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 2021-01024

Patent No. 7,521,052

Title: METHODS FOR TREATING INTERLEUKIN-6 RELATED DISEASES

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,521,052

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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 claim 1 of U.S. Patent No. 7,521,052 ("the '052 patent," Ex. 1001). Petitioners' request is supported by the Expert Declaration of Thomas M. Zizic, M.D. (Ex. 1002), and the other exhibits submitted herewith.

Claim 1 of the '052 patent—which is the only claim of the patent—is directed to a method for treating rheumatoid arthritis (RA) with an anti-IL-6 receptor antibody and methotrexate. Specifically, claim 1 recites "[a] method for treating rheumatoid arthritis, comprising administering an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody) and an effective amount of methotrexate (MTX) to a patient in need thereof, wherein the anti-IL-6R antibody is a humanized PM-1 antibody." This claim is invalid as anticipated and obvious

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

in view of prior art describing the treatment of rheumatoid arthritis with MRA[2] (a humanized PM-1 antibody) and methotrexate.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder that can affect many tissues and organs, but principally attacks the joints. By the April 28, 2003 priority date of the '052 patent, methotrexate—a common disease-modifying antirheumatic drugs (or "DMARD")—was considered the "treatment of choice" for RA patients, with well-established dosing parameters for controlling RA. Ex. 1002, ¶¶ 41-44; Ex. 1008 (Weinblatt 2003) at 2; Ex. 1007 (Matteson) at 2. However, patient response to methotrexate monotherapy was often inadequate to fully control disease activity, and so it was typically administered with other anti-rheumatic drugs in order to improve clinical response. Ex. 1002, ¶¶ 44-46; Ex. 1008 (Weinblatt 2003) at 2.

Because of methotrexate's prevalence as an RA treatment, and the known benefits of combining it with other RA drugs, it was understood that as new RA drugs were developed, they would be used to supplement methotrexate therapy.

[2] MRA was previously known as rhPM-1. Ex. 1002, ¶ 34; Ex. 1006 (Nishimoto) at 4 ("This humanized anti-IL-receptor antibody (reshaped human PM-1: rhPM-1) was initially intended as a treatment for multiple myeloma, and is hence referred to as myeloma receptor antibody (MRA).").

Indeed, in 1999 the FDA recognized that "it is inevitable that new agents will be used in combination with methotrexate." Ex. 1009 (1999 FDA Guidance) at 21. Under the guidelines issued by the American College of Rheumatology in 2002, "MTX as monotherapy or as a component of combination therapy should be instituted in patients whose treatment has not yet included MTX," and for patients who did not adequately respond to MTX, "treatment with biologic agents or with other DMARDs, either alone or in combination, is indicated." Ex. 1010 (2002 Guidelines) at 9. Thus, in the late 1990s and early 2000s, three biologic drugs—adalimumab, infliximab, and etanercept—were approved by the FDA for the treatment of RA, and all three were approved 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.

These FDA-approved biologic drugs targeted the TNF-α cytokine, known to be involved in RA. Another cytokine, interleukin-6 (IL-6), was also known to play a crucial role in the pathogenesis of RA. Ex. 1002, ¶¶ 33-35; Ex. 1005 (Yoshizaki) at 5-6. And MRA, an anti-IL-6 receptor antibody which inhibits the binding of IL-6 to its receptors and thus reduces pro-inflammatory activity, had been established as a safe and effective RA treatment through a multitude of clinical studies

reported in the prior art before the earliest claimed priority date. Ex. 1002, ¶¶ 37-39; Ex. 1005 (Yoshizaki) at 9-11; Ex. 1006 (Nishimoto) at 4-5.

As a new RA treatment, it was—as the FDA foresaw—"inevitable" that MRA would be administered in combination with methotrexate to treat RA. Or, as other prior art put it, "[i]n 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." Ex. 1014 (Amano) at 8.

Indeed, the successful treatment of RA patients by administering MRA along with methotrexate was reported in the prior art long before the '052 patent was filed. In one of the earliest studies identifying MRA as an effective treatment for RA, Yoshizaki disclosed that a patient with "severe RA" was administered combination therapy including both methotrexate and MRA, after which her clinical and laboratory abnormalities improved. Ex. 1005 (Yoshizaki) at 10-11. The authors concluded that MRA was "effective, safe and useful for the treatment of RA." *Id*. at 11. This disclosure was not before the Examiner during prosecution of the '052 patent, and plainly anticipates its only issued claim. *See* Ex. 1002, ¶¶ 134-142.

The claim of the '052 patent is also anticipated by a second prior art reference, Nishimoto, which disclosed an ongoing clinical trial of MRA in

combination with methotrexate for the treatment of RA. Ex. 1006 (Nishimoto). Like Yoshizaki, this printed publication anticipates the only issued claim of the '052 patent, yet was not disclosed to the Examiner during prosecution. *See* Ex. 1002, ¶¶ 143-148.

Even if the '052 patent claim were not anticipated, it would nevertheless have been obvious. The prior art indisputably disclosed effective amounts of both MRA and methotrexate, as well as the combined administration of both drugs for the treatment of RA. In view of these disclosures, a person of ordinary skill in the art would have been motivated to administer the known, effective amounts of MRA and methotrexate to RA patients in carrying out the combined therapy. *See* Ex. 1002, ¶¶ 149-162. A skilled artisan would have reasonably expected this regimen to be successful since each of the drugs had been independently established as safe and effective for treating RA, and the combined administration of these drugs had also been shown to be safe and effective. *Id.*

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 '052 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 '052 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 '052 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 '052 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. 10,744,201, which claims priority to the '052 patent.

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 '052 patent: Foley & Lardner LLP, 3000 K Street N.W., Suite 600, Washington, DC 20007-5109.

E. Power of Attorney (§ 42.10(b))

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 (RA) is a chronic, immune-mediated, systemic disease characterized by pain, swelling and progressive destruction of the small joints of the hands and feet. Ex. 1002, ¶ 33. By the earliest claimed priority date of the '052 patent— April 28, 2003—RA patients were commonly treated with methotrexate, a disease-modifying antirheumatic drug ("DMARD"), which was considered the "anchor therapy for RA." Ex. 1007 (Matteson) at 2; Ex. 1002, ¶¶ 41-44. In addition to its antiproliferative activity, methotrexate also has anti-inflammatory and immunomodulating properties, leading to its use in a wide range of doses for a broad range of therapeutic indications, including rheumatoid arthritis. Ex. 1002, ¶¶ 41-42. In low doses, at 7.5 mg to 25 mg given once per week, it has been used to treat RA and other rheumatic diseases for the past half-century. *Id.* ¶ 41. Because of its tolerability, prompt clinical response, efficacy and relative lack of serious side effects, it became the DMARD of choice for RA in the 1990s. *Id.* ¶ 43.

However, many RA patients were not sufficiently responsive to methotrexate, and so additional therapeutic interventions were often used to supplement methotrexate. *Id.* ¶¶ 44-46; Ex. 1008 (Weinblatt 2003) at 2. In a 2002 review for clinicians published by the Mayo Clinic, the authors stated that "[t]o improve disease control, therapies that contain combinations of DMARDs are often used" and "[a]bout 50% of patients with RA treated by rheumatologists are prescribed combination therapies with either 2 or 3 DMARDs." Ex. 1007 (Matteson) at 4. Even more pointedly, in a 1999 Guidance directed to the development of RA drugs, the FDA noted that "it is inevitable that new agents will be used in combination with methotrexate." Ex. 1009 (1999 FDA Guidance) at 21. Three years later, the American College of Rheumatology issued guidelines for the treatment of RA, stating that "MTX as monotherapy or as a component of combination therapy should be instituted in patients whose treatment has not yet included MTX," and for patients who did not adequately respond to MTX, "treatment with biologic agents or with other DMARDs, either alone or in combination, is indicated." Ex. 1010 (2002 Guidelines) at 9. Thus, as biologics became available for the treatment of RA, it was only natural to combine these agents with methotrexate for patients who had not adequately responded to methotrexate alone. Ex. 1002, ¶¶ 44-45.

By 2002, three other biologics—adalimumab, infliximab, and etanercept—had been approved by FDA for the treatment of rheumatoid arthritis. All three were approved for use in combination with methotrexate. Enbrel® (etanercept) was approved by FDA in 1998 for use in treating RA in combination with methotrexate. Ex. 1012 (2000 PDR – Enbrel) at 9; Ex. 1011 (Rebholz) at 1. That same year, the results of a multi-center clinical trial demonstrated "that additive or synergistic action could be obtained by combining [infliximab] and MTX." Ex. 1015 (Maini 1998) at 9. A year later, Remicade® (infliximab) was also approved by FDA for treatment of RA in combination with methotrexate. Ex. 1013 (2001 PDR - Remicade) at 4; Ex. 1036 (Moreland) at 3. And in 2002, FDA approved Humira® (adalimumab) for the treatment of RA in combination with methotrexate. Ex. 1033 (2002 Humira FDA Label) at 7, 14, 16; Ex. 1034 (Abbott 8K) at 5; Ex. 1035 (FDA Talk Paper) at 5. In short, by the 2003 priority date of the '052 patent, there was a track record of success in combining antibodies with methotrexate in the treatment of rheumatoid arthritis.

IL-6 is a principal inflammatory cytokine in the fluid within joints of patients with rheumatoid arthritis (RA) and plays a critical role in RA disease progression. Ex. 1002, ¶¶ 33-34. MRA, an anti-IL-6 receptor antibody, inhibits the binding of IL-6 to its receptors, and thus reduces the cytokine's pro-inflammatory activity by competing for both the soluble and membrane-bound

forms of the human IL-6 receptor. *Id.* ¶ 34. In view of this mechanism of action, efforts were undertaken to establish the safety and efficacy of MRA for treating RA. *Id.* ¶¶ 35-40; Ex. 1006 (Nishimoto) at 5.

In 1998, the results of a study in which MRA was combined with conventional RA regimens, including methotrexate, were published; the results "suggest[ed] that rhPM-1 is effective, safe and useful for the treatment of RA, and that IL-6 is a pathogenic key cytokine as an effector in RA." Ex. 1005 (Yoshizaki) at 11. Subsequent results of an open-label, multi-dose trial in which patients "received an intravenous infusion with either 2, 4, or 8 mg/kg of humanized anti-interleukin-6 receptor antibody (MRA) every 2 weeks for 6 months" confirmed MRA "appeared considerably safe" and "is therapeutically beneficial in RA." Ex. 1016 (Nishimoto Abstract A) at 2. A randomized, double-blind placebo-controlled study then showed that 4 mg/kg or 8 mg/kg MRA administered intravenously every four weeks "was well tolerated and significantly reduced the disease activity in patients with RA." Ex. 1017 (Nishimoto Abstract B) at 2. On the basis of these studies, the prior art recommended a dose of 8 mg/kg administered intravenously every 4 weeks. Ex. 1006 (Nishimoto) at 4-5.

As expected, based on the development of other biologics for the treatment of RA, these successful results prompted clinical trials of MRA in combination with methotrexate. *See* Ex. 1002, ¶¶ 40, 153-154. The existence of these trials

was disclosed in, *inter alia*, Nishimoto, well before the earliest claimed filing date of the '052 patent: "a phase II study of coadministration with methotrexate is currently underway in several European countries." Ex. 1006 (Nishimoto) at 5; *see also* Ex. 1019 (Hagihara) at 5-7.

Accordingly, by the time the '052 patent was filed, both MRA and methotrexate were known treatments for RA, and effective dosing regimens for each had been well established. Ex. 1002, ¶¶ 36-43. It was also well known that RA drugs were typically administered in combination in order to enhance their effect. Ex. 1002, ¶¶ 43-46. Not only was this the typical practice, a clinical study evaluating the specific combination of MRA and methotrexate for the treatment of RA had been disclosed. Ex. 1005 (Yoshizaki) at 11.

VI. THE '052 PATENT

The '052 patent, entitled "Methods for Treating Interleukin-6 Related Diseases," issued on April 21, 2009, from PCT Application No. 10/554,407, filed on April 28, 2004, and claims priority to an application filed in Great Britain, Application No. O3096195, filed on April 28, 2003. Petitioners challenge claim 1 of the '052 patent—the sole claim of the patent. Claim 1 is shown below:

> 1. A method for treating rheumatoid arthritis, comprising administering an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody) and an effective amount of methotrexate (MTX)

to a patient in need thereof, wherein the anti-IL-6R antibody is a humanized PM-1 antibody.

VII. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art ("POSA") to whom the '052 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. 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, any term not expressly discussed should be given its ordinary and customary meaning

to a POSA as of the invention date of the '052 patent, which Petitioners assume for purposes of this IPR only to be April 28, 2003.[3]

A. "A method of treating rheumatoid arthritis . . . in a patient"

Claim 1 recites a "method of treating rheumatoid arthritis . . . in a patient." The plain and ordinary meaning of the phrase "[a] method for treating rheumatoid arthritis . . . in a patient" is "a method attempting to cause a therapeutic improvement in rheumatoid arthritis in a patient." Ex. 1002, ¶ 120; Ex. 1032 (Webster's Dictionary) at 3-4. The plain meaning of "treating . . . a patient" does not require actually causing a therapeutic benefit in that particular patient. Ex. 1002, ¶ 120; *see, e.g.*, *Schering Corp. v. Mylan Pharms., Inc*., No. CIV. A. 09-6383 JLL, 2011 WL 2446563, at *2, 5 (D.N.J. June 15, 2011) ("To treat a disease does not imply that the progression of the disease will actually be slowed, arrested, or reversed . . . ."); *Novartis Pharms. Corp. v. Actavis, Inc.*, No. CV 12-366-RGA-CJB, 2013 WL 6142747, at *11 (D. Del. Nov. 21, 2013) ("[T]he Court agrees . . .

[3] Petitioners adopt these claim construction positions for purposes of this IPR only and reserve the right to change or modify their positions 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.

that the plain and ordinary meaning of 'treating' diseases or iron overload . . . is to *attempt* to cause a therapeutic improvement, without necessarily having assurance of what the outcome will be.") (emphasis in original).[4]

The specification of the '052 patent is consistent with this plain meaning. Ex. 1002, ¶ 121. In the sole example describing clinical results from use of the claimed method, the specification describes a Phase II trial "to determine the optimum dose of MRA given alone and in combination with methotrexate for the treatment of rheumatoid arthritis." Ex. 1001 ('052 patent) at 16:15-17. Patients enrolled in the study must have had "active disease and had ***an inadequate response to, or disease flare on MTX*** given for at least 6 months at a dose of at least 12.5 mg weekly or 10 mg weekly in the case of intolerance." *Id*. at 16:30-33 (emphasis added). The study was to evaluate "potential efficacy of repeated intravenous doses of MRA, both as monotherapy and in combination with methotrexate, were assessed in patients with active rheumatoid arthritis ***despite of the treatment*** with methotrexate for a specified period of time and compared to methotrexate monotherapy." *Id.* at 16:18-22 (emphasis added). In other words, a

[4] That the claim requires an "effective amount" of an anti-IL-6 receptor antibody and an "effective amount" of methotrexate does not alter this conclusion. *See* sections VIII.C and VIII.D, *infra*.

patient underwent "treatment" with methotrexate even though it provided an "inadequate response." *See* Ex. 1002, ¶¶ 120-122.

B. "administering an . . . anti-IL-6 receptor antibody . . and methotrexate (MTX)"

The term "administering an . . . anti-IL-6 receptor antibody . . . and methotrexate (MTX)" should be construed to include administration of the two drugs either simultaneously or sequentially (i.e., in which one drug is administered first, followed by administration of the second drug). Ex. 1002, ¶¶ 123-126. This is consistent with the specification, which discloses that "[t]he anti-IL-6R antibody and the immunosuppressant are administered simultaneously or with a time interval," and places no restriction on the time interval within which the two drugs are administered. *Id.* ¶ 124; Ex. 1001 at 3:63-64.

The file history reinforces this meaning of the term. During prosecution, the applicant pursued separate dependent claims to "simultaneously administering" and administering "with in a time interval" an anti-IL-6 receptor antibody and methotrexate, specifically claims 79 and 80 (reproduced below, along with claim 55 from which these claims depended):

> 55. (Currently Amended) A method for treating an IL-6 related disease, comprising administering an **anti-**IL-6 ~~antagonist~~ **receptor antibody (anti-IL-6R) that inhibits binding of IL-6 to the IL-6 receptor by binding to the IL-6 receptor to block signaling of IL-6 biological activity into cells,** and ~~an immunosuppressant~~ **methotrexate (MTX)** to a patient requiring such a treatment**, wherein said IL-6 related disease is rheumatoid arthritis**.
>
> 79. (Currently Amended) The method according to ~~claim 60~~ **claim 55**, wherein the anti-IL-6R antibody and said immunosuppressant are administered simultaneously.
>
> 80. (Currently Amended) The method of ~~claim 60~~ **claim 55**, wherein the anti-IL-6R antibody and said immunosuppressant are administered with in a time interval.

Ex. 1003 ('052 Patent File History) at 326-328. Thus, at this point, claim 55 encompassed both the simultaneous and sequential administration schedules of dependent claims 79 and 80. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("It is axiomatic that a dependent claim cannot be broader than the claim from which it depends."). After the Examiner noted that "the administration schedule of the anti-IL6-R antibody and the immuno-suppressant does not have any surprising effect" (Ex. 1003 at 351), the applicant cancelled claims 79 and 80 (*id.* at 359-363). While the applicant also amended claim 55, none of the changes were directed to the administration schedule, and therefore claim 55 still encompassed administering the drugs either simultaneously or sequentially:

> 55. **(Currently Amended)** A method for treating **rheumatoid arthritis** ~~an IL-6 related disease~~, comprising administering an **effective amount of an** anti-IL-6 receptor antibody (anti-IL-6R **antibody**) ~~that inhibits binding of IL-6 to the IL-6 receptor by binding to the IL-6 receptor to block signaling of IL-6 biological activity into cells,~~ and **an effective amount of** methotrexate (MTX) to a patient **in need thereof** ~~requiring such a treatment~~, wherein **the anti-IL-6R antibody is a humanized PM-1 antibody** ~~said IL-6 related disease is rheumatoid arthritis~~.
>
> 56. - 83. (Cancelled)

Id. at 363. Claim 55 issued as claim 1 of the '052 patent without further amendment. *Id*. at 381. Because the issued claim is not limited to either simultaneous or sequential administration, a POSA would have understood "administering an . . . anti-IL-6 receptor antibody . . . and methotrexate (MTX)" to include both modes of administration, consistent with the specification. *See* Ex. 1002, ¶¶ 123-126.

C. "an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody)"

The term "effective amount" is not defined in the '052 patent specification. However, a POSA would have understood the plain meaning of this term, in the context of the specification, to include amounts known to be effective in treating RA, regardless of whether it has such an effect on the particular patient to whom the drug is administered. *See* Ex. 1002, ¶ 128. Several MRA dosages were known to be effective in patients with RA when administered intravenously, including 4 mg/kg and 8 mg/kg every four weeks (Ex. 1017 (Nishimoto Abstract-B) at 2); and

50 mg once or twice weekly (Ex. 1005 (Yoshizaki) at 10-11). Ex. 1002, ¶ 128. Each of these dosages is an "effective amount" within the meaning of the claim. *Id.* Moreover, the specification of the '052 patent discloses a range of dosages of anti-IL-6R antibody that show an anti-rheumatic effect when administered in combination with MTX:

> When administered in combination with MTX, the dosage of the anti-IL-6R antibody is typically, for example, in the case of the rheumatoid arthritis treatment, the dosage more than 0.5 mg/kg per week or the dosage showing an equivalent or more anti-rheumatic effect. For instance, when the intravenous administration is carried out once [every] four weeks, the dosage is from 0.02 to 150 mg/kg, preferably from 0.5 to 30 mg/kg, and more preferably from 2 to 8 mg/kg.

Ex. 1001 ('052 patent) at 3:55-62. Accordingly, the term "effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody)" should be construed to include at least the amounts reported as effective for treating RA, and the range of dosages identified by the '052 patent: *e.g.*, 0.02 to 150 mg/kg administered intravenously every four weeks. *See* Ex. 1002, ¶¶ 128-130.

D. "an effective amount of methotrexate (MTX)"

The term "an effective amount of methotrexate (MTX)" is also not defined in the patent specification. As with the previous term, a POSA would have understood the plain meaning of the term to include amounts known to be effective in treating RA, regardless of whether it has such an effect on the particular patient

to whom the drug is administered. *See* Ex. 1002, ¶¶ 131. A range of methotrexate dosages were known to be effective in RA patients. Specifically, amounts of 7.5 to 25 mg/body per week of methotrexate administered orally had been previously shown to be effective in patients with RA. *Id.*; Ex. 1020 (2000 PDR - Methotrexate) at 7 (stating that at a recommended starting dosage of 7.5 mg weekly, "[t]herapeutic response usually begins within 3 to 6 weeks"); Ex. 1007 (Matteson) at Table 1 ("Single dose of 7.5-25 mg orally, subcutaneously, or intramuscularly per week"); Ex. 1010 (2002 Guidelines) at 4. Each of these dosages is an "effective amount" within the meaning of the claim. Ex. 1002, ¶ 131.

Furthermore, the specification of the '052 patent provides a range of dosages for administration of methotrexate to treat RA. The specification states that:

> When MTX is used as the immunosuppressant, the dosage of MTX is, for example, from 1 to 100 mg/body/weeks or the dosage showing the MTX concentration in blood equivalent thereto, preferably from 4 to 50 mg/body/week or the dosage showing the MTX concentration in blood equivalent thereto, and particularly preferably from 10 to 25 mg/body/weeks or the dosage showing the MTX concentration in blood equivalent thereto.

Ex. 1001 ('052 patent) at 2:60-67. The specification also states that:

> The dosage of the immunosuppressant is, for example when MTX is combined for the rheumatoid arthritis treatment, for example in the case of orally administering, from 1 to 100 mg/body per week, preferably from 4 to 50 mg, and more preferably from 7.5 to 25 mg/body.

Id. at 4:43-47. Accordingly, the term "effective amount of methotrexate (MTX)" should be construed to include at least the amounts known to be effective for treating RA, and the range of dosages identified by the '052 patent: *e.g.*, 1 to 100 mg/body per week when administered orally. *See* Ex. 1002, ¶¶ 131-133.

IX. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claim 1 of the '052 patent under §§ 102 and 103 for the reasons explained in this petition, which may be summarized as follows:

Ground No	Claims and Basis
1	Claim 1 is anticipated by Yoshizaki
2	Claim 1 is anticipated by Nishimoto
3	Claim 1 is obvious over Nishimoto and Weinblatt 2003

Each of these grounds relies upon at least one reference that discloses treating RA with a combination of MRA and methotrexate. Notably, at no point

during prosecution did the Examiner consider any prior art disclosing the administration of MRA in combination with methotrexate for the treatment of RA.[5]

A. Ground 1: Claim 1 Is Anticipated By Yoshizaki

Yoshizaki is an article titled "Therapy of rheumatoid arthritis by blocking IL-6 signal transduction with a humanized anti-IL-6 receptor antibody," published in Springer Seminars of Immunopathology, Vol. 20, pg. 247-59 in 1998. Ex. 1005. Yoshizaki is a printed publication, and prior art to the '052 patent under pre-AIA

[5] An abstract authored by one of the named inventors of the '052 patent that discloses administering MRA and methotrexate to treat RA patients was identified on an IDS during prosecution. *See* Ex. 1003 at 81 (October 24, 2005 Information Disclosure Statement) (identifying Maini & Charisma Study Group, "A Double-Blind, Parallel Group, Controlled, Dose Ranging Study of the Safety, Tolerability, Pharmacokinetics and Efficacy of Repeat Doses of MRA Given Alone or in Combination With Methotrexate in Patients with Rheumatoid Arthritis," Abstract of Presentation at Eular, Jun. 2003, 2 pages). However, the abstract was not published more than one year prior to April 28, 2004, and so is not prior art under 35 U.S.C. § 102(b). Moreover, to the extent the abstract discloses the inventor's own work, it cannot be used as prior art under 35 U.S.C. § 102(a).

§ 102(b). Ex. 1005; Ex. 1002, ¶ 94. Yoshizaki was not before the Examiner during prosecution of the '052 patent.

1. *Disclosure of Yoshizaki*

Yoshizaki discloses treating RA by administering rhPM-1,[6] an anti-IL-6 receptor antibody, to patients that were "resistant to any conventional therapy." Ex. 1005 (Yoshizaki) at 10. The "conventional therapy" included "NSAIDs, DMARDS, MTX and maintenance doses of steroids." *Id.* Patients were treated with 1-50 mg intravenously of rhPM-1 administered once or twice weekly. *Id.* at 11. Yoshizaki reports that "[t]he results of this open study suggest that rhPM-1 is effective, safe and useful for the treatment of RA." *Id.*

One of the patients whose RA treatment is disclosed in Yoshizaki was a 67 year-old woman with severe RA. *Id*. This patient was still exhibiting signs of RA despite ongoing "conventional" treatments, including MTX. *Id*. Following administration of "50 mg rhPM-1 twice a week or once a week combined with the conventional treatment," her "clinical and laboratory abnormalities improved." *Id*. Yoshizaki's disclosure of treating this RA patient with a combination of rhPM-1 and methotrexate anticipates claim 1 of the '052 patent. *See* Ex. 1002, ¶¶ 127-135.

[6] As noted in above (see footnote 2), rhPM-1 is also known as MRA.

2. *Claim 1 Is Anticipated by Yoshizaki*

a. "[a] method of treating rheumatoid arthritis . . . in a patient"

The preamble is disclosed in Yoshizaki. In a section of the article titled "Treatment of RA with rhPM-1," Yoshizaki discloses a study "[t]o evaluate the therapeutic effects of rHPM-1" in which patients were treated with "conventional therapy," including methotrexate and then treated with rhPM-1. Ex. 1005 (Yoshizaki) at 10. A 67 year-old patient is described as having "severe RA treated with rhPM-1." *Id*. at 11. Thus, Yoshizaki discloses a method of treating rheumatoid arthritis in a patient. *See* Ex. 1002, ¶ 135.

Even if the preamble requires actual efficacy—which, as discussed above, it does not—Yoshizaki discloses that this treatment regimen led to an improvement in the patient's RA symptoms. Ex. 1005 at 11 ("The clinical and laboratory abnormalities improved after the rhPM-1 therapy."); Ex. 1002, ¶ 135.

b. "administering an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody) and an effective amount of methotrexate (MTX) to a patient in need thereof"

Yoshizaki discloses that a patient had previously been treated with a number of RA drugs, including methotrexate, and that intravenous administration of 50 mg rhPM-1 twice or once a week was combined with this "conventional treatment" to

treat her RA. *Id.* The result of this combined administration[7] was an improvement in clinical and laboratory abnormalities associated with RA. *Id.*

rhPM-1 (*i.e.*, MRA) is an anti-IL-6R antibody. *Id*. at 252. The 50 mg once or twice weekly intravenous dose of rhPM-1 is an "effective amount" within the meaning of claim 1. Yoshizaki discloses that administration of rhPM-1 of 50 mg rhPM-1 intravenously once or twice a week was "effective, safe and useful for the treatment of RA." *Id*. at 11. Other prior art similarly characterizes the Yoshizaki dosing regimen as providing therapeutic benefits for RA patients. *See*, *e.g.*, Ex. 1006 (Nishimoto) at 4 (citing Yoshizaki for the proposition that "drip infusion of 50 mg twice a week or 100 mg once a week not only caused a dramatic normalization of inflammatory markers such as CRP, fibrinogen and SAA, but also rapidly improved joint symptoms and general symptoms"). Hence, Yoshizaki discloses administration of an amount of anti-IL-6R antibody that is effective for

[7] As explained *supra* § VIII.B, the claimed method recites "administering" both methotrexate and MRA, and includes simultaneous administration of both drugs or administration of each drug sequentially. Therefore, this limitation is met regardless of whether the "combined administration" in Yoshizaki was simultaneous or sequential. Ex. 1002, ¶¶ 136-141.

treating RA, i.e., an "effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody)." Ex. 1002, ¶¶ 138-141.

Furthermore, a dosage of 50 mg once a week corresponds to an every four week dosage of 200 mg, or 2.8 mg/kg for an average 70 kg patient, well within the range of dosages that the '052 patent identifies as effective. Ex. 1001 ('052 patent) at 3:55-62 ("when the intravenous administration is carried out once [every] four weeks, the dosage is from 0.02 to 150 mg/kg"). A dosage of 50 mg twice a week corresponds to a dosage of 400 mg every four weeks, or 5.7 mg/kg for an average 70 kg patient—also well within the range of 0.02 to 150 mg/kg every four weeks described in the '052 patent.[8] Ex. 1002, ¶ 138. Indeed, the dosages disclosed in Yoshizaki are within the "more preferabl[e]" range of 2 to 8 mg/kg every four weeks disclosed in the '052 patent. Ex. 1001 at 3:55-62. The method of treatment

[8] Although Yoshizaki does not disclose the weight of this patient, even if one assumes extreme weights, the resulting dosage would still be an "effective amount." For example, with a 50 mg twice weekly dosage, an adult patient weighing only 75 lbs (34 kg) would receive a dosage of 2.5 mg/kg every four weeks, while a patient weighing 300 lbs (159 kg) would receive a dosage of 1.3 mg/kg every four weeks, each of which is still well within the range disclosed by the '052 patent as effective. Ex. 1002, ¶ 139.

disclosed by Yoshizaki therefore comprises administering an effective amount of an anti-IL-6R antibody. Ex. 1002, ¶¶ 138-141.

Yoshizaki also discloses that the patient was administered methotrexate in accordance with "conventional treatment," including methotrexate. Ex. 1005 (Yoshizaki) at 11. By the time of Yoshizaki, methotrexate was already a known efficacious RA treatment, with well-established dosing parameters. *See, e.g.*, Ex. 1021 (PDR 1991 - Methotrexate) at 6; Ex. 1022 (ACR 1996) at 5; Ex. 1010 (2002 Guidelines) at 4. A POSA would have therefore understood that "conventional treatment" with methotrexate to an RA patient means an amount of methotrexate known to be effective for treating RA, i.e., an "effective amount of methotrexate (MTX)." Ex. 1002, ¶¶ 136-137. Yoshizaki therefore discloses, and a POSA would have reasonably understood, that the 67 year-old patient was administered methotrexate in "an effective amount." *Id*.

Furthermore, at that time Yoshizaki was published, the conventional methotrexate treatment for RA was administration of between 7.5 and 20 mg per week, which is squarely within the range of methotrexate doses the '052 patent deems effective. *See, e.g.*, Ex. 1023 (1992 PDR - Methotrexate) at 6 (directing a starting dose of "[s]ingle oral doses of 7.5 mg once weekly" or "[d]ivided oral dosages of 2.5 mg at 12-hour intervals for three doses given as a course once weekly," and "adjusted gradually to achieve an optimum response, but not

ordinarily to exceed a total weekly dose of 20 mg"); Ex. 1022 (ACR 1996) at 5 (identifying the "usual dose" of methotrexate for treating RA as "7.5-15 mg per week"); Ex. 1010 (2002 Guidelines) at 4. Yoshizaki therefore discloses a method of treating RA comprising administering an "effective amount" of both an anti-Il-6 receptor antibody and methotrexate. Ex. 1002, ¶¶ 136-141; *see In Re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) (" ("[E]xtrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference.").

c. "wherein the anti-IL-6R antibody is a humanized PM antibody"

Yoshizaki discloses that, "[t]o prevent the induction of antibodies to mouse immunoglobulin in patients, remodelled human anti-IL-6R antibody(rhPM-1) was generated from mouse monoclonal anti-IL-6R antibody(PM-1) in CHO cells which were transfected with reshaped human γ_1-immunoglobulin gene inserted mouse CDR region of PM-1 as shown in Fig. 6." Ex. 1005 (Yoshizaki) at 8. Figure 6 (reproduced below) depicts the reshaped humanized antibody:

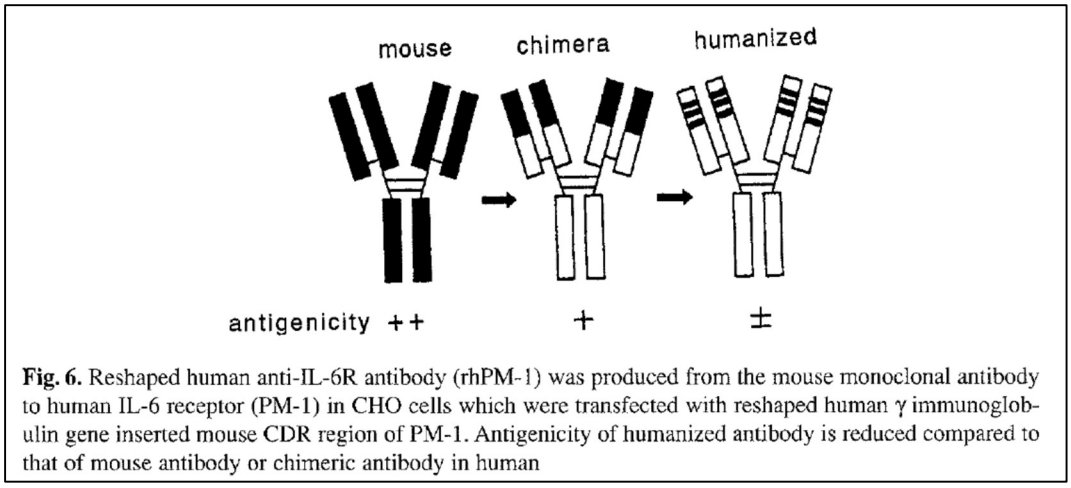

Fig. 6. Reshaped human anti-IL-6R antibody (rhPM-1) was produced from the mouse monoclonal antibody to human IL-6 receptor (PM-1) in CHO cells which were transfected with reshaped human γ immunoglobulin gene inserted mouse CDR region of PM-1. Antigenicity of humanized antibody is reduced compared to that of mouse antibody or chimeric antibody in human

Id. at 9. Thus, rhPM-1 is a humanized PM antibody. Ex. 1002, ¶ 142.

Yoshizaki thus discloses and enables each and every limitation of claim 1 of the '052 patent, and therefore anticipates the claim. Ex. 1002, ¶¶ 134-142.

B. Ground 2: Claim 1 Is 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. 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. Nishimoto was not before the Examiner during prosecution of the '052 patent.

1. *Disclosure of Nishimoto*

Nishimoto is generally directed to the role of the cytokine, IL-6, in the pathology of RA, and the use of IL-6 receptor antibodies in treating RA. Nishimoto explains that IL-6 "plays a major role in the formation of a state of

rheumatoid arthritis," is "increased in the blood and affected joints of rheumatoid arthritis patients," and "[b]locking the action of IL-6 may, therefore, offer itself as a novel treatment for rheumatoid arthritis." Ex. 1006 (Nishimoto) at 3-4.

Nishimoto describes the development of a particular IL-6 receptor antibody, MRA, which was expected to be useful for treating RA. *Id*. at 4. The article discloses a number of clinical studies in which MRA was administered intravenously to treat RA that established its safety and efficacy at various dosing amounts and frequencies. *Id*. at 4-5. As explained in Nishimoto, the early studies had shown that MRA "caused a dramatic normalization of inflammatory markers" and "rapidly improved joint symptoms and general symptoms" in patients who were resistant to methotrexate. *Id*. at 4. Further, as discussed in Nishimoto, subsequent studies established that MRA administered intravenously at 2 mg/kg, 4 mg/kg, or 8 mg/kg every two weeks provided clinical responses, "confirming excellent treatment efficacy." *Id*. at 5.

Nishimoto also discloses that "a placebo-controlled late phase II study was performed in Japan and on the basis of its results, treatment with 8 mg/kg of body weight of MRA every 4 weeks was recommended," and that "a phase II study of coadministration with methotrexate is currently underway." *Id*. The disclosure of this phase II study anticipates claim 1 of the '052 patent, as explained below. *See* Ex. 1002, ¶¶ 143-148.

2. *Claim 1 Is Anticipated by Nishimoto*

a. "[a] method of treating rheumatoid arthritis . . . in a patient"

The preamble is disclosed in Nishimoto. In a section of the article titled "Treatment of RA with humanized anti-IL-6 receptor antibodies," Nishimoto discloses that "a phase II study of coadministration with methotrexate is currently underway in several European countries." Ex. 1006 (Nishimoto) at 5. This disclosed coadministration of MRA and methotrexate is a method of treating RA in a patient. Ex. 1002, ¶ 144.

b. "administering an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody) and an effective amount of methotrexate (MTX) to a patient in need thereof"

Nishimoto discloses coadministration of MRA with methotrexate. Ex. 1006 (Nishimoto) at 5. MRA is an anti-IL-6R antibody. Ex. 1006 (Nishimoto) at 4 ("[A] humanized anti-IL-6 receptor antibody has been developed as an anti-cytokine therapy targeting IL-6 … This humanized anti-IL-receptor antibody … is hence referred to as myeloma receptor antibody (MRA).").

With respect to the amount of MRA (the anti-IL-6 antibody), Nishimoto describes the results of a series of clinical studies establishing the safety and efficacy of MRA at various dosage amounts. Ex. 1006 (Nishimoto) at 4-5. Nishimoto concludes this discussion by identifying a recommended dosage

regimen of treating RA of 8 mg/kg every four weeks, followed immediately by the disclosure of a phase II study combining MRA with methotrexate. *Id*. at 5. Therefore, Nishimoto discloses administering MRA in combination with methotrexate, according to the recommended dosage regimen, *i.e.*, 8 mg/kg administered intravenously every four weeks, which is an "effective amount" of MRA within the meaning of claim 1.[9] Ex. 1002, ¶ 138.

With respect to methotrexate, a POSA would have known that methotrexate was administered at a dose of between 7.5 mg and 25 mg once weekly to treat RA, whether as a monotherapy or in combination with other drugs. *See, e.g.*, Ex. 1002, ¶ 147; 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

[9] Prior clinical studies had found 8 mg/kg MRA administered intravenously every four weeks to be effective for treating RA. Ex. 1017 (Nishimoto Abstract B) at 2. Furthermore, the '052 patent itself identifies this regimen as "prefer[red]." Ex. 1001 ('052 patent) at 3:55-62 ("For instance, when the intravenous administration is carried out once [every] four weeks, the dosage is from 0.02 to 150 mg/kg, preferably from 0.5 to 30 mg/kg, and more preferably from 2 to 8 mg/kg.").

achieve an optimum 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 this same dosage range was used for clinical trials involving methotrexate in combination with other RA drugs. Ex. 1002, ¶ 147; 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). Therefore, a POSA would have reasonably inferred that the phase II study disclosed by Nishimoto involved administering methotrexate orally at a dose between 7.5 mg and 25 mg, which is an "effective amount" within the meaning of claim 1. Ex. 1002, ¶ 147; *see In Re Baxter Travenol Labs*, 952 F.2d at 390 (finding claims anticipated because "one skilled in the art would reasonably understand or infer" the presence of that limitation, notwithstanding that "there is no express disclosure" of that limitation in the prior art reference).

c. "wherein the anti-IL-6R antibody is a humanized PM antibody"

Nishimoto discloses that MRA, the anti-IL-6 receptor antibody administered in the phase II study, is a humanized anti-IL-6 receptor antibody. Ex. 1006 (Nishimoto) at 4 ("This humanized anti-IL-receptor antibody (reshaped human

PM-1: rhPM-1) was initially intended as a treatment for multiple myeloma, and is hence referred to as myeloma receptor antibody (MRA)."); Ex. 1002, ¶ 148.

Accordingly, Nishimoto discloses and enables each and every limitation of claim 1 of the '052 patent, and therefore anticipates the claim. Ex. 1002, ¶¶ 144-148.

C. Ground 3: Claim 1 Is Obvious Over Nishimoto and Weinblatt 2003

As set forth above for Ground 2, claim 1 of the '052 patent is anticipated by the disclosure in Nishimoto of an ongoing clinical trial involving administration of MRA and methotrexate for the treatment of RA. The claim would also have been obvious under 35 U.S.C. § 103 because a POSA would have been motivated to administer an effective amount of an anti-IL-6R antibody with an effective amount of methotrexate, and would have had a reasonable expectation of success in so doing. Ex. 1002, ¶¶ 149-162.

As of the earliest claimed priority date of the '052 patent, RA was known as a "common disease" and "one of the most common causes of disability." Ex. 1007 (Matteson) at 1; Ex. 1002, ¶ 150. Of the drugs known to treat RA, methotrexate was considered the "anchor therapy," and was typically administered orally at a dose of between 7.5 mg and 25 mg per week. Ex. 1007 (Matteson) at 2-3; *see also* Ex. 1008 (Weinblatt 2003) at 2 ("Over the last decade, methotrexate (MTX) has become the treatment of choice for rheumatoid arthritis (RA)."); Ex. 1010 (2002

Guidelines) at 4. More specifically, methotrexate was typically initiated at a dose of 7.5 mg per week, and titrated up to between 20-25 mg per week. Ex. 1007 (Matteson) at 2-3 (identify dose range of 7.5-25 mg orally); *see also* 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. 1002, ¶¶ 150-151.

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, ¶¶ 151, 155; 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 such monotherapy were found inadequate to fully control the RA symptoms once the optimal dose was reached, a second DMARD would be added to the regimen. Ex. 1002, ¶ 151; Ex. 1007 (Matteson) at 4; Ex. 1002, ¶ 144. 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, ¶ 152; Ex. 1014 (Amano) at 3. As with other DMARDs, these anti-cytokines were often used in combination with methotrexate, particularly in patients who had had an inadequate response to methotrexate alone. Ex. 1002, ¶ 152; Ex. 1014 (Amano) 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."). Indeed, 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.

By the earliest claimed priority date of the '052 patent, another anti-cytokine drug, MRA—an IL-6 receptor antibody—was reported to be safe and effective for treating RA. Ex. 1017 (Nishimoto Abstract-B) at 2. Specifically, the prior art disclosed a phase II study involving intravenously administering either placebo, 4 mg/kg, or 8 mg/kg MRA to RA patients resistant to DMARD therapy every four weeks for a total of twelve weeks in order to evaluate MRA's safety and efficacy, and to establish an optimal dose. *Id*. The study found that "treatment with MRA was well tolerated and significantly reduced the disease activity in patients with RA in a dose-dependent manner." *Id*. 78.2% of patients in the 8 mg/kg group achieved an ACR20 response (the primary endpoint of the study), which was statistically significantly higher than both the placebo group and the 4 mg/kg group. *Id*. 16.4% of patients in the 8 mg/kg group achieved an ACR70 response; again, statistically significantly higher than the placebo group. *Id*.[10]

[10] ACR20 and ACR70 were standard criteria for evaluating clinical response to RA treatment. Ex. 1009 (1999 FDA Guidance) at 6; Ex. 1002, ¶ 153. An ACR20 response requires a 20% improvement in tender and swollen joint counts, as well as a 20% improvement in three of the following five criteria: patient and physician global assessment, pain, disability, and an acute phase reactant. Ex.

Against this backdrop, Nishimoto summarized several clinical studies (including the study reported in Nishimoto Abstract B) establishing the safety and efficacy of MRA in treating RA patients when administered intravenously, including in patients who had had an inadequate response to methotrexate. Ex. 1006 (Nishimoto) at 4-5. Based on the results of these studies, Nishimoto concluded that MRA had "excellent treatment efficacy" for RA patients. *Id*. at 5. Nishimoto further disclosed that, on the basis of these studies, "treatment with 8 mg/kg of body weight MRA every 4 weeks was recommended." *Id*. at 5. Although acknowledging that, unlike infliximab, MRA "does not ***require*** such coadministration of methotrexate," Nishimoto disclosed an ongoing phase II clinical study "of coadministration with methotrexate." *Id*. (emphasis added).[11]

1009 at 3 n.2. ACR70 is analogous to ACR20, except it requires a 70% improvement rather than a 20% improvement. Ex. 1009 at 3; Ex. 1002, ¶ 153.

[11] 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, ¶ 157; Ex. 1008 (Weinblatt 2003) at 2 ("To

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. Ex. 1002, ¶¶ 155-157. These practices are exemplified in Weinblatt 2003. Weinblatt 2003 discloses that methotrexate is the "treatment 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, ¶ 155. Weinblatt 2003 illustrates the usefulness of this approach through a clinical trial involving administering the anti-cytokine drug, adalimumab, in combination with RA patients' existing methotrexate regimens. Ex. 1008 (Weinblatt 2003) at 2; Ex. 1002, ¶ 155. These 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. Ex. 1008 (Weinblatt 2003) at 2-4. When adding this additional agent, the patients' existing methotrexate regimens (*i.e.*, 10 to 25 mg oral methotrexate once per week) were maintained. *Id*. at 2 ("Dosing

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enhance the clinical response, MTX is frequently combined with one or more other traditional . . . DMARDs.").

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.

In view of the recent establishment of MRA as a viable RA treatment and Weinblatt 2003's disclosure that RA drugs should be added to methotrexate for patients who have not fully responded to methotrexate, a POSA would have been motivated to follow the express teaching of Nishimoto by administering a combination of effective amounts of MRA and methotrexate to treat RA patients who had inadequately responded to methotrexate alone. Ex. 1002, ¶ 156. The motivation to administer MRA in combination with methotrexate would have been further supported by Amano's disclosure that anti-IL-6R antibodies were "expected to be used in combination with MTX," as well as the FDA's assertion that it was "inevitable that new agents will be used in combination with methotrexate." *Id*.; Ex. 1014 (Amano) at 8; Ex. 1009 (1999 FDA Guidance) at 21.

Even if Nishimoto did not expressly disclose the amounts or frequencies of administration of the combined regimen, selection of these parameters would have been obvious. Ex. 1002, ¶¶ 156, 158-160. With regard to MRA, Nishimoto itself

discloses that the recommended dosage regimen to treat RA is 8 mg/kg administered intravenously every four weeks. Ex. 1006 (Nishimoto) at 5. 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, ¶ 159.

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, ¶ 160; 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. Indeed, that regimen encompasses 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 methotrexate orally every week, each of which is an "effective amount" within the meaning of claim 1 of the '052 patent. Ex. 1002, ¶¶ 155-160.

A person of ordinary skill in the art would 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." Ex. 1002, ¶ 161; Ex. 1007 (Matteson) at 3-4; *see also* 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."). Moreover, a POSA would have been aware of Yoshizaki's disclosure of the successful treatment of a RA patient by intravenous administration of MRA in combination with conventional methotrexate treatment. *See* Section IX.A; Ex. 1002, ¶ 161. And, as explained above, the track record of success in combining methotrexate with other anti-cytokine drugs would have led a POSA to reasonably expect similar success for an anti-IL-6R antibody in combination with methotrexate. Ex. 1002, ¶ 61. 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 treat a patient with rheumatoid arthritis. *Id.*; *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 and Weinblatt 2003 to administer a combination of an effective amount of MRA and an effective amount of methotrexate to a patient to treat RA.[12]

Petitioners are not aware of any relevant secondary considerations that have a nexus to, or are commensurate in scope, with the challenged claim. The specification of the '052 patent states that "it has not been known that synergistic effects can be obtained by the combination of anti-IL-6R antibody with immunosuppressants such as methotrexate (MTX) in the treatment of IL-6 related diseases." Ex. 1001 ('052 patent) at 1:62-66. But, this cryptic allegation

[12] Even if the preamble were construed to require efficacy, the claim is still obvious because, as discussed herein, a POSA would have been motivated to administer the claimed treatment regimen to treat RA, and would have reasonably expected the treatment to be successful. *See supra* 34-43.

notwithstanding, it is entirely unclear what "synergistic effects," if any, are allegedly obtained when combining an anti-IL-6R antibody with an immunosuppressant to treat IL-6 related diseases. Particularly in the absence of a specific allegation by Patent Owner to which Petitioners can reasonably respond, consideration of secondary considerations at this stage of the proceeding would be premature. *See Umicore AG & Co. KG v. BASF Corp.*, IPR2015-01124, Paper 8 at 22 (P.T.A.B. Nov. 2, 2015) (withholding consideration of secondary considerations until after institution because, "[a]t this stage of the proceeding, the record regarding such secondary considerations is incomplete, and Petitioner has not had the ability to fully respond to the specific arguments raised by Patent Owner in the Preliminary Response."); *see also Eli Lilly & Co. v. The Trustees of the Univ. of Pa.*, IPR2016-00458, Paper 7 at 21-22 ("[I]t would be premature at this stage of the proceeding to deny institution based on the secondary considerations evidence, or the alleged failure of Petitioner to address adequately such evidence. We will permit the parties to develop a more complete record during discovery before considering such evidence.").

Petitioners note that, during prosecution of U.S. Patent No. 10,744,201 (which claims priority to the '052 patent), the applicants alleged that "synergistic and unexpected results" supported the patentability of the then-pending claims; however, those alleged results were admittedly limited to the one specific dose of

MRA required by all of those claims, 8 mg/kg. *See* Ex. 1004 ("'201 Patent File History") at 770) (May 15, 2020 Amendment) ("***Combining MTX with 2 mg/kg or 4 mg/kg MRA*** resulted in an ACR70 response in 14% and 12.2%, respectively, and ***did therefore, not improve the likelihood of achieving an ACR70 response compared to MTX alone***. Accordingly, it was highly unexpected that administering MTX with 8 mg/kg MRA to the patients would result in that 36.7% of the patients had an ACR70 response compared to the 16.3% achieved with MTX alone as shown in Table l of the instant specification … Accordingly, the data disclosed in the present application showed that synergistic and unexpected results were achieved with the method recited by the present claims.") (emphasis added). The sole claim of the '052 patent recites any "effective amount" of MRA and methotrexate, and therefore encompasses the very same 2 mg/kg and 4 mg/kg dosing regimens Patent Owner asserted ***did not exhibit "synergistic" effects*** with methotrexate. Hence, even if the alleged "synergistic" effects were unexpected, they cannot support the patentability of this claim because a "showing of unexpected results must be commensurate in scope with the claimed range." *In re Peterson*, 315 F.3d 1325, 1330-31 (Fed. Cir. 2003).

Petitioners reserve the right to respond to any allegations of secondary considerations.

X. SECTION 325(D) SHOULD NOT PREVENT INSTITUTION

None of the references relied upon herein were before the Examiner during prosecution of the '052 patent. Moreover, none of the references relied upon by the Examiner disclosed the combination of an anti-IL-6 receptor antibody and methotrexate for the treatment of RA. Accordingly, Section 325(d) should not prevent institution.

XI. CONCLUSION

For the reasons set forth above, Petitioners respectfully submit that they have established a reasonable likelihood of success with respect to the challenged claim and request that trial be instituted and the challenged claim cancelled.

Dated: 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. 7,521,052 complies with the type-volume limits of 37 C.F.R. §42.24(a)(1)(i) because it contains 9,569 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. 7,521,052** and the exhibits cited therein by Federal Express Next Business Day 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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