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 7,521,052

PATENT OWNER'S RESPONSE

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I. INTRODUCTION

The single claim of U.S. Patent No. 7,521,052 covers treatment of rheumatoid arthritis ("RA") through a combined regimen of methotrexate and an anti-IL-6 receptor antibody. Relying on the unexamined and unrebutted testimony of Petitioners' expert, Dr. Thomas Zizic, the Board's Institution Decision found it reasonably likely that one of Petitioners' references, *Yoshizaki*, disclosed the claimed regimen before the April 2003 priority date and that two others—*Nishimoto 2002* and *Weinblatt 2003*—render the claim obvious.

At deposition, however, Dr. Zizic walked back much of the testimony the Board credited. And on the material points where Dr. Zizic stood by his opinions, Patent Owner's distinguished expert, Dr. Gregg Silverman of the NYU Langone Center, explains at length why Dr. Zizic is wrong. In particular, Dr. Silverman details: (i) why *Yoshizaki*, a report of experimental use in the mid-1990s, does not actually disclose the treatment of a patient with methotrexate and Patent Owner's experimental antibody, and (ii) why *Nishimoto 2002* and *Weinblatt 2003* would not have provided the POSA with any reasonable expectation the claimed combination would be successful by the standard both experts agree success should be measured.

For these reasons, the Board should confirm the challenged claim.

II. BACKGROUND

A. Rheumatoid Arthritis

Rheumatoid arthritis ("RA") is a crippling disease that afflicts an estimated one percent of the adult population worldwide. Ex. 2026 (*Kelley's 2001*) at 32. It is an autoimmune disorder that inflicts severe joint swelling and pain in the hands and feet of a patient and can worsen into destruction of the bone and cartilage in the joints, leading to deformities and causing decreased mobility and other serious handicaps. Because they are immunocompromised, RA patients have an increased risk of infection and serious heart disease. Ex. 2036 (Declaration of Gregg J. Silverman, M.D.), ¶ 9 (*Silverman Decl.*).

Despite years of study, the precise pathogenesis of rheumatoid arthritis still remains unknown. Unlike with many other diseases, there is not a single biomarker that informs a doctor whether her patient is suffering from RA. Clinical diagnosis and measurement of RA activity is based on a complete evaluation by the physician of factors, including the patient's demographic features, counts of involved joints, distribution of tender and swollen joints, and the absence of other obfuscating diagnoses and other conditions that have some overlap of clinical features. *Id*. ¶ 10.

There is no known cure for RA. Instead, "[t]he goal of treatment is to arrest the disease and achieve remission," but drug-free remission "occurs infrequently."

Ex. 1010 (*2002 Guidelines*) at 14. Consequently, rheumatologists treating RA patients look to control or limit the extent of their patients' joint damage; relieve their often-excruciating pain; prevent loss of function; and do all of this while closely monitoring the toxicities inflicted by the most common drugs used to treat the disease. Ex. 2036 (*Silverman Decl*.), ¶ 11.

Treatment goals are measured by the improvement of these conditions. The most common measurement tool is a scale developed by the American College of Rheumatology ("ACR") that measures improvement in seven aspects of disease activity. An ACR20 score, for example suggests that "the number of swelling joints and the number of pain joints are improved by 20% or more and improvement by 20% or more is observed in three out of the five remaining items[.]." Ex. 1001 (*'052 Patent*) at 16:54-57.

B. RA Treatments

As of the priority date, rheumatologists used four different types of drugs to treat RA patients:

-- Non-steroidal anti-inflammatory drugs ("NSAIDs") to relieve RA pain and reduce inflammation, swelling, and fever;

-- Steroids to reduce the inflammation levels that make RA joints swollen, stiff, and painful;

-- Traditional "disease-modifying antirheumatic drugs" ("DMARDs"), typically synthetic, small-molecule medicines that had been available to doctors for one purpose or another for some time; and

-- Biologic DMARDs, a new class of large-molecule, protein-based medicines produced through recombinant technologies.

The big difference between NSAIDs and steroids on the one hand, and the two types of DMARDs on the other, is that latter could slow disease progression while the former could not. Ex. 2036 (*Silverman Decl.*), ¶ 12.

1. NSAIDs, Steroids, and Traditional DMARDs

As of April 2003, the most common NSAIDs administered to RA patients were ibuprofen and naproxen. Clinicians would prescribe only one NSAID, switching one for another if the patient was unresponsive. When physicians included steroids in the treatment regimen, the most common were prednisone or solumedrol. Ex. 2036 (*Silverman Decl.*), ¶ 13.

The treatment regimen for a "majority of patients with newly diagnosed RA" also included "DMARD therapy within 3 months of diagnosis." Ex. 1010 (*2002 Guidelines*) at 2. The list of traditional DMARDs in use at the time was large and included hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine, D-penicillamine, gold (oral and intramuscular), minocycline, cyclosporine, and staphylococcal protein A immunoadsorption. *Id.* at 4; Ex. 2036

(*Silverman Decl.*), ¶¶ 14-15. Though DMARDs could slow or stall the progression of RA, eventually "adverse events emerge or [the] drugs become ineffective," so switching drugs was common. It was estimated that "50-60% of patients treated with a DMARD require[d] a subsequent course with another drug." Ex. 2001 (*Aleatha 2002*) at 3.

Among the traditional DMARDs, MTX—a drug initially developed as a chemotherapy agent —was widely prescribed even though very little was known about how MTX worked to alleviate RA symptoms, and why so many RA patients did not respond to it. Ex. 2036 (*Silverman Decl.*), ¶ 16; Ex. 2012 (*Frei 1975*) at 1; Ex. 2014 (*Kremer 1994*) at 1; Ex. 2015 (*Kremer 1998*) at 1-3. MTX was well-known to cause increased toxicity (particularly liver toxicity) with escalating dosages and contribute to additive toxicity in combination with other hepatoxic or immunosuppressive drugs. Ex. 2036 (*Silverman Decl.*), ¶¶ 16-17 (citing Ex. 2015 (*Kremer 1998*); Ex. 1020 (*2000 PDR – Methotrexate*); Ex. 2021 (*Rheumatrex Label 2003*); Ex. 2006 (*Conaghan 1995*); Ex. 2016 (*Kremer 2002*)). MTX had even been associated with deaths "in the treatment of . . . Rheumatoid Arthritis." Ex. 1020 (*2000 PDR – Methotrexate*) at 3.

2. Biologic DMARDs

In the 1990s researchers looking to develop new therapies employed emergent recombinant protein technology to develop monoclonal antibodies and

other biologic agents to treat RA. These prospective biologic treatments targeted various cytokines associated with joint inflammation, including tumor necrosis factor alpha ("TNFα"), interleukin-1 ("IL-1"), and interleukin-6 ("IL-6"). Ex. 2002 (*Bulpitt 1999*) at 1-2. But biologic therapy in RA was a nascent and unpredictable field at this time, and the RA landscape was dotted with various biologics that initially had been pursued with enthusiasm but eventually failed. Ex. 2013 (*Keystone 2003*) at 15:253-258; Ex. 2036 (*Silverman Decl.*), ¶ 18. As one article from the period explained: "The result of cytokine manipulation is far from predictable." Ex. 2002 (*Bulpitt 1999*) at 2.

Because these cytokines were known to be "proinflammatory," scientists theorized that targeting them could help patients suffering from crippling inflammation. Etanercept, a fusion protein that targeted TNFα, in 1998 became the first biologic to receive FDA approval to treat RA. Ex. 2026 (*Kelley's 2001*) at 5-6. FDA subsequently approved two monoclonal antibodies targeting the same cytokine: the chimeric antibody infliximab in 1999 and the fully human antibody adalimumab in 2002. Ex. 1013 (*2001 PDR – Remicade*); Ex. 1033 (*2002 Humira FDA Label*) at 7, 14, 16. Around the same time FDA approved anakinra, a biologic that targeted a different proinflammatory cytokine called interleukin-1 ("IL-1"). Ex 2026 (*Kelley's 2001*) at 23; Ex. 2036 (*Silverman Decl.*), ¶ 18.

Development of a biologic targeting IL-6 proceeded more slowly and in the face of skepticism that it would be as successful. Unlike TNFα, IL-6 was understood to have both "pro- and anti-inflammatory activity," meaning that therapies targeting this cytokine possibly could aggravate RA symptoms rather than mitigate them. Ex. 2026 (*Kelley's 2001*) at 5-6, 25. Antibodies targeting IL-6 directly might actually extend that cytokine's activity. *Id.* at 25. This meant that inhibiting IL-6 directly, for example, the same way infliximab and adalimumab target TNFα, could in theory actually worsen the patient's RA symptoms. *See id.* A number of experts had concluded that inhibiting IL-6 had "fallen by the wayside" as a potential method for treating RA. Ex. 2003 (*Calabrese 2003*) at 6; *see also* Ex. 2036 (*Silverman Decl.*), ¶ 32; Ex. 2017 (*Elliott 1995*) at 15. And when early development of tocilizumab commenced, those in the field were skeptical that a drug employing an IL-6 blockade could successfully treat RA given its broad mechanism of action and other biological differences from TNFα inhibitors. Ex. 2036 (*Silverman Decl.*), ¶¶ 20, 31-33.

Nevertheless, Chugai persisted in developing the antibody later known as tocilizumab, a humanized antibody that did not bind directly to IL-6 but instead to the receptor to which IL-6 would otherwise bind to trigger its biological function. After years of testing, Actemra®, Chugai's product comprising tocilizumab,

received FDA approval in 2010 and has become an important tool for clinicians treating patients with RA. Ex. 2036 (*Silverman Decl.*), ¶ 33.

3. Combination Therapies

Starting in the mid-1990s, clinicians began to administer treatment regimens that included two (and on occasion) three DMARDs with increasing frequency. A Mayo Institute publication in 2000 estimated that about half of RA patients being treated by rheumatologists were prescribed DMARD combinations. Ex. 1007 (*Matteson 2000*) at 4. The other half typically received DMARD monotherapy. *See* Ex. 2037 (*Zizic Tr.*) at 73:14-18; Ex. 2036 (*Silverman Decl.*), ¶ 21.

DMARDs that worked as monotherapies, however, did not always work in combination, and researchers who studied the practice published reports expressing skepticism. Ex. 2036 (*Silverman Decl.*), ¶¶ 22-25. In the mid-1990s, "reports of clinically useful combinations [of individually proven DMARDs] are rare," Ex. 2006 (*Conaghan 1995*) at 1, including combinations where MTX was one of the DMARDs. A study combining azathioprine and MTX "was no more effective than either of the agents alone." Ex. 2039 (*Willkens 1995*) at 7. A study combining MTX and auranofin "did not demonstrate any advantage in efficacy over single-drug treatment within the time frame of th[e] study." Ex. 2024 (*Williams 1992*) at 1. And studies combining sulfasalazine and methotrexate showed "no significant differences in efficacy," while also demonstrating "a trend suggesting a more toxic

profile of th[e] combination." Ex. 2040 (*Haagsma 1997*) at 1; Ex. 2041 (*Dougados 1999*) at 5. As one review article concluded: "Combination therapy, as it has been used in recent clinical trials, does not offer substantial improvement in efficacy, but does have higher toxicity than single drug therapy." Ex. 2010 (*Felson 1994*) at 1.

Once biologic DMARDs started showing safety and efficacy in the latter half of the 1990s, researchers began testing whether efficacy could be improved and safety maintained by administering them in combination with MTX. These efforts met with uneven success. Ex. 2036 (*Silverman Decl.*), ¶¶ 26-27. Trials combining MTX with the new TNFα inhibitors—infliximab, etanercept, and adalimumab—were successful in that patients receiving them generally fared better than on MTX alone without significantly elevated toxicity. Ex. 1008 (*Weinblatt 2003*) at 1; Ex. 1015 (*Maini 1998*) at 1; Ex. 2023 (*Weinblatt 1999*) at 1. In fact, infliximab was determined to require co-administration of MTX, an immunosuppressant, to block a dangerous immune reaction to infliximab itself. Ex. 1015 (*Maini 1998*) at 2.

But as with combinations of traditional DMARDs, combinations involving other biologic DMARDs did not always work. Ex. 2036 (*Silverman Decl.*), ¶¶ 28-30. Researchers focusing on an anti-CD5 immunoconjugate and an anti-CD4 antibody to remove targeted immune cells as potential RA therapies tested each of

them in combination with MTX, and both studies showed no significant benefit compared to MTX monotherapy. Ex. 2018 (*Moreland 1996*) at 3. They concluded that the combination "raises the concern of increasing the risk of serious adverse events including opportunistic infections or the development of malignancies." *Id.* at 4. Another study testing the combination of infliximab and leflunomide found that while the regimen showed "a substantial improvement in RA disease activity," there was such a "high frequency of adverse events" that more than half the patients enrolled had to drop out. Ex. 2066 (*Kiely 2002*) at 1 (adverse events "were common and in some cases severe").

III. THE '052 PATENT

The '052 Patent contains a single claim:

> 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.

Ex. 1001 (*'052 Patent*) at 22:31-35. The specification supporting it describes data collected during a phase II clinical trial (CHARISMA) that the inventors designed to further explore tocilizumab monotherapy dosages, evaluate the effectiveness and safety of a tocilizumab and MTX combination, and determine the safe and

effective dosages of MTX and tocilizumab when combined. Ex. 1001 (*'052 Patent*) at 16:10-18:67.

The trial divided 359 patients into seven groups, receiving various dosages MRA (2, 4, or 8 mg/kg four times total at four-week intervals), various dosages of MRA with 10-25 mg of MTX, or a placebo with MTX. *Id.* at 16:34-42. The inventors assessed patient improvement using the ACR scale. The results were as follows:

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 17:1-14. The trial "confirmed" the "safety of MRA . . . in both MRA monotherapy and for MRA combined with methotrexate." *Id.* at 18:61-67. The results showed that administering the combination did not produce frequent adverse reactions, nor did MRA often cause the immunogenic response other biologics routinely triggered. *Id.* at 18:19-33, 54-59. In terms of dosing, the study

showed that for patients hoping to achieve a "Major Clinical Response" (ACR70), combination therapy of 8 mg/kg of MRA combined with 10-25 mg/week MTX led to dramatic improvement. *Id.* at 17:15-27.

The '052 Patent issued from an application filed on April 28, 2004, and claims priority to an application filed in Great Britain on April 28, 2003.

IV. CLAIM CONSTRUCTION

Claim terms "are generally given their ordinary and customary meaning" as understood by the person of ordinary skill in the art ("POSA").[1] *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Petitioners and Patent Owner disagree on the construction of two terms.[2]

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

[1] Patent Owner does not dispute the definition of the POSA offered by Petitioners. *See* Ex. 2036 (*Silverman Decl.*), at ¶¶ 46-52.

[2] As the Board acknowledged in its Institution Decision, Patent Owners do not contest Petitioners' proposed construction of the phrase "[a] method for treating rheumatoid arthritis . . . in a patient." Decision at 6.

The Board's Institution Decision rejected Petitioners' proposed construction of this limitation to cover administering both drugs to a patient regardless of whether they were part of the same treatment regimen. Decision at 9. This is plainly correct for all the reasons the Board stated. It remains unclear, however, whether Petitioners intend to press their alternative construction. At his deposition, Dr. Zizic insisted that Board erred on this point and that claim 1 covers *any* treatment of a patient with both MTX and an anti-IL-6 receptor antibody, regardless of how much time passed between:

> **Q.** And how much time can pass between the administration of the one and administration of the other?
>
> **A.** Well, the patent wasn't clear. It didn't state it here. But even on the file history, it was just stated, as I recollect, that the administration could be simultaneously or with the time interval. There was no time interval specified in that dependent claim.
>
> **Q.** So it could be any amount of time, in your opinion?
>
> **A.** Well, according to the patent. . . .
>
> **Q.** So if someone got methotrexate on day one as a monotherapy and then got tocilizumab 500 days later as a monotherapy, that would be within the claim, in your opinion?

> **A.** It would be within the claim because it wasn't specified within the de[pendent] claims of the original patent submission.
>
> **Q.** What if a patient were prescribed methotrexate and then it was found to be either ineffective or toxic and was discontinued, and a year later, the doctor prescribes tocilizumab, is that within the claim? . . .
>
> **THE WITNESS**: Again, I mean, I can see what you're trying to say but that isn't what the patent history of this claim is. It doesn't specify. It doesn't preclude that situation from being within that. It just says within a time interval, is my recollection. And I think I'm right.

Ex. 2037 (*Zizic Tr.*) at 166:18-168:8.

As Patent Owner showed in its Preliminary Response, and as the Board recognized, the construction Dr. Zizic applies cannot be correct. The '052 Patent arises from a trial assessing the "potential efficacy of repeated intravenous doses of MRA, both as monotherapy and in combination with methotrexate." Ex. 1001 (*'052 Patent*) at 16:15-23. The specification makes it clear that even those patients in the "MRA alone" cohorts received MTX before the study began. *Id.* at 16:15-24, 17:15-26. They had to—the clinical trial protocol required that *all* study participants had been treated with MTX for at least six months prior to enrollment. *Id.* at 16:26-33. Only the patients who *continued* to receive MTX during the

course of the study, in the same treatment regimen as MRA, fell within the "MTX-combined groups." *Id.* Since the "specification [] draw[s] a direct contrast between" monotherapy and combination therapy, a construction where the monotherapy cohorts comprise a null set cannot be correct. *Baran v. Med. Device Tech., Inc.*, 616 F.3d 1309, 1315-16 (Fed. Cir. 2010); *see also ERBE Elektromedizin GmbH v. Int'l Trade Comm'n*, 566 F.3d 1028, 1034 (Fed. Cir. 2009) (generally improper to "construe claim language to be inconsistent with the clear language of the specification"). Accordingly, the Board should construe this claim to require that the anti-IL-6 receptor antibody and MTX be administered as part of the same treatment regimen.

B. "an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody)"; "an effective amount of methotrexate (MTX)"

With respect to the other term, the Board preliminarily credited Dr. Zizic's declaration testimony and construed "effective amount" to mean the effective monotherapy amount of each drug.

> Petitioners provide expert testimony that 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 any one particular patient to whom the therapy is administered. Pet. 18–20 (citing Ex. 1003 ¶¶ 128, 131). Based on the current record, we find that unrebutted testimony persuasive.

See Decision at 12; *see also id*. at 11 ("claim does not recite or refer to any required *combined effectiveness amount*") (emphasis in original).

The Board should revisit this question based on the different record before it, in particular Dr. Silverman's declaration and Dr. Zizic's deposition testimony. According to both experts, the POSA would not consider the dose of a drug used in combination with another to be "effective" unless it was expected to produce results with an acceptable level of toxicity, something that cannot be assessed until the two drugs are combined as the claim requires. Ex. 2036 (*Silverman Decl.*), ¶¶ 54-56; Ex. 2037 (*Zizic Tr.*) at 144:14-145:6.

Claim 1 requires that the claimed combination is "effective" for "treating RA" in "a patient in need thereof." Ex. 1001 (*'052 Patent*) at 22:31-35. As Dr. Silverman explains, the POSA would have understood this claim to require the administration, to a patient suffering from RA, amounts of MRA and MTX that in combination would be expected to reduce the patient's symptoms, inhibit disease progression, or both, with acceptable toxicity. Ex. 2036 (*Silverman Decl.*), ¶ 54. In his deposition, Dr. Zizic agreed that a successful RA treatment must take toxicity into account:

> **Q.** So in your opinion, what makes an RA treatment successful?
>
> **A.** You mean, what outcome . . . do I measure success by[?] . . . [W]ell, reduction of pain and symptoms and prevention of damage to the joints as an overall goal doing

> both of those, preventing long-term damage and disability and also to make them more functional and better quality of life.
>
> **Q.** Okay. And at an acceptable level of toxicity?
>
> **A.** Oh, of course.

Ex. 2037 (*Zizic Tr.*) at 144:14-145:6.

Based on this common ground, the POSA would have understood "effective amount" to mean, not the effective monotherapy amount of each drug, but the amount that was expected to be effective when used together. As Dr. Silverman explains: "a treating physician would understand that dosages of two drugs that are safe and efficacious alone could have significant side effects when used in combination and, in fact, be toxic in combination." Ex. 2036 (*Silverman Decl.*), ¶ 55.

This understanding of the claim's plain language comports with the specification's discussion of the inventors' work. In particular, they describe how, in the CHARISMA trial, "effectiveness of MRA" was assessed not just for "MRA monotherapy" but also "for MRA combined with methotrexate," and furthermore that "s*afety and tolerability*" were a critical part of their assessment. They concluded that "safety of MRA was confirmed in both MRA monotherapy and for MRA combined with methotrexate." Ex. 1001 (*'052 Patent*) at 18:65-67.

"[T]he term 'effective amount' has a customary usage." *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1277-78 (Fed. Cir. 2003). It is "the amount that is effective to accomplish the purpose of the claim." *Sanofi v. Lupin Atlantis Holdings S.A.*, No. 15-415-RGA, 2016 WL 5842327, at *4 (D. Del. Oct. 3, 2016); *see also Abbott Labs.*, 334 F.3d at 1277-78. As the testimony of both sides' experts confirms, the POSA would not understand an "effective" dose to be one that treated RA but subjected the patient to toxicity a treating physician would not tolerate. For this reason the Board should withdraw its tentative construction and enter the one Patent Owner has proposed: "effective amount[s]" of each drug are those that relieve RA symptoms without undue toxicity when administered in the same treatment regimen.

V. ARGUMENT

A. Ground 1: *Yoshizaki* Does Not Disclose a Combination Treatment with Effective Amounts of the Two Drugs

The Board's Institution Decision tentatively determined that *Yoshizaki*, a 1998 reference reporting on the treatment of RA patients in Japan, anticipates claim 1. The Board said it found no "ambiguity that the patient described by Yoshizaki received MTX along with rhPM-1," and credited Dr. Zizic's "currently unrebutted expert testimony" that this patient received what the POSA would consider "effective amounts" of the two drugs. Decision at 19, 21.

For the reasons detailed below, including Dr. Silverman's testimony and Dr. Zizic's concessions at his deposition about what constitutes "conventional treatment," the Board should revisit this question and reject Ground 1. Ex. 2036 (*Silverman Decl.*), ¶¶ 58, 61.

1. *Yoshizaki*

Yoshizaki discloses the use of "rhPM-1" to treat RA patients in Japan from 1995-1997. Ex. 1005 (*Yoshizaki 1998*); Ex. 2036 (*Silverman Decl.*), ¶ 59. RhPM-1 is an early designation for the humanized antibody later renamed tocilizumab.

The researchers who conducted the study observed that "conventional therapy with non-steroid anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) combined with methotrexate (MTX) and/or steroids is still unsatisfactory," so that "new therapeutic strategies need to be defined," Ex. 1005 (*Yoshizaki 1998*) at 6. *Yoshizaki* proposed a therapeutic approach to "interfere with the IL-6 signal transduction pathway" by "blocking [the] IL-6 signal with [an] anti-IL-6R antibody." *Id.* at 6-7.

The patients included in the study were patients with "severe RA who were resistant to any conventional therapy." *Id.* at 10. They suffered chronic RA symptoms—including "continuous arthralgia with or without joint deformity, swollen joints and morning stiffness, combined with systemic or general fatigue,

low appetite, loss of weight and subfever"—"despite treatment with NSAIDs, DMARDs, MTX, and maintenance doses of steroids." *Id.*

As the Board recognized, Petitioners' anticipation argument relies entirely on two sentences in Figure 8, where the authors describe the treatment received by one of the patients:

> A 67-year-old woman with severe RA given NSAIDs, DMARDs, MTX and 15 mg predomizolone [sic][3] received 50 mg rhPM-1 twice a week or once a week combined with the conventional treatment. The clinical and laboratory abnormalities improved after the rhPM1 therapy.

Id. at 11; Ex. 2036 (*Silverman Decl.*), ¶ 60.

2. Analysis

For multiple reasons, *Yoshizaki* does not anticipate claim 1.

[3] Patent Owners "agree with the Board that the reference to 'predomizolone' no doubt is an error and that the authors probably intended to say 'prednisolone,' a common steroid used in the treatment of RA patients." *See also* Ex. 2036 (*Silverman Decl.*), ¶ 60 n.2 (citing Decision at 16 n.6).

a. "Conventional Treatment" of RA Does Not Always Include MTX.

The reference to this patient receiving "conventional treatment" "combined with" with rhPM-1 does not disclose that she received MTX, because there was no single "conventional treatment" that all RA patients received. Ex. 2036 (*Silverman Decl.*), ¶¶ 62-64.

Yoshizaki itself confirms this. First, in describing the treatment cohort, it discloses that all of these patients "were resistant to *any* conventional therapy." Ex. 1005 (*Yoshizaki 1998*) at 10 (emphasis added). Were there only one conventional way to treat RA, *Yoshizaki* would have reported they were "resistant to *the* conventional therapy." *Yoshizaki* elsewhere confirms this and also makes it clear "conventional therapy" could include MTX but did not need to. It defines "conventional therapy" as "non-steroid anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) combined with methotrexate (MTX) *and/or* steroids." *Id.* at 6. The use of "and/or" is critical—the "conventional therapy" might include MTX, and it might not.

Both sides' experts agree with this. As Dr. Silverman explains:

> What therapies the POSA would have considered "conventional" for treating RA patients varied depending on, for example, the relevant time period and location, the patient's disease severity, prior treatment history, responses to treatment including the patient's tolerance of

> the toxicities associated with the known DMARDs, as well as other adverse effects.
>
> …
>
> "Conventional treatment" of an RA patient might include MTX or might not. Indeed, a patient's "conventional treatment" might include MTX from the start; it might exclude MTX initially but add it later; or it might withdraw MTX at some point from a patient's ongoing therapy, for one of a variety of reasons I discuss below.

Ex. 2036 (*Silverman Decl.*), ¶¶ 62, 63. Dr. Zizic also agreed:

> **Q.** Okay. Now with respect to [t]his description of conventional therapy, you agree that as it's used here, while it could include methotrexate, it did not necessarily need to include methotrexate.
>
> **A.** That's correct.

Ex. 2037 (*Zizic Tr.*) at 173:4-9. Indeed, Dr. Zizic pointed out that many RA patients, especially those who drink alcohol and are unwilling to stop, cannot ever receive MTX given its hepatotoxicity and therefore must be prescribed other DMARDs, *id.* at 38:7-22, and that sometimes patients who receive MTX are taken off the drug later, for example, if they cannot tolerate it, *id.* at 54:21-55:1.

b. "Conventional Treatment" Does Not Involve Administering Multiple DMARDs, NSAIDs, Prednisolone, and MTX as Part of the Same Regimen.

Yoshizaki discloses the following about the 67-year-old woman in question: (i) she was "resistant to any conventional therapy," (ii) during the course of her treatment was "given NSAIDs, DMARDs, MTX and 15 mg predomizolone," and (iii) remained on a "conventional treatment" while receiving the experimental antibody. Ex. 1005 (*Yoshizaki 1998*) at 10, 11. *Yoshizaki* does not disclose, and the POSA would never think, that the "conventional treatment" she was receiving included all of the identified drugs because, for example, a rheumatologist would never prescribe multiple NSAIDs at once. Ex. 2036 (*Silverman Decl.*), ¶¶ 65-68; Ex. 2037 (*Zizic Tr*.) at 187:10-12.

Rather, as Dr. Silverman explains, because this patient was described as "resistant to *any* conventional therapy," "the POSA would understand this to mean that the doctors treating these patients would have progressively tried different combinations of NSAIDs, DMARDs (alone as a monotherapy or in combination), and steroids, but with no long-term success." Ex. 2036 (*Silverman Decl*.), ¶ 66.

> The POSA would have understood that during her treatment, and prior to receiving rhPM-1, she was "given" a variety of NSAIDs and DMARDs—including at some point MTX—as part of different treatment regimens, looking for one that worked. But the POSA would not have known what combination she was

> receiving immediately prior to being given the rhPM-1. Nor would the POSA have concluded from this passage that the patient received, at any time, *all* of these in the same treatment regimen, because no rational, responsible clinician would do that.

Ex. 2036 (*Silverman Decl*.), ¶ 65. Instead, the POSA would read the passage "as listing the various drugs [the patient's] doctors had tried in their protracted and unsuccessful struggle to find her some relief," not "as disclosing the treatment regimen she was currently receiving, or was continuing to receive once the administration of MRA commenced." *Id*. Dr. Zizic agreed, testifying that the "conventional treatment" for someone who failed to respond to any DMARD was to take them off DMARDs (and NSAIDs) entirely, and keep them only on a maintenance dose of steroids. Ex. 1037 (*Zizic Tr*.) at 85:8-14.

In other words, just because the text references MTX, the POSA would not interpret *Yoshizaki* as disclosing this patient's "conventional treatment," just prior to or during the administration of rhPM-1, necessarily included MTX.

c. *Yoshizaki* Does Not Disclose Administering MRA and MTX in the Same Treatment Regimen.

It is undisputed, and critical, that *Yoshizaki* reports the first time clinicians treated RA patients with rhPM-1. Ex. 2036 (*Silverman Decl.*), ¶ 69.[4] Both sides' experts agree that "the common practice of researchers testing a biologic targeting a cytokine for the first time was to administer it as a *monotherapy*, not as part of a combination therapy with another DMARD, be it MTX or one of the others." *Id.*; Ex. 2037 (*Zizic Tr.*) at 112:22-113:14 ("[I]t wouldn't be logical to do that."). The POSA would require proof that a new DMARD was safe and effective as a monotherapy before testing it in combination with MTX or another DMARD. Ex. 2036 (*Silverman Decl.*), ¶¶ 70-74.

Indeed, the literature is replete with examples confirming that the "conventional treatment" for RA patients receiving an experimental DMARD like

[4] Dr. Zizic disputed this only because some human subjects previously received the murine antibody from which rhPM-1 was humanized. Ex. 2037 (*Zizic Tr.*) at 202:21-204:3 (referencing Ex. 1037 (*Wendling 1993*)). But that murine antibody, anti-IL-6-Mab, and rhPM-1 are different antibodies, and the POSA would not consider the use of the former to be a prior use of the latter. Ex. 2036 (*Silverman Decl.*), ¶ 69 n.5.

rhPM-1 discontinued any DMARDs they might have been taking while allowing them to stay on whatever steroid or NSAID they were receiving. *See* Ex. 2036 (*Silverman Decl*.), ¶ 70 (citing Ex. 2046 (*Horneff 1991*) at 2 ("DMARD treatment was discontinued at least 8 weeks prior to the start of [CD4] antibody therapy" while allowing "concomitant treatment consist[ing] only of . . . NSAIDs and . . . prednisone"); Ex. 2047 (*Maini 1995*) at 3 (infliximab not administered until "[a]fter a minimum 'wash-out' period of cessation of DMARDS lasting at least 4 weeks" but continuing "a stable dose of non-steroidal anti-inflammatory drugs (and prednisolone if already prescribed)"); Ex. 2048 (*Bresnihan 1998*) at 1 (before trial of anakinra, "[a]ny disease-modifying antirheumatic drugs that were being administered were discontinued at least 6 weeks prior to enrollment" but "[d]oses of nonsteroidal antiinflamatory drugs and/or oral corticosteriods . . . remained constant throughout the study"); Ex. 2049 (*Strand 1999*) at 2 (for patients in leflunomide monotherapy trial, "treatment with all other DMARDS must have been discontinued for at least 30 days); Ex. 2050 (*Smolen 1999*) at 2 ("treatment with all other DMARDs had been discontinued at least 28 days before enrollment" but NSAIDS "including aspirin, and oral corticosteroids . . . were allowed at daily doses that had been constant for at least 30 days before study enrolment [sic]"); Ex. 2051 (*Kempeni 1999*) at Table 2 (first clinical testing of adalimumab in humans did not allow use of any concurrent DMARDs); Ex. 2052 (*Van de Putte 2004*) at 2-

3 (in adalimumab monotherapy trial, "[p]atients taking traditional DMARDs at the time of recruitment were required to undergo a 4-week washout period before initial injection of the study drug" though "[u]se of non-steroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids before the study was allowed at stable pre-enrolment [sic] doses"); Ex. 2053 (*Moreland 1999*) at 2 (1-month washout period of previous DMARDs before starting etanercept); Ex. 2054 (*Sewell 1993*) at 2 (all previous DMARDs discontinued 3 weeks prior to administration of study drug, an IL-2-toxin fusion protein); *see also* Ex. 1017 (*Nishimoto Abstract B*) at 2 (patients were administered MRA "without DMARDs," including MTX, but "were allowed to continue taking prednisolone . . . and/or NSAIDs during the trial")).

As both experts acknowledge, researchers followed this DMARD "washout" procedure "because the impact of a new DMARD could not be accurately assessed if the patient were receiving another DMARD at the same time," Ex. 2036 (*Silverman Decl*.), ¶ 70; Ex. 2037 (*Zizic Tr*.) at 120:4-16, and allowed the continued administration of NSAIDs and steroids because stopping those could create a flare of the disease for the patient which may make the DMARD appear less effective. Ex. 2036 (*Silverman Decl*.), ¶ 73; Ex. 2037 (*Zizic Tr*.) at 125:16-126:19.

Furthermore, Dr. Silverman explains that "the POSA conducting the initial testing on the safety and efficacy of an IL-6R antibody like rhPM-1 would be *particularly averse to administering it to RA patients who were still receiving MTX*." Ex. 2036 (*Silverman Decl*.), ¶ 71 (emphasis added). That is because "[t]he POSA knew that IL-6 is important to the health of hepatocytes and therefore an antibody that inhibited it was at least potentially hepatotoxic." *Id.* Because MTX was known amongst the DMARDs for causing liver toxicity and injuring or killing liver cells, Ex. 2044 (*Hamada 2003*) at 2, "[u]ntil the POSA could assess the impact of rhPM-1 on liver health, she would never combine it with another hepatotoxic drug like MTX." Ex. 2036 (*Silverman Decl*.), ¶ 71.

Finally, it is undisputed that at the time of the study clinicians in Japan typically had greater concern about drug toxicity than their colleagues in America and Europe. Ex. 2036 (*Silverman Decl*.), ¶ 72; Ex. 2037 (*Zizic Tr*.) at 209:4-8. ("[The Japanese] tended to be a little bit more conservative [in dosing]."). As previously discussed, MTX was known to be hepatotoxic—something rheumatologists at the time closely monitored. Ex. 2036 (*Silverman Decl*.), ¶ 72. "The POSA would not think the treating physician in *Yoshizaki* would have combined MTX with a novel, experimental antibody whose toxicity and efficacy in humans was unknown." *Id*. And Japanese regulators had not yet even approved MTX for use in RA patients—approval would not even occur until 1999, and then

only at a maximum approved dose of 8 mg/week. Ex. 2043 (*Kameda 2019*) at 1. Thus, even if a POSA assumed MTX was given in combination with rhPM-1, the POSA would not assume that the dose given to this Japanese patient was that same as the dose assumed to be "effective" by Dr. Zizic.

* * * * *

In light of this, it can hardly be said that the "conventional treatment" that was "combined with" rhPM-1 for this patient *necessarily* included MTX, and—as Dr. Silverman has opined—it almost certainly did not. Ex. 2036 (*Silverman Decl.*), ¶¶ 73, 74. Anticipation requires that "each and every element is found within a single prior art reference." *Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1294 (Fed. Cir. 2015), which must "disclose every limitation of the claimed invention, either explicitly or inherently." *CommScope Tech. LLC v. Dali Wireless Inc.*, 10 F. 4th 1289, 1295 (Fed. Cir. 2021) (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1381 (Fed. Cir. 2007)). And for a reference to inherently disclose a limitation, it must be "necessarily present, or inherent, in the single anticipating reference"—but "inherency . . . may not be established by probabilities or possibilities." *In re Montgomery*, 677 F.3d 1375, 1379 (Fed. Cir. 2012) (quoting *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011)). Because *Yoshizaki* does not disclose administering MTX in

combination with rhPM-1 within the same treatment regimen, either expressly or inherently, the Board should reject Ground 1.

B. Ground 2: *Nishimoto* Does Not Disclose a Combination Treatment of Effective Amounts of the Two Drugs

The Board's Institution Decision properly rejected Petitioner's argue that *Nishimoto* also anticipates Claim 1. No basis exists to revisit that determination.

1. *Nishimoto 2002*

Nishimoto 2002 is a review article disclosing the details of "MRA" (tocilizumab) monotherapy at various doses and dosing regimens. Ex. 1006 (*Nishimoto 2002*) at 4; Ex. 2036 (*Silverman Decl.*), ¶ 75. One was a Phase I where patients in Japan and healthy individuals in the United Kingdom received a single dose in one of four amounts: 0.1, 1, 5, or 10 mg/kg of body weight. *Id.* Positive results seen only in the 5 mg/kg group two days after receiving the antibody. *Id.*

Another was a Phase I/II trial in Japan in 1999 where patients received either 2, 4, and 8 mg/kg of the antibody intravenously every two weeks, with "excellent treatment efficacy" at all doses as measured by the percentage of patients achieving ACR20 and ACR50 scores. *Id.* at 5.

The third disclosed a "late phase II study" in Japan, and "recommended" treatment of patients with "8 mg/kg of body weight of MRA every 4 weeks." *Id.* at 4-5.

Nishimoto 2002 also makes reference to *Yoshizaki*, describing its regimen as where the antibody was used "to treat patients with intractable rheumatism who were resistant to anti-rheumatics including methotrexate." *Id.* at 4.[5] *Nishimoto 2002*, written by one of the *Yoshizaki* co-authors, does not state that any of those patients received methotrexate in combination with the antibody. Rather, the only disclosed use in *Nishimoto 2002* of MTX and MRA is a one-sentence reference to "a phase II study of coadministration with methotrexate [that] is currently underway in several European countries." *Id.* at 5. It is this sentence that Petitioners argue anticipates claim 1.

2. Analysis

As the Board noted, *Nishimoto 2002*'s reference to the European Phase II trial includes no disclosure of what doses of either drug were used. Decision at 24. Petitioners argue that the trial would have utilized the 8 mg/kg dose of MRA "recommended" in the Phase II monotherapy trial, but as the Board pointed out, "it

[5] Dr. Nishimoto co-authored *Yoshizaki*. If MTX and MRA had actually been tried in combination in that earlier study, the POSA would expect that *Nishimoto*'s detailed discussion of the *Yoshizaki* results to make some reference to that fact. Ex. 2036 (*Silverman Decl.*), ¶ 45-46 n.6. It does not.

is unclear whether the MRA dosage amount disclosed by Nishimoto was known, much less employed, by those conducting the phase II study in Europe." *Id*. The Board also noted that "there is no indication in *Nishimoto* that the phase II study employed a MTX dosage amount used in conventional treatment." *Id*.; *see also* Ex. 2036 (*Silverman Decl.*), ¶¶ 76-78.

The conclusion that *Nishimoto 2002* does not anticipate claim 1 is correct for another reason. As noted *supra* in the discussion of claim construction, "the POSA would understand the term 'effective amount' in claim 1 to mean amounts of MRA and MTX that are effective *in combination* and would be expected to reduce the patient's symptoms, inhibit disease progression, or both, with acceptable toxicity." Ex. 2036 (*Silverman Decl.*), ¶ 79. Should the Board agree with this construction, *Nishimoto 2002* cannot anticipate Claim 1 because it does not disclose or assert any efficacy for the combined use of whatever dosages of MRA and MTX were used in reducing a patient's RA symptoms or inhibiting disease progression.

C. Ground 3: *Nishimoto 2002* and *Weinblatt 2003* Do Not Render Claim 1 Obvious

The Institution Decision tentatively agreed with Petitioners that *Nishimoto 2002* and *Weinblatt 2003*, a report on a clinical trial testing MTX and adalimumab combinations, would have motivated the POSA to try the claimed combination of MTX and an anti-IL-6R antibody with a reasonable expectation of success. Decision at 29. On the latter issue, the Board found "[b]ased on the current

record," that "Patent Owner has not identified evidence sufficient to establish that such concerns or unpredictability involved in the combined therapy would have caused a POSA to have not even a reasonable expectation of success of such therapy." *Id*. at 31. The Board encouraged "Patent Owner [to] develop these arguments at trial." *Id*.

The declaration of Dr. Silverman and the deposition testimony of Dr. Zizic now establish a powerful record on that point—the POSA would *not* have had a reasonable expectation that the claimed therapy would be successful as both experts define that term.

1. Both Experts Agree That a "Successful" RA Combination Therapy Requires Improved Efficacy Without Undue Toxicity.

In *Eli Lilly and Co. v. Teva Pharmaceuticals Int'l, GmbH*, 8 F.3d 1331 (Fed. Cir. 2021), the Federal Circuit explained what is required to show "reasonable expectation of success" when challenging a method-of-treatment claim like this one under 35 U.S.C. § 103.

> [It is] not enough for the appellant-defendant to have shown that a skilled artisan would have pursued the claimed method as a treatment option, but the appellant-defendant also had to show that the skilled artisan would have reasonably expected to achieve success in the treatment.

Id. at 1344; *see also Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1062 (Fed. Cir. 2019).

Dr. Silverman explains that that would mean to the POSA:

> For the POSA, combining methotrexate with another drug is done in hopes of achieving increased efficacy with no or little increase in toxicity in comparison to methotrexate monotherapy. A combination regimen that achieves this goal is considered a success. By contrast, the POSA would consider a combination regimen unsuccessful if it proves no more efficacious than methotrexate alone, or if it causes an unacceptable increase in toxicity.

Ex. 2036 (*Silverman Decl*.), ¶ 84. At his deposition, Dr. Zizic articulated the same standard:

> **Q**. So in your opinion, what makes an RA treatment successful?
>
> **A**. You mean, what outcome is—
>
> **Q**. Yeah.
>
> **A**. –do I measure success by—
>
> **Q**. I assume it's a reduction of symptoms, or signs and symptoms would—
>
> **A**. well, reduction of pain and symptoms and prevention of damage to the joints as an overall goal doing both of those,

> preventing long-term damage and disability and also to make them more functional and better quality of life.
>
> **Q**. Okay. And at an acceptable level of toxicity?
>
> **A**. Oh, of course

Ex. 2037 (*Zizic Tr*.) at 144:14-145:6. Dr. Zizic illustrated this with an example, the combination therapy of MTX and cyclophosphamide (Cytoxan), noting that it was highly effective in treating RA but nonetheless deemed a "failure" because it was too toxic. *Id*. at 43:22-44:22.

The record now before the Board establishes that the POSA would not have had a reasonable expectation that the claimed combination of MTX and an anti-IL-6 antibody would meet this standard.

2. There Was No Reasonable Expectation that the Claimed Combination Would Demonstrate Increased Efficacy.

At paragraph 161 of his declaration, Dr. Zizic gives three reasons why the POSA would have reasonably expected success from combining methotrexate with an anti-IL6R antibody. First, "because both the anti-IL-6R antibody and methotrexate regimens were known to be *individually* effective for treating RA," he asserts the POSA would have likewise expected success from using the two drugs in combination. Ex. 1002 (*Zizic Decl.*), ¶ 161 (emphasis added).

Second, the POSA would have expected the same success combining MTX and an IL-6R antibody as others had achieved combing MTX with the TNFα

inhibitors. *Id*. *Weinblatt 2003*, as noted, reports the results of a trial combining MTX with adalimumab.

Third, the POSA would have known from *Yoshizaki* that MRA and MTX had been combined to "successful[ly]" treat the 67-year-old patient that reference mentions. *Id*.

None of those arguments hold up.

a. No Reasonable Expectation That Successful Monotherapies Would Also Work in Combination.

In his list of reasons why the POSA administering the claimed combination would have reasonably expected success, Dr. Zizic points to the success MRA and methotrexate had shown as monotherapy treatments for RA. Ex. 1002 (*Zizic Decl.*), ¶ 161. In fact, as Dr. Silverman explains, developing successful combination therapies in RA is highly unpredictable, and as of 2003, the prior art demonstrated that RA combination regimens—including combinations with methotrexate—often showed no benefit over their use as monotherapies. Ex. 2036 (*Silverman Decl*.), ¶¶ 80-86.

In 1994, the *Felson* meta-analysis evaluating "the overall efficacy and toxicity of combination therapy in RA" concluded that "[c]ombination therapy as it has been used in clinical trials is not a valuable therapeutic alternative for most patients with RA" because such trials "did not show a substantial clinical difference in efficacy between combination drug regimens and single second-line

drugs." Ex. 2010 (*Felson 1994*) at 5; Ex. 2036 (*Silverman Decl*.), ¶ 87. From a scan of "214 published second-line drug trials," the meta-analysis determined that "individual trials that have compared combination therapy with single second-line drug therapy have not generally shown differences in efficacy, and any differences demonstrated have often not reached statistical significance." *Id.* at 1. Notably, *Felson 1994* cited two MTX combination therapies—an MTX and auranofin combination, Ex. 2024 (*Williams 1992*), and an MTX and azathioprine combination, Ex. 2072 (*Willkens 1992*)—neither of which succeeded. Ex. 2036 (*Silverman Decl*.), ¶ 88.

Nor was *Felson 1994* a lone voice reporting that DMARD combinations generally provided no advantage over MTX monotherapy. Ex. 2036 (*Silverman Decl*.), ¶¶ 89-90. Publications before and after *Felson 1994* confirmed that just because a given drug was effective as a monotherapy, that did not mean it would be effective in a combination therapy. For instance, a 1991 comprehensive literature review "critically appraised the clinical trials that compared the efficacy and toxicity of a single [DMARD] to that of a combination of such drugs in patients with RA," finding that "*none* conclusively demonstrated benefit of a drug combination" and that "[t]he advantages of antirheumatic drug combinations over any single drug remain *unproven*." Ex. 2056 (*Boers 1991*) at 1, 2, 9 (emphases added); *see also id.* at 1 ("to date only a few controlled studies have compared

multiple drug regimens with a single drug; these studies have yielded *conflicting results*").

Three years later, the group updated its analysis to review a total of 385 clinical studies, finding only three new studies that were sufficiently reliable to be included. Ex. 2057 (*Tugwell 1994*) at 3. Two of those related to MTX combinations and "suggested no benefit of [the] methotrexate-containing combination strategies over the single drug." *Id.* at 9; Ex. 2036 (*Silverman Decl*.), ¶ 91.

A second update to the analysis published four years later reported screening "231 new citations" and found only twenty new studies that had sufficiently reliable data for inclusion, most of which failed to demonstrate more efficacy in combination. Ex. 2022 (*Verhoeven 1998*) at 2, Table 1. Notably, most of the studies (five out of seven) comparing MTX-containing combinations with MTX monotherapy demonstrated "no difference" in efficacy or merely "a positive trend" favoring the combination therapy. *Id.* at 2, Table 1; Ex. 2036 (*Silverman Decl*.), ¶ 92.

One such study was a three-armed clinical trial comparing MTX and sulfasalazine combination therapy with MTX monotherapy and sulfasalazine monotherapy. Ex. 2040 (*Haagsma 1997*). There, the authors reported "no significant differences in efficacy between combination and single therapy,"

despite observing "greater toxicity" in the combination arm than in either comparator monotherapy arm. *Id.* at 1, 6; Ex. 2036 (*Silverman Decl*.), ¶ 93.

And of the two studies *Verhoeven 1998* thought demonstrated improved efficacy for the combination, one was an MTX and chloroquine combination trial that concluded its data did not support a benefit for the combination because it was only "slightly more efficacious" than MTX monotherapy while having higher levels of toxicity. Ex. 2067 (*Ferraz 1994*) at 1; Ex. 2036 (*Silverman Decl*.), ¶ 94.

Even years after the priority date, those skilled in the art continued to doubt that DMARD combination therapies provided increased efficacy over monotherapy. Ex. 2036 (*Silverman Decl*.), ¶ 95. A 2005 analysis remarked:

> Numerous studies have failed to show any superiority of combination therapy with traditional, small-molecule DMARDs over monotherapy, especially in conjunction with the use of MTX.

Ex. 2058 (*Smolen 2005*) at 7 ("[t]he available data on the superiority of combinations of DMARDs are controversial"). Similarly, a meta-analysis published in 2008 and focusing specifically on MTX combination therapies concluded:

> In summary, when the balance of efficacy and toxicity is taken into account, the evidence from our systematic review showed no significant advantage of the MTX combination versus monotherapy.

Ex. 2059 (*Katchamart 2008*) at 7.

Given this track record of failure and unpredictability, the POSA would not have reasonably expected the combination of MRA and MTX to provide better efficacy than MTX alone. Ex. 2036 (*Silverman Decl*.), ¶ 96.

b. No Reasonable Expectation of Success Based on Prior Combinations of TNFα Inhibitors and MTX.

Dr. Zizic also cites the successful combinations of MTX with three biologics targeting TNFα as grounds for why the POSA would expect similar success with the claimed combination. Ex. 1002 (*Zizic Decl.*), ¶ 161. But the POSA would not have automatically assumed, as Dr. Zizic does, that these results would translate from one immunological pathway to another.

As Dr. Silverman explains, the POSA would have understood that there are several crucial mechanistic differences between the TNFα and IL-6 cellular pathways that would have undermined a reasonable expectation of success. Ex. 2036 (*Silverman Decl.*) at ¶¶ 97, 99-103. To start, while TNFα is a proinflammatory cytokine, IL-6 was known to exhibit both proinflammatory and *anti*-inflammatory effects. *Id.* at ¶ 99; Ex. 2026 (*Kelley's 2001*) at 5-6, 25; Ex. 2008 (*Deon 2001*) at 1. To the POSA, this characteristic of IL-6 would have created a risk of *negative* synergy if combined with MTX, which also had anti-inflammatory effects. Ex. 2036 (*Silverman Decl.*) at ¶ 99. The POSA therefore would not have reasonably expected MTX to combine effectively with MRA as it had with TNFα inhibitors. *Id.*

There were other differences as well. MRA primarily targets B cells by suppressing antibody production, but TNFα inhibitors do not. Ex. 2036 (*Silverman Decl.*) at ¶ 101. That mechanistic difference, Dr. Silverman explains, would have led the POSA to believe that MRA did not need to be co-administered with MTX because it did not require any assistance in suppressing the formation of neutralizing anti-drug antibodies. *Id.* at ¶¶ 101-102. This belief was also confirmed by the literature at the time, such as *Nishimoto 2002*, which discloses that infliximab requires coadministration with MTX "to suppress the appearance of autoantibodies and limit the appearance of neutralizing antibodies to the chimeric antibodies," but MRA "does not require such coadministration of methotrexate." Ex. 1006 at 5.

The prior art confirms the distinction drawn by Dr. Silverman. *Maini 1998*, which reported the results of a study combining MTX with infliximab, attributed the increased efficacy of combination therapy to MTX's ability mitigate the immunogenicity problem infliximab monotherapy was known to inflict on patients. Ex. 2015 (*Maini 1998*) at 10; Ex. 2036 (*Silverman Decl.*), ¶ 100.

That *Weinblatt 2003* involved adalimumab and not infliximab does not tip the balance in Petitioners' favor. As Dr. Silverman explains, in light of all of the uncertainty generated by abundant other prior art, the POSA would not have interpreted *Weinblatt 2003* as a license to combine MTX with every conceivable

RA biologic agent with any expectation of positive results. Instead, *Weinblatt 2003* confirms that the success of a combination therapy can only be determined after the sort of careful testing *Weinblatt* undertook. Ex. 2036 (*Silverman Decl.*), ¶¶ 102-103.

Finally, Petitioners completely ignore the prior art establishing that RA therapies combining biologics DMARDs were considerably less successful than the Board might have believed from Dr. Zizic's selective presentation. In one early example, researchers combined MTX with an anti-CD4 mAb designated cm-T412. Ex. 2018 (*Moreland 1996*). Cm-T412 had shown promise as a monotherapy in early clinical trials, but when combined with MTX the treatment regimen "was not associated with efficacy." *Id.* at 3; Ex. 2022 (*Verhoeven 1998*) at 2-4 (noting that the study in *Moreland 1996* "did not show any relevant between-group difference in clinical efficacy or toxicity"). And although the authors of *Moreland 1996* encouraged further study of the combination of biologics and DMARDs, they also noted that there remained "concerns [over] increasing the risk of serious adverse events" in light of the toxicities associated MTX monotherapy. Ex. 2018 (*Moreland 1996*) at 4. Likewise, an attempt to combine a biologic and a synthetic DMARD—infliximab and leflunomide—resulted in "a high frequency of adverse events, sufficiently severe to cause premature withdrawal from the study in 55% of the patients" and the death of one

patient, leading the authors to recommend against its widespread use and search for an alternative "well-tolerated anti-TNF-α/DMARD combination." Ex. 2066 (*Kiely 2002*) at 1, 2, 6. In other words, biologic DMARDs were like traditional DMARDs in one way—combining them with MTX yielded uncertain, unpredictable results. Ex. 2036 (*Silverman Decl.*), ¶ 98.

c. No Reasonable Expectation of Success Based on *Yoshizaki*.

Yoshizaki is the only publication Dr. Zizic identifies as purportedly disclosing successful treatment of RA with MTX and an anti-IL-6 receptor antibody. Ex. 1002 (*Zizic Decl.*), ¶ 161. For all of the reasons previously discussed in § V.A, that characterization of *Yoshizaki* simply is not true. Moreover, as Dr. Silverman explains, even if *Yoshizaki did* disclose that combination, the fact that this was a small, uncontrolled, non-blinded case study that even under Petitioners' reading would at most disclose a single patient receiving both drugs would not prompt the POSA to give it any weight when determining whether tocilizumab could be successfully combined with MTX. Ex. 2036 (*Silverman Decl*.), ¶ 104.

d. No Reasonable Expectation of Success Based on FDA's 1999 Guidance.

Though not cited within Dr. Zizic's single paragraph of analysis on reasonable expectation of success, Ex. 1002 (*Zizic Decl*.) ¶ 161, Petitioners also

appear to rely on FDA's 1999 Industry Guidance to establish this point. Ex. 1009 (*1999 FDA Guidance*). In doing so, they misinterpret that Guidance. While the Petition and Dr. Zizic's declaration accurately quote FDA's statement that "it is inevitable that new agents [for treating RA] will be used in combination with methotrexate" Ex. 1002 (*Zizic Decl*.) ¶ 44 (quoting Ex. 1009 (*1999 FDA Guidance*) at 21), they notably omit and ignore the full text of the quoted paragraph from the Guidance:

> Studies in RA patients, except in those with very mild disease, are carried out in the presence of concurrent active therapies, including steroids, NSAIDS, hydroxychloroquine, etc. This concurrent therapy creates numerous challenges in patient selection, toxicity monitoring, and clinical trial design. For example, 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. Therefore, unless a prohibition on concurrent methotrexate is supportable, *data regarding use of the investigational agent in combination with methotrexate are needed to evaluate the potential for immunosuppression from combination therapy*. Other agents should be similarly evaluated.

Ex. 1009 (*1999 FDA Guidance*) at 21 (emphasis added).

As Dr. Silverman explains, the POSA reading this Guidance in the proper context would understand that FDA was *not* encouraging clinicians to haphazardly combine MTX with new biologics. FDA's statement is not a prediction of likely success but rather a *warning* that MTX combination therapy for new biologics should only be attempted where the data supported it, and the POSA would have read it that way. Ex. 2036 (*Silverman Decl*.), ¶¶ 105-106

3. There Was No Reasonable Expectation That the Claimed Combination Would Have Been Safe.

Both sides' experts agree that a treatment regimen combining DMARDs would not be considered successful absent evidence of an acceptable level of toxicity. Ex. 2036 (*Silverman Decl.*), ¶ 84; Ex. 2037 (*Zizic Tr.*) at 144:14-145:6. Drs. Silverman and Zizic both recount examples in which an RA combination therapy demonstrated promising efficacy but was nonetheless deemed a failure due unacceptable toxicity. Ex. 2036 (*Silverman Decl.*), ¶¶ 107-110, 118-120; Ex. 2037 (*Zizic Tr.*) at 43:22-44:22. Combining MTX with sulfasalazine, for example, "showed a trend in favour of a more potent effect of the combination but also a trend suggestion a more toxic profile of this combination," leading the authors to conclude that the study "was unable to demonstrate a clinically relevant superiority of the combination therapy." Ex. 2041 (*Dougados 1999*) at 1, 6. Likewise, the combination of a biologic and synthetic DMARD—infliximab and leflunomide—"appear[ed] to be highly efficacious in the treatment of adult RA" but also caused

"a high frequency of adverse events, sufficiently severe to cause premature withdrawal from the study in 55% of the patients" and the death of one patient, leading the authors to recommend against its widespread use and search for an alternative "well-tolerated anti-TNF-α/DMARD combination." Ex. 2066 (*Kiely 2002*) at 1, 2, 6.

Dr. Zizic testified that he was well-aware of the MTX/leflunomide combination but never prescribed it due to the "additive chance of getting liver toxicity with both drugs." Ex. 2037 (*Zizic Tr.*) at 73:4-5. And he recounted how the combination of MTX with cyclophosphamide (Cytoxan) was a "failure" despite strong efficacy in RA "because the toxicity" was too high. *Id*. at 43:22-44:22. Despite this, Petitioners and Dr. Zizic never bother to account for the POSA's well-founded toxicity concerns with the claimed combination in their analysis, notwithstanding Dr. Zizic's repeated concessions that toxicity concerns guide his personal decisions as a practitioner to *avoid* administering certain combinations or treatments. Ex. 2037 (*Zizic Tr.*) at 144:14-145:6, 250:6-254:6, *id.* at 58:22-59:1 ("if [a patient] can't give up alcohol, then I'm not going to prescribe them methotrexate" due to hepatotoxicity risk).

It is undisputed that MTX is a toxic drug that poses serious dangers to liver health. Ex. 2036 (*Silverman Decl.*), ¶¶ 111-12; Ex. 2037 (*Zizic Tr.*) at 38:8-11, 38:20-22. The 2000 edition of Physicians' Desk Reference, a standard source for

information about therapeutic drugs, reported that hepatotoxicity had been observed in patients with long-term use of MTX, and had even been associated with deaths in the treatment of RA. Ex. 1020 (*2000 PDR – Methotrexate*) at 3. Other sources likewise reported on the "serious complications of methotrexate therapy, especially hepatic and pulmonary toxicity." Ex. 2006 (*Conaghan* 1995) at 3. For these reasons, patients prescribed MTX were required to perform regular blood tests "to assess the very real potential for liver damage." Ex. 2016 (*Kremer* 2002) at 3; Ex. 2036 (*Silverman Decl.*), ¶ 112; *see also* Ex. 2015 (*Kremer 1998*) at 3 (MTX was well known to be "associated with the potential for serious toxicity"); Ex. 2021 (*Rheumatrex Label 2003*) at 8 ("Methotrexate has the potential for serious toxicity").

As Dr. Silverman explains, the POSA treating RA patients in 2003 would have had similar concerns about tocilizumab. Ex. 2036 (*Silverman Decl.*), ¶ 113. *Nishimoto* warned that "since IL-6 has an important function in the body, for instance in regulation of immune and hematopoietic responses, due care must be taken to watch for the appearance of adverse drug reactions [with MRA], particularly reduced immunocompetence against infections." Ex. 1006 (*Nishimoto 2002*) at 5. Like with MTX, one of the adverse drug reactions that tocilizumab was known to cause is hepatotoxicity. In fact, patients administered tocilizumab monotherapy were monitored with "liver function tests" because of an observed

dose-dependent liver toxicity. Ex. 2020 (*Okuda 2003*) at 24; Ex. 2036 (*Silverman Decl.*), ¶¶ 113-15.

The POSA would have had a reasonable concern over administering two drugs like MTX and tocilizumab with overlapping toxicities even though he or she may have been comfortable administering either drug as a monotherapy. Ex. 2036 (*Silverman Decl.*), ¶¶ 116-17. The leflunomide/MTX combination addressed by both experts is a textbook example of overlapping hepatotoxicity concerns that materialized into serious harm. *Id.* at ¶ 118. Like the claimed combination of MRA and MTX, both leflunomide and MTX were successful monotherapies known to individually cause hepatotoxicity, leading those skilled in the art to predict—before any clinically testing of the combination—that these two drugs would cause "additive" hepatotoxicity. Ex. 2015 (*Kremer 1998*) at 4; Ex. 2036 (*Silverman Decl.*), ¶ 118.

These overlapping hepatotoxicity concerns were then reflected in the "modified" dosing regimen for the leflunomide/MTX combination trial, which administered only *half* the normal monotherapy dose of leflunomide due to "concern regarding potential toxicity and lack of relevant safety data in animal models." Ex. 2042 (*Weinblatt 1999*) at 2; Ex. 2036 (*Silverman Decl.*), ¶ 119. But even with this significantly modified dosing, three patients withdrew from treatment because of "persistent elevation of plasma liver enzyme concentrations,"

where "elevated transaminase levels were not seen with methotrexate alone, and became evident only following addition of leflunomide to methotrexate." *Id.* at 6. *Weinblatt 1999* cautioned that "[t]he occurrence of elevated liver enzyme levels with this drug is of concern" and warned that "because the overall risk of serious liver damage when methotrexate and leflunomide are used together is *unknown*, careful dose titration and patient monitoring will be necessary when this combination is used." *Id.* (emphasis added); Ex. 2036 (*Silverman Decl.*), ¶ 119.

The risk of serious liver damage that *Weinblatt 1999* warned of soon materialized. As he explained in a letter published in the same journal a year later, Dr. Weinblatt reported that one enrolled patient who had completed the study had suffered "serious liver disease," despite receiving lower-than-monotherapy doses of *both* drugs (5 mg/week MTX and 10 mg/day leflunomide). Ex. 2064 (*Weinblatt 2000*) at 1. Even more concerning, while the patient had experienced "intermittent elevations of his serum transaminase levels," those elevations had never risen to the level of "meet[ing] the published criteria for liver biopsy in the monitoring of patients receiving MTX." *Id.* As Dr. Silverman explains, even when a patient's liver enzyme levels do not rise to the level of causing concern or requiring a liver biopsy, the risk of "serious liver disease" persists. Ex. 2036 (*Silverman Decl.*), ¶ 120.

That same risk, Dr. Silverman opines, would have been on the forefront of the POSA's mind with respect to the proposed combination of MRA and MTX, given that the two drugs were known to have overlapping hepatotoxicity, and no safety data (or any clinical data whatsoever) existed for the combination, whether in animal studies or in humans, as of 2003. Ex. 2036 (*Silverman Decl.*), ¶ 121. As *Weinblatt 2000* noted, "[s]erious liver disease does occur with MTX," and "[b]oth MTX and leflunomide have been associated with elevated liver enzyme levels." Ex. 2064 (*Weinblatt 2000*) at 1. The same is true for the claimed combination of MTX and MRA. MRA, like leflunomide, had been disclosed in *Okuda* to cause with elevated liver enzyme levels, and the risk of serious liver disease with MTX was at that point well established. Ex. 2036 (*Silverman Decl.*), ¶ 122. Given these toxicity concerns, the POSA would not have reasonably expected the claimed combination of MRA and MTX—especially at the highest 8 mg/kg monotherapy dose of MRA—to be safe.

Dr. Zizic agrees that overlapping hepatotoxicity concerns would have caused the POSA to reasonably expect a combination was unsafe for RA patients, and he even testified at deposition that he does not prescribe the combination of MTX and leflunomide "[b]ecause you've got an additive change of getting liver toxicity with both drugs." Ex. 2037 (*Zizic Tr.*) at 73:4-5. And, out of the same hepatotoxicity concern, he noted, MTX is contraindicated for patients who continue to consume

alcohol given the latter's capacity to inflict liver damage, such that in his personal practice, "if [a patient] can't give up alcohol, then I'm not going to prescribe them methotrexate" due to hepatotoxicity risk. Ex. 2037 (*Zizic Tr.*) at 58:22-59:1.

Thus, as Dr. Silverman explains, the overlapping hepatotoxicity risk "would have led the POSA to question whether MTX and tocilizumab could be combined with acceptable levels of toxicity," a concern that did not exist for the TNFα inhibitors that were commonly co-administered with MTX. Ex. 2036 (*Silverman Decl.*), ¶ 123. The POSA would have concluded that the overlapping toxicities from combining MTX and tocilizumab would outweigh any expected benefit (which as explained *supra* was uncertain in any event.) *Id*. ¶ 123.

* * * * *

Obviousness requires that "skilled artisan would have reasonably expected to achieve success in the treatment." *Eli Lilly*, 8 F.3d at 1344. Because combining DMARDs including MTX generally had a spotted record, and because combining MTX with other hepatoxic DMARDs like tocilizumab was known to be fraught, Petitioners simply cannot make the required showing. Ground 3 should be denied.

VI. CONCLUSION

For the reasons set forth above Patent Owner respectfully submits that the Board should confirm the validity of Claim 1 of the '052 Patent.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that a true and correct copy of the foregoing was served on April 21, 2022, by delivering a copy via electronic mail on the following counsel of record for the Petitioners:

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the foregoing Patent Owner Preliminary Response complies with the type-volume limits of 37 C.F.R. § 42.24(b) because it contains 10,861 words (as calculated by the word processing system used to prepare this document), excluding the parts of the document exempted by 37 C.F.R. § 42.24.

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