipated by Nishimoto.

B. Ground 2: Claims 1-15 Are Obvious Over Nishimoto in View of Weinblatt 2003

Claims 1-15 would also have been obvious over Nishimoto in view of Weinblatt 2003 because a POSA would have been motivated to administer the claimed regimen to a RA patient, and would have had a reasonable expectation of success. Ex. 1002, ¶¶145-155. Furthermore, although the claimed results (e.g., increasing the likelihood of an ACR70 response and achieving an ACR70 response) are the "natural result" of following the claimed method steps, and hence inherent in the method itself, a POSA would also have been motivated to, and reasonably expected to achieve these results. *Id.* While Nishimoto was disclosed during prosecution, it was never the subject of a rejection.

As discussed above, by the earliest claimed priority date of the '201 patent, RA patients were typically treated with combinations of DMARDs, with methotrexate—at an initial dose of between 7.5 mg and titrated up to as much as 20 to 30 mg per week—considered the "anchor therapy" of such combinations. Ex. 1007 (Matteson) at 1-3; Ex. 1020 (2000 Methotrexate Label) at 7; Ex. 1010 (2002 Guidelines) at 4 ("[u]sual maintenance dose] of methotrexate is 7.5-20 mg/week"). As disclosed in Weinblatt 2003, "[o]ver the last decade, methotrexate (MTX) has become the treatment of choice for rheumatoid arthritis (RA)." Ex. 1008 (Weinblatt 2003) at 2;

Many patients, however, did not adequately respond to methotrexate alone, and so physicians often administered methotrexate in combination with other DMARDs to improve disease control. Ex. 1002, ¶147; Ex. 1007 (Matteson) at 2-4; Ex. 1008 (Weinblatt 2003) at 1 ("[M]any patients continue to have some degree of disease activity despite receiving therapeutic doses of MTX."). Generally speaking, while a newly-diagnosed patient may begin treatment for RA with methotrexate alone, if monotherapy was inadequate to fully control the RA symptoms, a second agent would be added to the regimen. Ex. 1007 (Matteson) at 4; Ex. 1002, ¶147. Indeed, in 2002 the American College of Rheumatology issued guidelines of the treatment of RA, stating that

> MTX as monotherapy or as component of combination therapy should be instituted in patients whose treatment has not yet included MTX. For patients in whom MTX is contraindicated or has failed to achieve satisfactory disease control either because of lack of efficacy (in doses up to 25 mg/week) or intolerance, treatment with biologic agents or with other DMARDs either alone or in combination, is indicated.

Ex. 1010 (2002 Guidelines) at 9.

Cytokines were known to be involved in the pathology of RA, and hence several new anti-cytokine drugs had recently been developed and approved for the treatment of RA. Ex. 1002, ¶148; Ex. 1014 (Amano) at 3. As with other agents, these anti-cytokines were often used in combination with methotrexate, particularly in patients who did not adequately respond to methotrexate alone. Ex. 1014 at 8 ("In the patient cases in which activity could not be sufficiently controlled even with MTX, anti-cytokine therapy such as anti-TNF therapy and anti-IL-6 receptor antibody is expected to be used in combination with MTX."). By 2002, three anti-cytokine drugs, all of which are anti-TNF therapies—adalimumab, infliximab, and etanercept—had been approved by FDA for the treatment of rheumatoid arthritis in patients who had an inadequate response to MTX, and all three were approved for use in combination with methotrexate. Ex. 1012 (2000 PDR – Enbrel) at 4; Ex. 1011 (Rebholz) at 1; Ex. 1013 (2001 PDR - Remicade) at 4; Ex. 1036 (Moreland) at 3; Ex. 1033 (2002 Humira FDA Label) at 7, 14, 16; Ex. 1035 (Abbott 8K) at 5; Ex. 1035 (FDA Talk Paper) at 5.

MRA, another anti-cytokine drug, had been established as a safe and effective treatment for RA, and Nishimoto disclosed that its optimal dose was 8 mg/kg intravenously every four weeks, and that a clinical trial of MRA in combination with MTX was ongoing. Ex. 1006 (Nishimoto) at 5. A POSA would have been motivated to combine Nishimoto's disclosure of coadministration of MRA and methotrexate, with standard dosing practices for combining methotrexate with other RA drugs.[10] Ex. 1002, ¶¶151-154. These practices are exemplified in Weinblatt 2003, which discloses that methotrexate is the "treatment

[10] Nishimoto states that, unlike infliximab, MRA "does not ***require*** such coadministration of methotrexate," Ex. 1006 at 5 (emphasis added). According to Nishimoto, infliximab was required to be used with methotrexate in order to limit neutralizing antibodies, whereas neutralizing antibodies were "very rare" from treatment with MRA. Ex. 1006 (Nishimoto) at 5. However, a POSA would have known that the primary benefit from combined treatment of a biologic DMARD with methotrexate was because of the improved efficacy, not to limit neutralizing antibodies. Ex. 1002, ¶ 153; Ex. 1008 (Weinblatt 2003) at 2 ("To enhance the clinical response, MTX is frequently combined with one or more other traditional . . . DMARDs.").

of choice" for RA patients, but notes that "many patients continue to have some degree of activity despite receiving therapeutic doses of MTX," and therefore "MTX is frequently combined with one or more other traditional disease-modifying antirheumatic drugs (DMARDs)." Ex. 1008 (Weinblatt 2003) at 2; Ex. 1002, ¶151.

Weinblatt 2003 illustrates the usefulness of this approach through a clinical trial involving administering adalimumab in combination with RA patients' existing methotrexate regimens. Ex. 1008 (Weinblatt 2003) at 2. The RA patients had continued to exhibit RA symptoms notwithstanding having received methotrexate therapy, titrated to a stable weekly dose of between 10 and 25 mg, most of whom received the drug orally. *Id*. at 2-4. When adding adalimumab, the patients' existing methotrexate regimens (*i.e.*, 10 to 25 mg oral methotrexate once per week) were maintained. *Id*. at 2 ("Dosing tapering or changes in the route of administration of the concomitant medications were not permitted during the study."). Weinblatt 2003 disclosed that this combined therapy "substantially and rapidly improves standard measures of disease activity, including signs and symptoms, the acute-phase response, and quality of life scores in RA patients not adequately responding to therapy with MTX alone." *Id*. at 9.

Even if Nishimoto does not expressly disclose the amounts or frequencies of administration of the combined regimen, selection of these parameters would have

been obvious. With regards to the dosage of the anti-IL-6R antibody, a POSA would have been motivated to use the 8 mg/kg every 4 week regimen that had "excellent treatment efficacy" and was "recommended," as disclosed in Nishimoto. Ex. 1006 (Nishimoto) at 5; Ex. 1002, ¶¶150-152. Moreover, DMARDs are generally administered in the same dosage amount and frequency when given in combination with methotrexate as they are when given alone, and a POSA would have expected this to be the case for MRA. Ex. 1002, ¶ 150.

With regard to methotrexate, a POSA would have maintained the patient's existing regimen as disclosed by Weinblatt 2003, which was typical when supplementing methotrexate treatment with a new drug. Ex. 1002, ¶ 154; Ex. 1008 (Weinblatt 2003) at 2; Ex. 1007 (Matteson) at 4-5; *see also*, *e.g.*, Ex. 1025 (Kalden) at 3; Ex. 1014 (Amano) at 7. Weinblatt 2003 discloses that typical inadequate methotrexate responders receive oral doses of between 10 and 25 mg once per week, and so a POSA would have been motivated to administer methotrexate in accordance with that regimen. Ex. 1008 (Weinblatt 2003) at 2; Ex. 1002, ¶154. Indeed, that regimen falls within the standard methotrexate dosing regimen for treating RA. Ex. 1007 (Matteson) at 2-3 (reporting that "the DMARDs currently in use are listed in Table 1," which identifies methotrexate at a "single dose of 7.5-25 mg orally"); Ex. 1020 (2000 PDR - Methotrexate) at 7 (recommending a starting dose schedule of "[s]ingle oral doses of 7.5 mg once

weekly" and "adjusted gradually to achieve an optimum response, but not ordinarily to exceed a total weekly dose of 20 mg"); Ex. 1010 (2002 Guidelines) at 4 ("Usual maintenance dose" of MTX is oral 7.5-20 mg/week). Accordingly, a POSA would have been motivated to treat an RA patient by administering a combination of 8 mg/kg MRA intravenously every four weeks and 10 to 25 mg MTX orally every week. Ex. 1002, ¶¶149-154.

A POSA would also have reasonably expected this combined regimen to be successful because both MRA and methotrexate were known to be individually effective for treating RA, and combining methotrexate with other RA drugs was known to "improve disease control," particularly in patients who were not fully responsive to methotrexate alone. Ex. 1002, ¶155; Ex. 1007 (Matteson 2000) at 3-4; Ex. 1008 (Weinblatt 2003) at 2 ("[M]any patients continue to have some degree of disease activity despite receiving therapeutic doses of MTX … To enhance the clinical response, MTX is frequently combined with one or more traditional disease-modifying antirheumatic drugs."). And, as explained above, a POSA would have been aware of the track record of success in combining methotrexate with other anti-cytokine drugs, which would have led a POSA to reasonably expect similar success for an anti-IL-6R antibody in combination with methotrexate. *See supra* pgs. 7-8. Furthermore, earlier studies had already shown that intravenous MRA could be combined with a RA patient's existing MTX regimen to safely and

effectively treat the disease. Ex. 1005 (Yoshizaki) at 11. For all of these reasons, a POSA would have had a reasonable expectation that a combination of known efficacious regimens of MRA and methotrexate could be used to effectively treat a patient with RA. Ex. 1002, ¶155; *see BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1074 (Fed. Cir. 2019) ("[T]he record shows that a PHOSITA would have a reasonable expectation of success in combining abiraterone and prednisone because they were both together and individually considered promising prostate cancer treatments at the time.").

Accordingly, it would have been obvious over Nishimoto in view of Weinblatt 2003 to administer a combination of 8 mg/kg intravenous MRA every four weeks and 10 to 25 mg oral MTX every week to an RA patient. Ex. 1002, ¶¶145-155.

1. Independent Claims 1, 6, and 11 are Obvious

a. Claim 1

(1) "[a] method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone"

As discussed above, it would have been obvious to administer a combination of 8 mg/kg intravenous MRA every four weeks and 10 to 25 mg oral MTX every week to a RA patient. The '201 patent discloses that a greater percentage of patients receiving 8 mg/kg MRA every four weeks in combination with 10 to 25

mg methotrexate achieved an ACR70 response as compared to those receiving methotrexate alone. Ex. 1001 at 17:28-39. Nothing in the patent suggests that achieving this increased likelihood of response requires anything beyond administering the same regimen disclosed by the prior art; the only steps the '201 patent teaches are required to obtain the claimed result are administering MRA and methotrexate in the same amounts and frequencies that would have been obvious from the prior art. Ex. 1002, ¶¶122-123. Accordingly, increasing the likelihood of achieving an American College of Rheumatology ACR70 response in a RA patient compared to treating the patient with methotrexate alone is a natural result of administering the claimed regimen, and cannot render the claim patentable. *See Persian Pharm. v. Alvogen Malta Oper.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) ("[I]nherency may supply a missing claim limitation in an obviousness analysis where the limitation at issue is the natural result of the ***combination of prior art elements***.") (quotations omitted; emphasis in original); *King Pharm.*, 616 F.3d at 1275-76.

Even if this limitation were not an inherent result of the claimed regimen, it would nevertheless have been obvious. As discussed above, for patients who did not adequately respond to methotrexate, it would have been obvious to combine the existing methotrexate therapy with 8 mg/kg MRA administered intravenously every four weeks, as disclosed by Nishimoto. Ex. 1002, ¶ 157. Achieving an

ACR70 response—which reflects a 70% improvement in a number of clinically relevant parameters—was known to be desirable for an RA regimen. *See*, *e.g.*, Ex. 1009 (1999 FDA Guidance) at 6 (identifying "ACR 70" as an acceptable outcome measure for identifying a "major clinical response"). However, continuation of methotrexate therapy was known to produce an ACR70 response in a only small percentage of patients who had previously responded inadequately to MTX. *See*, *e.g.*, Ex. 1008 (Weinblatt 2003) at 5 (~5% of patients exhibited an ACR70 response within 12 weeks). By contrast, MRA administered intravenously at a dose of 8 mg/kg every four weeks was known to provide an ACR70 response in 16.4% of patients resistant to DMARD therapy, even without co-administration of methotrexate. *See* Ex. 1017 (Nishimoto Abstract B) at 2. A POSA would have thus been motivated to increase the likelihood of achieving an ACR70 response as compared to administration of methotrexate alone, and would have had a reasonable expectation of success in so doing, when combining the patient's methotrexate therapy with MRA, as discussed above. Ex. 1002, ¶¶156-158.

(2) "administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously"

It would have been obvious to administer the MRA regimen expressly recommended by Nishimoto—8 mg/kg administered intravenously every four

weeks—when combining MRA with an existing methotrexate regimen to treat an RA patient who had failed to adequately respond to methotrexate alone. Ex. 1006 (Nishimoto) at 5; Ex. 1002, ¶¶145-155.

(3) "(ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg"

It would have been obvious to continue administering methotrexate to a RA patient who had thus far failed to adequately respond to therapy when adding MRA to the regimen. Ex. 1002, ¶¶145-155. Weinblatt 2003 discloses that patients designated as having an inadequate response to methotrexate had been receiving methotrexate orally at a dose of 10 to 25 mg, and that this methotrexate regimen was continued when the biologic DMARD was added to the regimen. Ex. 1008 (Weinblatt 2003) at 2. As explained above, a POSA would have been motivated to treat an RA patient by administering a combination of MRA with methotrexate at a dosage of 10 to 25 mg orally, and would have reasonably expected the treatment to be successful.

b. Claim 6

(1) "[a] method for achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient … wherein the patient would not have achieved an ACR70 response with administration of MRA alone or methotrexate (MTX) alone"

The ’201 patent discloses that a greater percentage of patients receiving 8 mg/kg MRA every four weeks in combination with 10 to 25 mg methotrexate achieved an ACR70 response as compared to those receiving either MRA or methotrexate alone. Ex. 1001 at 17:28-39. Nothing in the patent suggests that achieving this increased likelihood of response requires anything beyond administering the same regimen disclosed by the prior art; the only steps the ’201 patent teaches are required to obtain the claim-recited result are administering MRA and methotrexate in the same amounts and frequencies that would have been obvious from the prior art. Ex. 1002, ¶¶129-130. Accordingly, achieving an ACR70 response in a rheumatoid arthritis patient wherein the patient would not have achieved such a response with either MRA or methotrexate (MTX) alone is a natural result of administering the claimed regimen, and cannot render the claim patentable. *See Persian Pharm.*, 945 F.3d at 1191; *King Pharm.*, 616 F.3d at 1275.

Even if this limitation were not an inherent result of the claimed regimen, it would nevertheless have been obvious. As discussed above, for patients who did not adequately respond to methotrexate, it would have been obvious to combine the existing methotrexate therapy with 8 mg/kg MRA administered intravenously every four weeks, as disclosed by Nishimoto. Ex. 1002, ¶¶145-155. Achieving an ACR70 response was known to be desirable for an RA regimen. *See*, *e.g.*, Ex. 1009 (1999 FDA Guidance) at 6. Continuation of methotrexate therapy was

known to produce an ACR70 response in some patients who had previously responded inadequately to methotrexate. *See*, *e.g.*, Ex. 1008 (Weinblatt 2003) at 5 (~5% of patients exhibited an ACR70 response within 12 weeks). MRA administered intravenously at a dose of 8 mg/kg every four weeks was also known to provide an ACR70 response in some patients resistant to DMARD therapy. *See* Ex. 1017 (Nishimoto Abstract B) at 2 (16.4% of patients exhibited an ACR70 response within 12 weeks). A POSA would have also known that combinations of RA drugs generally provide increased efficacy as compared to mono-therapy. Ex. 1007 (Matteson) at 4 ("To improve disease control, therapies that contain combinations of DMARDs are often used"); Ex. 1008 (Weinblatt 2003) at 2 ("To enhance the clinical response, MTX is frequently combined with one or more other traditional disease-modifying antirheumatic drugs"). A POSA would have thus been motivated to achieve an ACR70 response in patients that would not have had such a response if administered either MRA or methotrexate alone by administering the combination of MRA and methotrexate discussed above, and would have had a reasonable expectation that at least some patients would have such a response. Ex. 1002, ¶¶162-163.

(2) "administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously"

This limitation is also present in claim 1. For the same reasons discussed above, this limitation would have been obvious to a POSA. *See supra* pgs. 31-38, 40-41.

(3) "(ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg"

This limitation is also present in claim 1. For the same reasons discussed above, this limitation would have been obvious to a POSA. *See supra* pgs. 31-38, 41.

c. Claim 11

(1) "[a] method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient … wherein administration of (i) and (ii) in a tested population of rheumatoid arthritis patients resulted in an American College of Rheumatology (ACR) 70 response in a larger percentage of patients than the sum of percentages for administration of (i) alone and (ii) alone"

The '201 patent discloses that, in a tested population of rheumatoid arthritis patients, a greater percentage of patients receiving 8 mg/kg MRA every four weeks in combination with 10 to 25 mg methotrexate achieved an ACR70 response than the sum of those receiving either MRA or methotrexate alone. Ex. 1001 at 17:28-

39. Nothing in the patent suggests that achieving this increased likelihood of response requires anything beyond administering the same regimen disclosed by the prior art; the only steps the '201 patent teaches are required to obtain the claim-recited result are administering MRA and methotrexate in the same amounts and frequencies that would have been obvious from the prior art. Ex. 1002, ¶¶133-134. Accordingly, increasing the likelihood of achieving an ACR70 response in a rheumatoid arthritis patient such that a larger percentage of patients achieve an ACR70 response in a tested population of RA patients than the sum of percentages for MRA and MTX alone is a natural result of administering the claimed regimen, and cannot render the claim patentable. *See Persian Pharm.*, 945 F.3d at 1191; *King Pharm.*, 616 F.3d at 1275-76.

Even if this limitation were not an inherent result of the claimed regimen, it would nevertheless have been obvious. Ex. 1002, ¶¶167-169. As discussed above, for patients who did not adequately respond to MTX, it would have been obvious to combine the existing MTX therapy with 8 mg/kg MRA administered intravenously every four weeks, as disclosed by Nishimoto. Achieving an ACR70 response was known to be desirable for an RA regimen. *See*, *e.g.*, Ex. 1099 (1999 FDA Guidance) at 6. Continuation of MTX therapy was known to produce an ACR70 response in some patients who had previously responded inadequately to MTX. *See*, *e.g.*, Ex. 1008 (Weinblatt 2003) at 5 (~5% of patients exhibited an

ACR70 response within 12 weeks). MRA administered intravenously at a dose of 8 mg/kg every four weeks was also known to provide an ACR70 response in some patients resistant to DMARD therapy. *See* Ex. 1017 (Nishimoto Abstract B) at 2 (16.4% of patients exhibited an ACR70 response within 12 weeks). A POSA would have also known that combinations of RA drugs generally provide increased efficacy as compared to mono-therapy. Ex. 1017 (Matteson) at 4; Ex. 1008 (Weinblatt 2003) at 9. In fact, a POSA would have known that MTX and other cytokine inhibitors provided a greater than additive response when administered in combination. Ex. 1015 (Maini 1998) at 7-9 (administration of infliximab plus MTX "demonstrates an apparent synergy of action" in RA patients). A POSA would have thus been motivated to increase the likelihood of an ACR70 response in patients such that the percentage of RA patients in a tested population achieving an ACR70 response would be greater than the sum of percentages of patients achieving such a response when administered either regimen alone, and would have had a reasonable expectation of success in so doing.

Moreover, it would have been obvious to carry out the claimed method in the context of a clinical trial. As discussed above, Nishimoto discloses that such a trial was underway, but does not disclose the results. Therefore, a POSA would have been motivated to administer the combined regimen to a population of

patients in order to confirm its expected efficacy and safety in a controlled manner. Ex. 1002, ¶¶167-169.

A POSA would also have reasonably expected to achieve such a result. Clinical studies results are subject to variability, and a POSA would have reasonably expected that, in some tested populations, the percentage of patients receiving the combined regimen would not only exceed those receiving MRA or MTX alone, but would exceed the sum of percentages of patients receiving either regimen alone. Ex. 1002, ¶¶167-169.

(2) "administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously"

This limitation is also present in claims 1 and 6. For the same reasons discussed above, this limitation would have been obvious to a POSA. *See supra* pgs. 31-38. 40-41.

(3) "(ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg"

This limitation is also present in claims 1 and 6. For the same reasons discussed above, this limitation would have been obvious to a POSA. *See supra* pgs. 31-38, 41.

2. Dependent Claims 2-5, 7-10, and 12-15 are Obvious over Nishimoto in View of Matteson

a. Claims 2, 7, and 12

Claims 2, 7, and 12 depend from claims 1, 6, and 11, respectively, and further require that "the patient, prior to treatment had an inadequate response or disease flare on methotrexate (MTX) treatment alone." As discussed above, a POSA would have found it obvious to administer the claimed regimen specifically to patients who had previously had an inadequate response to MTX alone. Ex. 1002, ¶172. Accordingly, claims 2, 7, and 12 are obvious for substantially the same reasons as set forth with respect to claims 1, 6, and 11.

b. Claims 3, 8, and 13

Claims 3, 8, and 13 depend from claims 1, 6, and 11, respectively, and further require that "the patient has no anti-MRA antibodies following administering the combination of anti-IL-6R antibody MRA and MTX." As with the claimed ACR70 response, the lack of appearance of anti-MRA antibodies is the natural result of administering the claimed regimen, and therefore does not contribute to the patentability of the claim. Ex. 1001 at 19:10-17. Furthermore, Nishimoto discloses that one benefit to administering MRA to RA patients is that the appearance of antibodies to MRA is "very rare." Ex. 1006 (Nishimoto) at 5. Accordingly, a POSA would have been motivated to administer the claimed regimen such that the patient would have no anti-MRA antibodies following administration, and would have reasonably expected that to be the case. Ex. 1002,

¶173. Claims 3, 8, and 13 are therefore obvious for these reasons as well as the reasons set forth with respect to claims 1, 6, and 11.

c. Claims 4, 9, and 14

Claims 4, 9, and 14 depend from claims 1, 6, and 11, respectively, and further require that "the patient does not experience hypersensitivity following administering the combination of anti-IL-6R antibody MRA and MTX." The lack of hypersensitivity is the natural result of administering the claimed regimen, and therefore cannot render these claims patentable. Ex. 1001 at 18:42-57. A POSA would also have known that both methotrexate and MRA were "well-tolerated" protocols, meaning that they caused limited harmful side effects for patients, such as hypersensitivity. Ex. 1005 (Yoshizaki) at 11 ("No major side effects were observed except for the appearance of anti-idiotypic antibody in one case."); Ex. 1017 (Nishimoto Abstract-B) at 2 ("The treatment with RA was well tolerated . . ."); Ex. 1007 (Matteson) at 2 (characterizing methotrexate as "well tolerated"); Ex. 1010 (2002 Guidelines) at 10 ("more than 50% of patients who take MTX continue the drug beyond 3 years, which is longer than any other DMARD"). Therefore, a POSA would have reasonably expected that the RA patient to whom the claimed regimen was administered would not experience hypersensitivity. Ex. 1002, ¶173. Claims 4, 9, and 14 are therefore obvious for these reasons as well as the reasons set forth with respect to claims 1, 6, and 11. Ex. 1002, ¶174.

d. Claims 5, 10, and 15

Claims 5, 10, and 15 depend from claims 1, 6, and 11, respectively, and further require that "the anti-IL-6R antibody MRA is administered four times at four week intervals." As discussed above, in combining MRA with MTX to treat an RA patient, a POSA would have found it obvious to administer the MRA in accordance with the regimen recommended by Nishimoto, *i.e.*, 8 mg/kg every four weeks. This regimen involves administering MRA at four week intervals. Furthermore, as discussed above, the clinical study from which this recommended regimen was derived involved administering MRA pursuant to this regimen for a total of 12 weeks, which is four administrations (weeks 0, 4, 8, and 12). Ex. 1017 (Nishimoto Abstract B) at 2. A POSA implementing Nishimoto's combined MRA/MTX regimen would have therefore been motivated to continue the regimen for at least twelve weeks, such that MRA would be administered four times. Claims 5, 10, and 15 are therefore obvious for these reasons as well as the reasons set forth with respect to claims 1, 6, and 11. Ex. 1002, ¶175.

C. Secondary Considerations

As discussed above, Patent Owner alleged during prosecution that the patentability of the claims are supported by unexpected results. Ex. 1004 at 769-770. Specifically, Patent Owner alleged that (1) it was unexpected that administering MRA 8 mg/kg every four weeks and methotrexate every week

would result in a greater percentage of patients achieving an ACR70 response than administration of methotrexate alone; and (2) it was unexpected that the percentage of patients administered MRA 8 mg/kg every four weeks and methotrexate every week achieving an ACR70 response would be greater than the sum of the percentages of patients achieving an ACR70 response on each regimen alone. *Id.* Neither of these allegations support the patentability of the claims.

Patent Owner did not compare results of the claimed methods to the closest prior art. To support a finding of nonobviousness, purported unexpected results must be compared with the closest prior art. *In re Baxter Travenol Labs*, 952 F.2d at 392. The claims of the '201 patent are all directed to a method of administering a combination of specific doses of MRA and methotrexate to an RA patient. Hence, the closest prior art to the claimed invention of the '201 patent is Nishimoto, which discloses not only administering a combination of MRA and methotrexate to an RA patient, but the same 8 mg/kg every four week MRA regimen recited in the claims. However, neither Patent Owner nor the Examiner properly compared the results of the claimed regimen to Nishimoto. Instead, they compared the results of the claimed regimen to other combinations of MRA and methotrexate disclosed in the '201 patent itself—*i.e.*, 2 mg/kg and 4 mg/kg MRA every four weeks in combination with methotrexate. Patent Owner alleged that, because those regimens did not result in a higher percentage of patients achieving

an ACR70 response compared to methotrexate alone, it was unexpected that the claimed regimen did so. Ex. 1004 at 769-770. This comparison does not support the patentability of the claims for at least two reasons.

First, as noted above, Nishimoto already disclosed the claimed regimen of administering 8 mg/kg MRA with methotrexate to an RA patient. Accordingly, even assuming that it was unexpected that the claimed regimen achieved an ACR70 response in a higher percentage of RA patients than treatment with methotrexate alone, that is insufficient to support a finding of nonobviousness because the results would be no different than those attained by following the closest prior art. *See In re de Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) ("[A]n applicant relying on comparative tests to rebut a prima facie case of obviousness must compare his claimed invention to the closest prior art."). As the Federal Circuit has explained, "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Baxter*, 952 F.2d at 392.

Second, it would have been expected from the prior art that administering 8 mg/kg MRA every four weeks in combination with methotrexate would result in a greater percentage of patients achieving an ACR70 response as compared to methotrexate alone. Ex. 1002, ¶¶179-180. It was well known that administering methotrexate alone yielded an ACR70 response in only a small fraction of RA patients. *See*, *e.g.*, Ex. 1008 (Weinblatt 2003) at 5 (~5% of patients exhibited an

ACR70 response within 12 weeks). By contrast, Nishimoto Abstract B disclosed that administering 8 mg/kg MRA every four weeks resulted in an ACR70 response in a substantially greater percentage (16.4%) of patients. Ex. 1017 (Nishimoto Abstract B) at 2. Thus, a POSA would have expected that administering 8 mg/kg MRA every four weeks—even if administered without MTX—would result in a greater percentage of patients achieving an ACR70 response than methotrexate alone. Ex. 1002, ¶¶179-180. There is no reason why a POSA would have thought that combining the two regimens would somehow result in less efficacy than MRA alone; therefore, a POSA would not have found it surprising that the claimed regimen of 8 mg/kg every four weeks combined with MTX would allow a greater percentage of patients to achieve an ACR70 response than methotrexate alone. Ex. 1002, ¶¶179-180. That result is precisely what the prior art taught to expect. Notably, Nishimoto Abstract B (Ex. 1017)—the prior art reference that disclosed the ACR70 response for administration of MRA—was not disclosed to the Examiner during prosecution.

Patent Owner's allegation of superior results when compared to a 2 mg/kg and 4 mg/kg MRA regimen also lacks support. The limited data in the '201 patent does indicate that the percentage of patients achieving an ACR70 response when administered 4 mg/kg or 2 mg/kg MRA in combination with methotrexate was slightly lower than when methotrexate was administered alone. Ex. 1001 at 17:28-

40. But subsequent clinical trials established that these results are likely an anomaly, and not reflective of the actual results when these regimens are administered to RA patients. For example, the current Actemra®[11] FDA label reports the results of several clinical studies comparing the efficacy of MRA administered intravenously at a dose of 4 mg/kg every four weeks in combination with methotrexate to administration of methotrexate alone. Ex. 1038 (Actemra Label) at 34. In every instance—and in contrast to the data reported in the '201 patent—these studies showed that a greater percentage of patients receiving both 4 mg/kg MRA and methotrexate achieved an ACR70 response than those receiving methotrexate alone: 11% vs. 2%; 12% vs. 2%; 5% vs. 1%. Notably, these were all larger studies, involving more patients than the small phase II study reported in the '201 patent, and strongly suggest that, just like the claimed regimen, any combination of an effective amount of MRA with methotrexate increases the likelihood of achieving an ACR70 response as compared to methotrexate alone, just as a POSA would have expected from the prior art. Ex. 1002, ¶180.

[11] MRA, or tocilizumab, is marketed under the brand name, Actemra®. Ex. 1038 ("Actemra Label"); Ex. 1039 ("Maini 2006") at 1 ("tocilizumab (previously known as MRA)").

Patent Owner's allegation of a "synergistic" response when 8 mg/kg MRA is combined with methotrexate is similarly unavailing. Ex. 1004 at 769-770. Specifically, during prosecution Patent Owner pointed to the results of the phase II study disclosed in the '201 patent to argue that the percentage of patients achieving an ACR70 response when administered both MRA and methotrexate (36.7%) was greater than the sum of patients achieving an ACR70 response when administered either regimen alone (i.e., 32.0% = 15.7% and 16.3%). *Id.* But the evidence does not support that conclusion. While 36.7% is nominally higher than 32.0%, there is no indication that this minor numerical difference reflects a meaningful distinction. In fact, as explained below, subsequent studies confirm that there is no such "synergistic" effect. Ex. 1002, ¶181.

The phase II clinical study reported in the '201 patent was published in 2006, and is identified as the CHARISMA study. Ex. 1039 (Maini 2006). By the authors' own admission, the study design was flawed, which could easily account for the anomalous results. *Id.* at 10. Specifically, while the study was intended to include only MTX non-responders, "our patients were not MTX nonresponders, but rather [] they had not yet fully responded to MTX at the time of trial entry." *Id.* The authors clarified the impact of this distinction: "The study design required that background MTX be withdrawn abruptly at the start of the study in the groups receiving tocilizumab monotherapy, ***thus placing these groups at a relative***

disadvantage in terms of efficacy in a population of incomplete MTX responders." *Id*. (emphasis added). There is no basis to conclude that, had the 8 mg/kg MRA group not been improperly placed at such a disadvantage, the percentage of patients receiving the combined regimen achieving an ACR70 response would have been greater than the sum of the patients receiving each regimen alone. Ex. 1002, ¶182.

The small CHARISMA trial was also not powered to establish superiority of the combined MRA/methotrexate regimen as compared to MRA alone, much less as compared to MRA alone plus methotrexate alone. This limitation of the CHARISMA study was expressly noted by subsequent researchers who sought to determine whether 8 mg/kg MRA administered intravenously every four weeks in combination with methotrexate was, in fact, superior to MRA alone. Ex. 1040 (Dougados) at 2. These researchers noted that "[t]he only data comparing the two strategies is from a phase II study with a small sample size and no structural outcome measures to indicate superiority of the add-on strategy." *Id.* They thus intended to carry out "the first study comparing the efficacy and safety of tocilizumab in combination with methotrexate and as monotherapy in inadequate responders to methotrexate with a sufficient sample size to address this question properly." *Id*. at 6. Like the CHARISMA study, the ACT-RAY study involved RA patients who had inadequately controlled disease despite methotrexate therapy,

and, at study initiation, the patients were randomized to receive either 8 mg/kg MRA intravenously every four weeks in combination with their existing MTX regimen, or 8 mg/kg MRA without MTX. *Id.* at 2. Each study group had more than 250 patients (more than five times as many as in the CHARISMA study). *Id*. at 3. Notably, the ACR70 response of each group was essentially identical (24.5% and 25.4% for the MRA alone group and MRA/MTX group, respectively). *Id*. at 4. Although acknowledging the existence of "numerically small and not clinically meaningful differences," the authors concluded that "[t]he study did not succeed at demonstrating that add-on strategy efficacy (combination therapy of tocilizumab plus methotrexate) was superior to the switch strategy (monotherapy tocilizumab plus placebo)." *Id*. at 5. In view of this peer-reviewed study, Patent Owner's allegation—that a greater percentage of patients achieve an ACR70 response to 8 mg/kg every four weeks plus weekly methotrexate than the sum of patients receiving both MRA alone and methotrexate alone—cannot plausibly be correct. Ex. 1002, ¶¶183-184.

Others have similarly concluded that the data in the '201 patent does not support the existence of a "synergistic" effect between MRA and methotrexate.

For example, in a review of U.S Patent Publication No. 20150010554,[12] the author evaluated the same data presented in the '201 patent and concluded that, while MRA's "clinical efficacy was well resolved … it has not been shown that synergistic effects can be achieved by the combination of anti-IL-6R antibody with immunosuppressants." Ex. 1041 (Chin) at 1.

In sum, Patent Owner's allegations of unexpected results are based on flawed, superseded data, and even if accurate, would nevertheless be legally irrelevant to the patentability of the claims of the '201 patent. Petitioners are unaware of any other secondary considerations supporting the nonobviousness of the claims. Accordingly, all of the claims of the '201 patent should be found unpatentable.

D. Section 325(d) Should Not Prevent Institution

Section 325(d) provides discretion to deny institution where (1) the same or substantially the same art or arguments were previously presented to the patent office; and (2) the petitioner has failed to demonstrate that the Examiner erred in a manner material to the claims. *Sony Interactive Entertainment LLC*, 2020 WL

[12] The '201 patent is a continuation of U.S. Patent Application No. 14/495,001, which published as U.S. Patent Publication No. 20150010554, and the specifications of the two are substantially identical.

5924211, at *2. A material error includes, for example, the Examiner "overlooking specific teachings" of the relevant prior art. *Id*. at *5.

The so-called *Becton Dickinson* factors are applied to aid in answering these questions. These factors include: "(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Becton, Dickinson & Co. v. B. Braun Melsungen, AG*, IPR2017-01586, Paper 8, at 17-18 (PTAB Dec. 15, 2017).

1. Ground 1

With regard to Ground 1, Petitioners rely upon Nishimoto, and in particular, its disclosure of the combined administration of MRA and methotrexate, and the recommended MRA dosing regimen of 8 mg/kg every four weeks. Although Nishimoto was disclosed on an IDS during prosecution, it was never substantively

evaluated by the Examiner. Mere inclusion of a reference on an IDS does not mean that it was involved or evaluated during prosecution. *See Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, Paper 8, at 7-9 (PTAB April 3, 2017). Factors (a) and (b) therefore favor institution.

Factor (d) similarly favors institution. Petitioners rely upon Nishimoto as anticipatory of all claims of the '201 patent. At no point during prosecution did the Examiner contend that a single reference disclosed each and every limitation of any of the claims.

The remaining factors demonstrate that the Examiner erred in a material way by failing to reject the claims over Nishimoto, and strongly counsel against denying institution. As noted, Nishimoto was never substantively evaluated during prosecution. Hence, factor (c) weighs in favor of institution. *See Digital Check Corp. v. E-ImageData Corp.*, Case No. IPR2017-00178, Paper 6, at 12-13 (P.T.A.B. April 25, 2017). Also, as discussed above, the references the Examiner did rely upon were missing materially important limitations that are found within Nishimoto. Nishimoto fills a gap in the cited references by expressly disclosing administration of methotrexate with MRA and implicitly disclosing the dosage of methotrexate administered. The Okuda reference cited by the Examiner did not fill this gap. As the Examiner recognized, Okuda does not disclose either (1) the claimed MRA dosing regimen of 8 mg/kg every four weeks, but rather 2 mg/kg, 4

mg/kg, or 8 mg/kg every two weeks, or (2) the claimed MTX regimen of 10-25 mg every week. Ex. 1004 at 156. To the contrary, Nishimoto expressly discloses the claimed MRA regimen of 8 mg/kg every four weeks and implicitly discloses the claimed methotrexate regimen, as discussed above.

Factors (e) and (f) also strongly support institution. As discussed above, Nishimoto discloses and enables each and every limitation of all of the claims of the '201 patent. The Examiner's failure to appreciate that a single reference anticipates the claims reflect a plain error in evaluating the prior art (factor (e)) and the arguments set forth in Petitioners' Ground 1 reflect additional evidence and facts presented in the Petition that warrant reconsideration of the prior art or arguments (factor (f)).

2. Ground 2

Ground 2, discussed above, asserts that all claims of the '201 patent are obvious over a combination of references—Nishimoto and Weinblatt 2003. Thus, for substantially the same reasons set forth with respect to Ground 1, discretionary denial of institution would be inappropriate for Ground 2 under Section 325(d).

Additionally, Weinblatt 2003's disclosure provides further bases upon which to grant institution. Although Weinblatt 2003 was disclosed to the Examiner, it too was never the subject of any rejection. Petitioners rely upon Weinblatt 2003 for, *inter alia*, its disclosure that RA patients are treated with methotrexate

administered as an oral dose between 10 and 25 mg once weekly, the exact same methotrexate regimen required by the claims. At no point during prosecution did the Examiner identify any reference as disclosing this range. To the contrary, the Examiner repeatedly relied upon a different reference, Maini 1998, for its disclosure of administering methotrexate at a dose of 7.5 mg per week, which a POSA "would have to optimize" to fall within the claimed range of 10-25 mg per week. Ex. 1004 at 154.

Moreover, as discussed above, the Examiner allowed the claims in view of alleged unexpected results that administering MRA in combination with methotrexate increased the likelihood of an ACR70 response as compared to methotrexate alone. *Id.* at 2094-2095. However, the Examiner was without the benefit of Nishimoto Abstract B (Ex. 1017), which disclosed that administering MRA in accordance with the claimed regimen provided an ACR70 response in a substantial percentage of patients; this would have suggested precisely the results the Examiner found unexpected. Factors (e) and (f) therefore demonstrate that the Examiner materially erred in accepting Patent Owner's allegation of unexpected results as supporting a finding of nonobviousness.

Accordingly, Section 325(d) should not prevent institution of either Ground presented in this petition.

X. CONCLUSION

Petitioners respectfully submit that they have established a reasonable likelihood of success with respect to the challenged claims and request that trial be instituted and the challenged claims cancelled.

Date: June 28, 2021

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 10,744,201 complies with the type-volume limits of 37 C.F.R. §42.24(a)(1)(i) because it contains 13,789 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: June 28, 2021

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,744,201** and the exhibits cited therein by Federal Express Priority Overnight Delivery on this day, June 28, 2021, on the Patent Owner's correspondence address of record for the subject patent as follows:

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