UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

CHUGAI SEIYAKU KABUSHIKI KAISHA
Patent Owner.

IPR 2021-01025
Patent 10,744,201

PATENT OWNER'S RESPONSE

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I. INTRODUCTION

U.S. Patent No. 10,744,201 claims the administration of specified doses of MRA (tocilizumab) and methotrexate to achieve specific clinical outcomes in patients with rheumatoid arthritis ("RA"). Relying heavily on the unexamined and unrebutted testimony of Petitioners' expert, Dr. Thomas Zizic, the Board at institution found it reasonably likely that all claims were obvious over two cited references—*Nishimoto 2002*, an article disclosing only tocilizumab monotherapy trials, and *Weinblatt 2003*, a report on a clinical trial testing methotrexate ("MTX") with an entirely different biologic, adalimumab. The Board found the POSA would have been motivated to combine the tocilizumab monotherapy dosage "recommended" in *Nishimoto 2002* with the MTX dosage *Weinblatt 2003* utilized, and would have done so with an expectation of the same success *Weinblatt 2003* discovered with the different drug combination those researchers tested.

Under cross-examination, however, Dr. Zizic walked back several key assertions from his declaration that the Board had relied on in instituting trial, including his assertion that disease-modifying anti-rheumatic drugs ("DMARDs") like methotrexate and tocilizumab "are generally administered in the same dosage amount and frequency when given in combination with methotrexate as they are when given alone." Decision at 30 (quoting Ex. 1002 (*Zizic Decl.*), ¶ 150). Dr. Zizic conceded that when combining DMARDs with known toxicities, researchers

commonly used *reduced* doses at the low end of their known effective range. Ex. 2037 (*Zizic Tr.*) at 230:21-231:4, 232:8-234:15, 293:21-294:14. This is the precise argument Patent Owner advanced in its Preliminary Response, which relied on the prior art's teaching that "individual agents [used in RA combination therapies] tended to be prescribed at the *minimal* effective therapeutic dosage" due to toxicity concerns. POPR at 47-48 (quoting Ex. 2010 (*Felson 1994*) at 4-5).

The record now includes substantial evidentiary support beyond just the concessions Dr. Zizic made in his deposition, principally the testimony of Dr. Gregg Silverman of the NYU Langone Center, an expert with more relevant experience. Citing numerous key references that Dr. Zizic omitted from his declaration, Dr. Silverman explains why the POSA would not have been motivated to use the claimed dosages; why, given the full history of treating RA with DMARD combinations, there was no reasonable expectation of success; and why the clinical trial results reported in the '201 Patent's specification were unexpected.

The current record also supplies further support, if it were needed, for the Board's conclusion in the Institution Decision that *Nishimoto 2002* does not anticipate.

Based on the full record and the law that controls patentability under 35 U.S.C. §§ 102, 103, the challenged claims should be confirmed.

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 (*'201 Patent*) at 17:12-15.

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 generally 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 only prescribe one NSAIDs, 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 "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 it worked to alleviate RA symptoms, and why it remained ineffective for so many RA patients. 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 hepatotoxic 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 RA 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 were initially pursued with enthusiasm but that had eventually failed. Ex. 2013 (*Keystone 2003*) at 1; 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.*), ¶ 19.

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 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.*), ¶ 32.

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.*), ¶¶ 20, 31-33.

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 from 1994 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, combining MTX with 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.

III. THE '201 PATENT

The '201 Patent issued on August 18, 2020, with fifteen claims. Claim 1 is illustrative of the subject matter:

> A method for increasing the likelihood of achieving an America College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone, comprising administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously, and (ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg.

Ex. 1001 (*'201 Patent*) at 22:30-39. Claims 6 and 11 are the other independent claims. All three claim require (1) an ACR70 response; (2) 8 mg/kg Q4W of MRA; and (3) 10-25mg/week of methotrexate. Claim 6 also requires an MRA and MTX combination better than MTX monotherapy *or* MRA monotherapy, and claim 11 requires an MRA and MTX combination better than the additive results from MRA monotherapy and MTX monotherapy. *See id.* at 22:30-39, 22:49-61; 23:7-20.

Each independent claim has four dependent claims that add a separate limitation. Claims 2, 7, and 12 require that "the patient prior to treatment had an inadequate response or disease flare on methotrexate (MTX) treatment alone." Claims 3, 8, and 13 require that "the patient has no anti-MRA antibodies following administering the combination of anti-IL-6R antibody MRA and MTX." Claims 4, 9, and 15 require that "the patient does not experience hypersensitivity following administering the combination of anti-IL-6R antibody MRA and MTX." Finally, Claims 5, 10, and 15 require "the anti-IL-6R antibody MRA is administered four times at four week intervals." *Id.* at 22:40-23:32.

The specification supporting the claims describes data collected during a phase II clinical trial ("CHARISMA") conducted from 2001 to 2003 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 (*'201 Patent*) at 19, Table 1.

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 immunogenetic 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 of MTX led to dramatic improvement. *Id.* at 17:15-27.

IV. ARGUMENT[1]

A. Ground 1: *Nishimoto 2002* Does Not Anticipate

The Board's Institution Decision properly rejected Petitioners' argument that *Nishimoto 2002* anticipates the claims. No basis exists to revisit that.

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 trial where patients in Japan and healthy individuals in the United Kingdom received a single dose of MRA in one of four amounts: 0.1, 1, 5, or 10 mg/kg of body weight. *Id.* Positive results were 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, or 8 mg/kg of MRA 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.

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

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 references the *Yoshizaki* study, where the antibody was used "to treat patients with intractable rheumatism who were resistant to anti-rheumatics including methotrexate." *Id.* at 4. *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. 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 the claims.

2. Analysis

As the Board noted, *Nishimoto 2002*'s reference to the European Phase II trial includes no disclosure of the doses used. Decision at 22-23. 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 is unclear whether the MRA dosage amount disclosed by Nishimoto was known, much less employed, by those conducted the phase II study in Europe." *Id*. at 22-23. 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*.; Ex. 2036 (*Silverman Decl.*), ¶¶ 76-78.

The Board's rejection of *Nishimoto 2002* is correct for another reason: for *Nishimoto 2002* to anticipate, it must also disclose that patients were more likely to achieve an ACR70 response from the combination treatment than from MTX alone, as claim 1 requires. But *Nishimoto 2002* makes no such disclosure. In fact, it is entirely silent as to whether *any* ACR70 responses were achieved with either MRA monotherapy or in combination with MTX. Ex. 2036 (*Silverman Decl.*), ¶ 79.

Though the Board need not go further than the independent claims, it bears noting that at his recent deposition, Dr. Zizic effectively recanted all of the opinions in his declaration that *Nishimoto 2002* anticipates the dependent claims. Ex. 1002 (*Zizic Decl.*), ¶¶ 137-144.

For example, claims 2, 7, and 12 require that "the patient, prior to treatment had an inadequate response or disease flare on methotrexate (MTX) treatment alone." Ex. 1001 ('201 Patent) at 21-22. But *Nishimoto 2002* includes no discussion about the patients enrolled—patients, Dr. Zizic acknowledged, who might very well have never received MTX prior to the trial:

> **Q.** Isn't it possible that the enrollees [of the European trial] were never on methotrexate at all?
>
> **A.** Then you can't do a combination trial.
>
> **Q.** No. Prior to the trial, they were never on methotrexate. Isn't that possible?
>
> **A.** I guess that's possible.

Ex. 2037 (*Zizic Tr.*) at 239:2-8.

Dr. Zizic continued to qualify his testimony for the remaining dependent claims. Claims 3, 8, and 9 require that the patient have no anti-MRA antibodies. But as *Nishimoto 2002* is silent on this point, Dr. Zizic admitted some patients could have had some anti-MRA antibodies. *Id.* at 239:13-21. Dr. Zizic also qualified the statements in his declaration regarding anticipation of dependent claims 4, 9, and 14:

> **Q.** Okay, Dependent Claims 4, 9, and 14 require that the patients do not exhibit hypersensitivity. Do you remember that?
>
> **A.** That is correct.
>
> **Q.** [Hypersensitivity] [m]ight be exceedingly rare, but it could conceivably occur?
>
> **A.** Yeah. I hadn't seen it in the side effects, adverse effects in the various studies reported, but doesn't mean it couldn't happen, sure.

Id. at 240:11-241:5. He also acknowledged that the dosing schedule specified in dependent claims 5,10, and 15, which his declaration attested were inherently disclosed, actually were not. *Id.* at 241:8-242:4.

B. Ground 2: *Nishimoto 2002* and *Weinblatt 2003* Do Not Render Obvious the Claims.

On the limited record at institution, the Board tentatively determined that *Nishimoto 2002* and *Weinblatt 2003* would have motivated the POSA to combine 8 mg/kg monthly MRA and 10-25 mg/week MTX in RA patients with a reasonable expectation of achieving the claimed ACR70 efficacy limitations. In doing so, the Board provisionally credited Dr. Zizic's declaration testimony that: (1) a DMARD's dosage and frequency of administration would have been the same as a monotherapy and in combination with MTX; (2) the POSA would have maintained a patient's existing MTX dosing regimen when combining with another drug like MRA; and (3) the POSA would have reasonably expected the claimed combination regimen to achieve better ACR70 responses than MTX alone because each drug was known to be individually successful for treating RA and combining MTX with other drugs was known to improve disease control. Decision 29-32.

The current record that now includes Dr. Silverman's declaration and the cross-examination of Dr. Zizic on his declaration testimony demonstrates that all of these assertions are wrong. This is principally because Dr. Zizic's declaration and the Petition failed entirely to consider the safety risks of combining two

hepatotoxic drugs—a consideration Dr. Zizic repeatedly admitted at deposition would have been paramount to the POSA and instrumental to the "success" of a combination therapy. Ex. 2037 (*Zizic Tr.*) at 144:14-145:6. Indeed, at his deposition neither Dr. Zizic nor Petitioners' counsel could identify any paragraph of Dr. Zizic's declaration that considered whether MRA and MTX could be safely administered in combination. Ex. 2037 (*Zizic Tr.*) at 250:6-254:6.

The record now before the Board confirms that when combining a DMARD with MTX for the first time, those skilled in the art out of safety concerns would often use something less than the highest effective monotherapy dose of the DMARD, MTX, or both. This was especially true of drug combinations with overlapping toxicities, such as the liver toxicity MTX and MRA were both known to cause.

But even were the POSA somehow motivated to combine the highest known effective dose of MRA with 10-25 mg/week of MTX, she would not have reasonably expected this combination to succeed. The prior art was simply devoid of any data on the safety or efficacy of combining MRA with MTX at any dosage; and the field was replete with reports of unsuccessful DMARD combinations that had failed to demonstrate *any* appreciable benefit over monotherapy with acceptable toxicity, let alone the improved or synergistic ACR70 responses the patent claims.

1. The POSA Would Not Have Been Motivated to Combine MTX with 8 mg/kg MRA.

Petitioners argue that the POSA would have been motivated to use the claimed 8 mg/kg monthly dose of MRA in combination with MTX because that was the MRA monotherapy dose "recommended" in *Nishimoto 2002*. In instituting, the Board credited Dr. Zizic's "currently unrebutted testimony" that "DMARDs are generally administered in the same dosage amount and frequency when given in combination with methotrexate as they are when given alone." Decision at 30. But Dr. Silverman flatly refutes that assertion and substantiates his opinion with several references that demonstrate when combining MTX with another DMARD, the common practice in 2003 was to use a DMARD dosage that was *lower* than the highest monotherapy dosage known to be effective in order to minimize toxicity—particularly where there was a risk of overlapping toxicity with MTX. Ex. 2036 (*Silverman Decl.*), ¶¶ 138-47. Dr. Zizic, when confronted at his deposition with some of these examples, conceded that the definitive statement in his declaration—the one the Board relied on at institution—was not accurate and the POSA would have accounted for these toxicity concerns. Ex. 2037 (*Zizic Tr.*) at 264:9-265:11.

Were the POSA motivated to combine these two drugs at all, Dr. Silverman explains that this principle would have motivated the POSA to combine MTX, not with the 8 mg/kg of MRA *Nishimoto 2002* "recommended" for monotherapy use,

but instead with the 4 mg/kg dose the same trial showed was less toxic yet equally if not more effective in achieving an ACR70 response in patients. Ex. 2036 (*Silverman Decl.*), ¶¶ 137, 146-47. This comparative data is disclosed in the prior art reference, *Okuda 2003* (Ex. 2020), that was considered by the Examiner during prosecution, Ex. 1004 (*'201 File History*) at 156-58, but inexplicably goes unmentioned in Dr. Zizic's analysis.[2] The comparative efficacy data is also disclosed in *Nishimoto Abstract B* that Petitioners have cited as Ex. 1017.

As Dr. Silverman explains, Ex. 2036 (*Silverman Decl.*), ¶ 139, the practice of using lower doses in combination was first described in a 1994 meta-analysis evaluating the efficacy and toxicity of RA combination therapies. *Felson 1994* reviewed 214 RA combination therapy trials and observed that "the individual agents tended to be prescribed at the *minimal* effective therapeutic dosage." Ex. 2010 (*Felson 1994*) at 4 (emphasis added). It cites as an example a clinical trial of azathioprine and MTX where the "most aggressive combination regimen" utilized 100 mg of azathioprine daily and 7.5 mg of methotrexate weekly, compared to

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[2] At his deposition Dr. Zizic admitted that he had never even reviewed *Okuda 2003*, let alone considered its toxicity data, despite acknowledging that it was an important reference in the '201 patent's prosecution history. Ex. 2037 (*Zizic Tr.*) at 272:13-273:1, 274:20-275:12.

monotherapy regimens of 150 mg azathioprine daily and 15 mg of methotrexate weekly. *Id.*

The Institution Decision observes that *Felson 1994*'s disclosure of using lower effective dosages to minimize toxicity does not "appear to be a statement of any general practice in the field." Decision at 30. As Dr. Silverman explains, it is, providing multiple examples that support *Felson 1994*'s teachings. Ex. 2036 (*Silverman Decl.*), ¶¶ 141-146.

One comes from the combination therapy trials of MTX and leflunomide. Ex. 2036 (*Silverman Decl.*), ¶ 142. Leflunomide is a small-molecule DMARD developed in the 1990s to treat moderate-to-severe RA but comes with a significant hepatotoxicity risk Ex. 2069 (*1998 ARAVA® Label*) at 4, 11-13, 16-17, 21. A 1999 monotherapy trial reported that leflunomide was effective as a monotherapy when patients were given a loading dose of 100 mg for up to 3 days, followed by a daily dose of 20 mg. Ex. 2050 (*Smolen 1999)* at 1, 7. But when leflunomide was later tested in combination with MTX, the same Dr. Weinblatt who authored the reference Petitioners assert in this Ground lowered the dose out of toxicity concerns. Ex. 2042 (*Weinblatt 1999*). Dr. Weinblatt explained his thinking:

> Because of concern regarding potential toxicity and lack of relevant safety data in animal models, the dosing

> regimen of leflunomide was modified from that *normally used for treatment of RA*.

Id. at 2 (emphasis added). Specifically, the protocol called for a loading dose of 100 mg/day for two days (not the normal three days), followed by daily doses of 10 mg—*half* the dose used in the successful monotherapy trial.

The practice of using lower doses in combination regimens also occurred with the combination of MTX with biologics. Ex. 2036 (*Silverman Decl.*), ¶ 143. For example, the 2002 label for adalimumab recommends a 40 mg *every-other-week* dose when it is administered in combination with MTX, but then advises that "[s]ome patients *not taking concomitant MTX* may derive additional benefit from *increasing the dosing frequency* of HUMIRA to 40 mg *every week*." Ex. 1033 (*Humira Label 2002*) at 14 (emphases added). As Dr. Silverman explains, limiting the combination dosage to *half* that of the highest recommended monotherapy dosage reflects toxicity concerns from using the two drugs in combination. Ex. 2036 (*Silverman Decl.*), ¶ 143.

The same reduced dosing for combination therapy can be seen in the *Weinblatt 2003* reference that Petitioners assert invalidates the claims. Ex. 2036 (*Silverman Decl.*), ¶ 143. *Weinblatt 2003* discloses clinical results of combining adalimumab with MTX. *See generally* Ex. 1008. A prior clinical trial had already established adalimumab's effectiveness as a monotherapy at dosages of 20 mg, 40

mg, or 80 mg *every week*. Ex. 2071 (*Van de Putte 1999*) at 1. That monotherapy trial had concluded that all three dosages "were nearly *equally efficacious* when given s.c. in patients with active RA" and were all "statistically significantly superior to placebo ($p < 0.001$)." *Id.* But when combining adalimumab with MTX, the *Weinblatt 2003* trial utilized lower adalimumab dosages of 20 mg, 40 mg, or 80 mg *every other week*. Ex. 1008 (*Weinblatt 2003*) at 1. Were Petitioners correct that the POSA would have used the "*same* dosage amount and frequency" in combination with MTX as was known to be effective for monotherapy, Decision at 30, *Weinblatt 2003* would not have used 20 mg, 40 mg, and 80 mg *every-other-week* dosages when combining adalimumab with MTX. Ex. 2036 (*Silverman Decl.*), ¶ 143. This example directly addresses the Board's question of whether *Felson*'s statement of general practice was applicable to "combination of MTX with a cytokine [receptor] antagonist, such as MRA." Decision at 30. It was.

Nor would another example Petitioners rely on, etanercept, have motivated the POSA to combine the higher 8 mg/kg dose of MRA with MTX, as Dr. Silverman explains. Ex. 2036 (*Silverman Decl.*), ¶ 145. Etanercept had been studied in "a randomized controlled trial" comparing two doses in RA patients—25 mg twice weekly and 50 mg twice weekly. Ex. 2060 (*Enbrel® 2002 Label*) at 23. Yet this biologic was approved at only the lower dose (25 mg twice weekly) to be taken with or without MTX. *Id.* at 23. While the higher dose (50 mg twice

weekly) was also clinically effective, it was not pursued due to a "higher incidence of adverse reactions [with] similar ACR response rates" compared with the lower dose. *Id.* In other words, where two dosages offered comparable efficacy, the greater toxicity concerns associated with that higher dose led to selection of only the lower dosage. Ex. 2036 (*Silverman Decl.*), ¶ 145.

As Dr. Silverman explains, the POSA would have applied these teachings to the clinical data available for tocilizumab. Ex. 2036 (*Silverman Decl.*), ¶ 146. The prior art disclosed that: (1) 4 mg/kg of tocilizumab monotherapy was equally or more effective than 8 mg/kg at achieving an ACR70 score, Ex. 1017 (*Nishimoto Abstract B*) at 2, Ex. 2020 (*Okuda 2003*) at 23; and also that (2) MRA exhibits a dose-dependent increase in liver toxicity, going from 7.4% of patients affected with the 4 mg/kg dose to 25.5% of patients affected with the 8 mg/kg dose, Ex. 2020 (*Okuda 2003*) at 24.[3]

Especially given the liver toxicity that was known to be associated with MTX alone, Ex. 2036 (*Silverman Decl.*), ¶¶ 111-12, the POSA would have read

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[3] Dr. Silverman explains the relevance of elevated liver enzymes to hepatotoxicity in ¶¶ 114-15 of his declaration. Dr. Zizic also acknowledged the relevance of these liver function tests to assessing hepatotoxicity at deposition. Ex. 2037 (*Zizic Tr.*) at 70:15-71:12.

Nishimoto Abstract B and *Okuda* to counsel against combining MTX and with the claimed 8 mg/kg tocilizumab dose. Ex. 2036 (*Silverman Decl.*), ¶ 147. The POSA would not have risked combining the higher dose of tocilizumab with another hepatotoxic drug (MTX) to improve ACR70 response when she believed that such a result could be achieved just as easily (if not even *easier*), and with considerably less toxicity risk, by using a 4 mg/kg dose of tocilizumab. *Id.*

2. The POSA Would Not Have Been Motivated to Use the Claimed Dosage of MTX with MRA.

Petitioners and Dr. Zizic are also incorrect regarding the POSA's motivation to use the claimed dose of MTX (10 to 25 mg weekly). They once again assume that the POSA would have been motivated to use the same dosages that had been established as effective in monotherapy treatment because in *Weinblatt 2003*, the volunteers maintained their existing MTX dose they had been receiving as monotherapy before the combination trial started. Ex. 1008 (*Weinblatt 2003*) at 2. But as Dr. Silverman explains, *Nishimoto 2002* never discloses whether the patients enrolled in the European trial were on an existing dose of MTX, but even if they were, the POSA would have lowered the dosages of both tocilizumab *and* MTX to address concerns about toxicity. Ex. 2036 (*Silverman Decl.*), ¶ 148.

Maini 1998 is instructive on this issue. Ex. 2036 (*Silverman Decl.*), ¶ 149. That study reported the results of a trial combining methotrexate and infliximab. Not only was this the first trial testing this particular combination, it was also the

first trial testing *any* combination of MTX and one of the new biologic TNFα inhibitors. That made a difference to the study authors. Although by 1998 administering MTX at more than 10 mg/week was well established as an RA treatment, the study authors, citing toxicity concerns, opted to use a lower, 7.5 mg weekly dose. Study participants who were taking a higher MTX dose than that had their doses lowered before the trial started. As the authors explained:

> A fixed low dosage of MTX was chosen because this trial was the *first clinical experience* of the combined use of anti-TNF therapy with MTX. A low dose, it was reasoned, *might minimize toxicity* without compromising the additive benefit.

Ex. 1015 (*Maini 1998*) at 2 (emphases added). In fact, *Maini 1998* reports that this dosage of MTX was selected even though "[a]t this dosage, MTX would not be expected to be effective in this patient population." *Id.* In other words, the authors of *Maini 1998* chose to prioritize patient safety and reduction of toxicity over efficacy.

Others in the field exhibited the same caution, selecting a lower-than-average dose of MTX when testing it in combination with new DMARDs. Ex. 2040 (*Haagsma 1997*) (sulfasalazine and 7.5 mg/weekly MTX); Ex. 2039 (*Willkens 1995*) (azathioprine and 7.5 mg/weekly MTX); Ex. 2024 (*Williams 1992*) (auranofin and 7.5 mg/weekly MTX). As Dr. Silverman explains, the POSA

testing the then-new combination of tocilizumab and MTX would have shared the same motivation that inspired the *Maini* researchers when they were testing the infliximab/MTX combination for the first time, and the POSA would have been motivated to use a dosage of *less than* 10 mg/week MTX to lower the risk of liver toxicity. Ex. 2036 (*Silverman Decl.*), ¶ 150.

That *Weinblatt 2003* used a higher dosage of MTX in combination with adalimumab does not alleviate the concerns the POSA would have had with a tocilizumab/MTX combination, as Dr. Silverman explains. Ex. 2036 (*Silverman Decl.*), ¶ 151. Adalimumab, like infliximab, is an anti-TNFα antibody. By the time the study in *Weinblatt 2003* was conducted, *Maini 1998* had already proven that this class of molecule could be safely combined with MTX, without any significant increase in toxicity. *Id.* Nor was there known overlapping hepatotoxicity with the two drugs. As such, it made sense for *Weinblatt 2003* to test a higher dose of MTX in combination with adalimumab. *Id.*

By contrast, in 2003, anti-IL-6R therapy was a new and still largely unproven concept, and several more years would pass until FDA approved such a therapy. Ex. 2036 (*Silverman Decl.*), ¶ 151. There were limited data on tocilizumab's safety and efficacy in treating RA as a monotherapy and no data whatsoever addressing its safety and efficacy when combined with MTX, although it was known that both drugs were individually hepatotoxic. When approaching

"the first clinical experience," Ex. 1015 (*Maini 1998*) at 2, of combining anti-IL-6R therapy and MTX, the POSA would have taken the more cautious approach illustrated by *Maini 1998* and reduced the amount of MTX that was administered to patients to less than 10 mg/week. Ex. 2036 (*Silverman Decl.*), ¶ 151.

3. The POSA Would Not Have Reasonably Expected the Claimed Combination Regimen to Be Successful.

Petitioners and Dr. Zizic offer three reasons why the POSA would reasonably have expected success from combining 8 mg/kg MRA with 10 to 25 mg/week MTX. Pet. 37-38; Ex. 1002 (*Zizic Decl.*), ¶¶ 155, 158, 163, 168. None withstands scrutiny. All fail, by Dr. Zizic's own admission, to account for overlapping hepatotoxicity concerns that would have led the POSA to reasonably expect the claimed combination regimen to be unsafe. Nor would the POSA have reasonably expected the claimed combination regimen to provide improved efficacy over monotherapy, particularly at the claimed ACR70 level, based on the extensive history of RA combination failures now of record. Ex. 2036 (*Silverman Decl.*), ¶¶ 152-53. Either reason alone is sufficient for the Board to find that Petitioners have failed to meet their burden to prove unpatentability of the claims.

a. No Reasonable Expectation That the Claimed Combination Regimen Would Be Safe.

Both sides' experts agree that a treatment regimen combining DMARDs would not be considered successful absent evidence of acceptable toxicity. Ex.

2036 (*Silverman Decl.*), ¶¶ 84, 156; 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 to 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 suggesting 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 bothered 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, *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 MRA. Ex. 2036 (*Silverman Decl.*), ¶ 113. *Nishimoto 2002* 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 reasonable concern over administering two drugs like MTX and tocilizumab with overlapping toxicities even if the POSA were 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 as discussed *supra* § III.B.1, 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." Ex. 2042 (*Weinblatt 1999*) 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 chance 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. *Id.* 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—notably, a concern that did not exist for the TNFα inhibitors that were previously co-administered with MTX. Ex. 2036 (*Silverman Decl.*), ¶¶ 123, 155. The POSA would have concluded that the

overlapping toxicities from combining MTX and tocilizumab would outweigh any expected benefit, which, as explained *infra,* was uncertain in any event. *Id*., ¶¶ 123, 156-57.

b. No Reasonable Expectation that Successful Monotherapies Would Also Work in Combination.

In his list of reasons why the POSA administering the claimed regimen would have had a reasonable expectation of success, Dr. Zizic points to the success MRA and methotrexate had shown as monotherapy treatments for RA patients. Ex. 1002 (*Zizic Decl*.), ¶ 155. 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.*), ¶ 86.

As Dr. Silverman explains, the *Felson* meta-analysis (discussed *supra* § IV.B.3.a) 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—a MTX and auranofin combination, Ex. 2024 (*Williams 1992*), and a MTX and azathioprine combination, Ex. 2072 (*Willkens 1992*) and Ex. 2039 (*Willkens 1995*)—neither of which succeeded in demonstrating a benefit in efficacy over monotherapy. 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. Several literature reviews published both before and after the priority date repeatedly concluded that combination therapy generally provided no benefit over monotherapy. 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.

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

Yoshizaki is the only publication Petitioners identify as purportedly disclosing successful treatment of RA with MTX and an anti-IL-6 receptor antibody. It is the main anticipation reference asserted by Petitioners in related proceeding IPR2021-01024 challenging related U.S. Patent No. 7,521,052. *Yoshizaki* discloses the experimental use of "rhPM-1" to treat RA patients in Japan from 1995 to 1997. Ex. 1005 (*Yoshizaki 1998*). RhPM-1 is an early designation for the humanized antibody later renamed tocilizumab.

The patients described in *Yoshizaki* had "severe RA who were resistant to any conventional therapy." *Id.* at 10. They suffered chronic RA symptoms "despite treatment with NSAIDs, DMARDs, MTX, and maintenance doses of steroids." *Id.*

Petitioners rely entirely on two sentences in Figure 8 of *Yoshizaki*, describing the treatment received by one particular patient, to argue that this reference discloses combination therapy of MRA and MTX within the same treatment regimen:

> A 67-year-old woman with severe RA given NSAIDs,

> DMARDs, MTX and 15 mg predomizolone [sic][4] 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. Under Petitioners' strained reading of *Yoshizaki*, this 67-year-old patient was concomitantly administered *all* the NSAIDs, DMARDs, MTX, and steroids previously tried without success within a *single* "conventional treatment" regimen that she received in combined with rhPM-1. But as Dr. Silverman explains, the POSA would never have interpreted *Yoshizaki* in that manner for a number of reasons: (1) a "conventional treatment" regimen for RA patients did not necessarily include MTX at the time; (2) no rational clinician would have administered the laundry list of drugs recited in Figure 8 concomitantly, and this list instead refers to multiple treatment regimens that were progressively tried without success; (3) because *Yoshizaki* reports the *first* administration of rhPM-1 to RA patients, the common practice was to administer the experimental therapy as a

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[4] 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.

monotherapy, rather than in combination with other DMARDs like MTX, to avoid unknown toxicity risks and contaminating efficacy results; and (4) neither MTX nor rhPM-1 were approved therapies in Japan at the time, and the POSA would not have administered two experimental therapies in combination, especially given the conservative approach Japanese clinicians take to MTX administration even today. Ex. 2036 (*Silverman Decl.*), ¶¶ 58-74, 104, 154.

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 (and not at the claimed dosages) would not prompt the POSA to give it any weight when determining whether tocilizumab could be successfully combined with MTX at the claimed dosages. Ex. 2036 (*Silverman Decl.*), ¶ 104.

d. 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*.), ¶ 155. 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.*), ¶¶ 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.*), ¶ 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.*), ¶ 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 (*Nishimoto 2002*) 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 2003* 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.

e. No Reasonable Expectation of Achieving the Claimed ACR70 Limitations.

An ACR70 response is considered a "Major Clinical Response" in the treatment of RA and by definition requires a 70% improvement in tender and swollen joint counts and a 70% improvement in three of the five remaining core set measures: patient and physician global assessment, pain, disability, and an acute phase reactant. Ex. 1009 (*1999 FDA Guidance*) at 6-7. As Dr. Silverman

explains, ACR70 responses are considered significantly more rigorous and more difficult to achieve than either an ACR20 or ACR50 response, and many RA treatments at the time failed to achieve even ACR50 responses, let alone ACR70. Ex. 2036 (*Silverman Decl.*), ¶ 158. For instance, in a historical database compiling results from three clinical trials performed by the Cooperative Systematic Studies of Rheumatic Diseases group, the percentage of patients in the active drug arm (either low-dose methotrexate, D-penicillamine, injectable gold, or auranofin) who achieved improvement at the ACR20 level was 40.3%, which dropped dramatically to 9.0% for ACR50 and even further to 0.6% for ACR70. Ex. 1009 (*1999 FDA Guidance*) at Appendix A. In a head-to-head trial of auranofin versus MTX, the percentage of MTX-treated patients achieving ACR20 was 64.7%, which dropped to 35.3% for ACR50, and finally 9.2% for ACR70. Ex. 2036 (*Silverman Decl.*), ¶ 158.

The challenged claims all require comparative efficacy involving ACR70 responses. Specifically, the claimed combination regimen must achieve greater ACR70 responses than either MTX and/or MRA alone (claims 1 and 6), or *synergistic* ACR70 responses that are greater than the additive result of MTX and MRA monotherapies (claim 11). But as discussed *supra* (§ IV.B.3.b), the field was plagued with failed RA combination therapies—including combinations with MTX—that had not demonstrated increased efficacy over monotherapy at any

level, let alone ACR70. Ex. 2036 (*Silverman Decl.*), ¶ 159. And while some TNFα biologics demonstrated improvement when combined with MTX, many other biologics did not, leaving the POSA unable to predict whether a possible combination of MRA and MTX would achieve *any* increased efficacy over monotherapy, let alone greater ACR70 response. *Supra* IV.B.3.d.; Ex. 2036 (*Silverman Decl.*), ¶ 159.

Nor would the POSA have reasonably expected to achieve the claimed ACR70 limitations based on the prior combination TNFα biologics and MTX. Ex. 2036 (*Silverman Decl.*), ¶¶ 160-62. This is most readily apparent with regards to claim 11's synergistic efficacy limitation. As Dr. Silverman explains, synergy exists when the combination of two drugs produces results than are greater than those one would expect to achieve by adding together the results of the drugs taken alone. *Id*., ¶ 160. Determining whether synergy exists therefore requires at least three sets of data: (1) efficacy data on the first drug as a monotherapy; (2) efficacy data on second drug as a monotherapy; and (3) efficacy data on the combination therapy. As of April 2003, adalimumab had not been evaluated in combination with MTX in a three-armed clinical trial. *Id.* The *Weinblatt 2003* reference Petitioners assert as the basis for this Ground not only is missing one of these sets of data—an arm testing monotherapy use of adalimumab—but acknowledges that absence as a "limitation" of the trial. Ex. 1008 (*Weinblatt 2003*) at 10. The

authors explain that another trial rectifying this deficiency "is currently under way and will provide further insight into the utility of adalimumab in the treatment of RA." *Id*. Without knowing what that data shows, the POSA could not reliably determine whether the combination therapy produced results that were synergistically higher than what the two drugs achieved in monotherapy. Ex. 2036 (*Silverman Decl.*), ¶ 160.[5]

In the absence of data necessary to prove synergy, the POSA would not have simply assumed that the outcome of the new trial *Weinblatt 2003* reported was "currently under way" would demonstrate synergy at the ACR70 level with the combination of adalimumab and MTX. Ex. 2036 (*Silverman Decl.*), ¶ 161. And in

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[5] Nor would *Maini 1998* (Ex. 1015) have provided a reasonable expectation of achieving synergistic ACR70 responses with the claimed combination regimen. Ex. 2036 (*Silverman Decl.*), ¶ 162. As Dr. Silverman explains, this reference did not report any ACR70 results and any "apparent synergy" observed with the combination of infliximab and MTX was only at the lowest dosage of infliximab tested—1 mg/kg—and not the higher 3 mg/kg and 10 mg/kg dosages. Ex. 1015 at 9-10; Ex. 2036 (*Silverman Decl.*), ¶ 162. The authors also attributed the observed results to MTX's ability to suppress immunogenic responses to infliximab, which the prior art taught was a problem that MRA did not have.

fact, when the three-armed PREMIER study was completed years later, the authors found no synergy at the ACR70 level with the adalimumab/MTX combination. Ex. 2063 (*Breedveld 2004*) at 1. Certainly there was no reasonable expectation that synergy would exist with an entirely different biologic that targets a different cytokine and having a different mechanism of action.

C. The Claimed Combination Regimen Produces Unexpected Results That Support the Claims' Non-Obviousness.

"Evidence that a combination of known components results in an effect greater than the predicted additive effect of the components can support a finding of nonobviousness." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1362 (Fed. Cir. 2012); *see also Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1309 (Fed. Cir. 2010); *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 808 (Fed. Cir. 1989).

In its Institution Decision, the Board deferred consideration of unexpected results to allow the record to be developed further. Decision at 34. As demonstrated below and as explained by Dr. Silverman, the CHARISMA trial's results were both unexpected and surprising and underscore the non-obviousness of the claimed dosing regimen.

1. The Closest Prior Art Is MRA Monotherapy.

"Unexpected results are shown in comparison to what was known, not what was unknown." *Millennium Pharms., Inc. v. Sandoz, Inc.*, 862 F. 3d 1356, 1368

(Fed. Cir. 2017). While there is no single test for determining which prior art is the closest, generally speaking, the closest prior art will be the reference that shares the most limitations in common with the patented claims. *See*, *e.g.*, *Application of Merchant*, 575 F.2d 865, 868 (C.C.P.A. 1978).

Petitioners argue that the closest prior art is *Nishimoto 2002*, alleging that it discloses not only administering a combination of MRA and MTX to an RA patient, but the same 8 mg/kg every four-week MRA regimen recited in the claims. Decision at 33; Ex. 2001 (*Zizic Decl.*) at 177. But as the Board observed in tentatively rejected Petitioners' *Nishimoto 2002* anticipation argument, the reference plainly does *not* disclose any dosing regimen for combination therapy with MTX and MRA. Decision at 22-23. The only disclosure of combination therapy is the passing reference to the European clinical trial that was "currently underway." Ex. 1006 (*Nishimoto 2002*) at 5. More importantly, it does not contain any data whatsoever regarding the percentage of patients who achieved an ACR70 response when given 8 mg/kg MRA, either as a monotherapy or in combination. *Nishimoto 2002* therefore fails to establish a baseline against which the issue of unexpected results can be evaluated and therefore serves no useful purpose in analyzing this issue. *Millennium*, 862 F. 3d at 1368.

Because the issue of unexpected results requires a comparison against what was known, *Millennium*, 862 F. 3d at 1368, the closest prior art for purposes of

analyzing unexpected results is *Okuda*. Ex. 2036 (*Silverman Decl.*), ¶¶ 171-75. It includes the most comprehensive data concerning MRA monotherapy and, unlike *Nishimoto 2002*, includes ACR70 data as a baseline against which the '201 Patent's data from CHARISMA may be evaluated. Ex. 2019 (*Okuda 2003*) at 8. Specifically, *Okuda* reports that about 20% of patients who received 4 mg/kg MRA achieved ACR70 response while 16% achieved the same response on the 8 mg/kg dose.

These results would have shaped the POSA's expectations about what would result from treatment with MRA, Ex. 2036 (*Silverman Decl.*), ¶¶ 163-70, and based on these results, the POSA would have expected a 4 mg/kg MRA regimen to be more, or at least equally, effective than an 8 mg/kg MRA regimen. Put another way, the POSA would not have expected the higher, 8 mg/kg dosage of MRA to show added benefit over the 4 mg/kg in view of these data from *Okuda*. Rather, the POSA would have expected the lower, 4 mg/kg dose to perform the best when paired with MTX given these data.

2. The Combination of 8 mg/kg MRA and 10-25 mg/week MTX Exhibits Surprising Efficacy.

Against these expectations, the CHARISMA data reported in Table 1 demonstrates efficacy (as measured by ACR70) that was surprisingly different in both kind and degree. An ACR70 response is considered a "Major Clinical Response," and it is the most desirable and difficult to achieve of these ACR

responses Ex. 1009 (*FDA Guidelines*) at 6-7. The following table compares the ACR70 results from MRA monotherapy disclosed in *Okuda* as compared to the ACR70 results from combination therapy achieved in CHARISMA and reported in the patent:

MRA Dose	**ACR70 (*Okuda 2003* at 23[6])**	**ACR70 with MTX (Ex. 1001 at 17, Table 1)**
4 mg/kg	20.4%	12.2%
8 mg/kg	16.4%	36.7%

As shown above, the combination of 8 mg/kg MRA and MTX substantially outperformed the combination with 4 mg/kg MRA. The POSA could not have predicted these results from the disclosure in *Okuda*. Ex. 2036 (*Silverman Decl.*), ¶ 175.

At 2 mg/kg MRA + MTX, 14.0% of patients achieved an ACR70 response, compared to 16.3% of patients who achieved that response on MTX alone. When the MRA dosage was increased to 4 mg/kg that percentage of patients achieving an

[6] Although decimal point values cannot be discerned from *Okuda 2003*'s bar graph, Ex. 2020 at 23, the values recited in this table are confirmed by referring to Ex. 1017 (*Nishimoto Abstract B*), which describes the same ACR70 values as found in *Okuda 2003*. *Compare* Ex. 2020 (*Okuda 2003*) at 23 and Ex. 1017 (*Nishimoto Abstract B*) at 2.

ACR70 response actually dropped down to 12.2%. This is significant because the prior art (*Nishimoto Abstract B* and *Okuda*) disclosed that 4 mg/kg was an effective dose, particularly in providing an ACR70 response. Given that both dosage levels resulted in ACR70 scores below that of MTX alone, the POSA would reasonably have questioned whether combination therapy with MRA and MTX could be effective. The apparent decrease in ACR70 response between the 2 mg/kg combination and the 4 mg/kg combination also would have led the POSA to believe that there was no dose-dependent response, and that further increasing the dosage of MRA would not produce substantial benefits. Ex. 2036 (*Silverman Decl.*), ¶¶ 164-65.

Surprisingly, however, the data from Table 1 show that the opposite is true. When MRA dosage was increased to 8 mg/kg, the percentage of patients achieving ACR70 responses from combination therapy increased to 36.7%. Fig. 2 of the scientific counterpart of the patent (Ex. 1039 (*Maini 2006*)) demonstrates that the ~37% ACR70 rate with the 8 mg/kg MRA + 10-25 mg MTX was statistically significant ($P < 0.05$) compared to treatment with MTX alone. And this ACR70 response rate was more than three times higher than the ACR70 response achieved with the 4 mg/kg combination. Ex. 2036 (*Silverman Decl.*), ¶ 166.

The POSA also would recognize from these data that the combination of 8 mg/kg MRA and MTX exhibited unexpected synergistic effects. Ex. 2036

(*Silverman Decl.*), ¶¶ 167-68. In the RA field, "synergistic effects" refers to the phenomenon where a combination of two or more drugs produces more than additive benefits, exceeding those that would be expected from combining monotherapies. *Id.* In Table 1, monotherapy with 8 mg/kg MRA produced an ACR70 response in 15.7% of patients, and monotherapy with MTX produced the same response in 16.3% of patients. Looking at these data alone, the POSA would have expected that adding 8 mg/kg MRA to MTX would produce an ACR70 response in—at most—32% of patients (15.7% + 16.3% = 32%). In fact, given the failure of combination therapy using 2 mg/kg and 4 mg/kg MRA to produce any benefits above those seen with MTX alone, the POSA reasonably would have expected that the combination of 8 mg/kg MRA and MTX would not even produce such additive results. But when the combination of 8 mg/kg MRA and MTX was tested, the result was not only better than MTX alone, it was better than the sum of the respective monotherapies. By exceeding the sum of the ACR70 responses achieved by the respective monotherapies, the ACR70 response from the 8 mg/kg combination therapy represents both an improvement in degree and kind over the prior art's treatment regimens that the POSA would have considered unexpected and valuable for patients suffering from RA.

Petitioners suggest that *Weinblatt 2003*, a paper reporting on combinations of adalimumab and MTX, would have led the POSA to expect this surprising

result. But as explained above, data from adalimumab usage would not have informed POSA's expectations concerning MRA given that the drugs have completely different mechanisms of actions. Ex. 2036 (*Silverman Decl.*), ¶ 176.

Even if the POSA were to form expectations about MRA's utility when combined with MTX based on how a completely different drug combines with MTX, Petitioners' assertion remains incorrect because the clinical trial disclosed in *Weinblatt 2003* did not test or otherwise report data on adalimumab *mono*therapy, without which the POSA could not form an expectation about whether the combination therapy produced results that were synergistically higher than what the two drugs achieved in monotherapy. Ex. 2036 (*Silverman Decl.*), ¶ 177.

In the absence of the necessary data, the POSA would not simply have assumed based on *Weinblatt 2003* that combination therapies with MTX would produce synergistic effects. Ex. 2036 (*Silverman Decl.*), ¶ 177. And the POSA would have been right not to make such assumptions, because subsequent testing of the MTX/adalimumab combination in the PREMIER trial demonstrated that adalimumab lacks synergy with MTX for achieving ACR70 responses. Ex. 2063 (*Breedveld 2004*) at 1; Ex. 2036 (*Silverman Decl.*), ¶ 178.

The claimed combination regimen also results in another unexpected benefit—a surprisingly high remission rate. Ex. 2036 (*Silverman Decl.*), ¶ 169. Remission, as Dr. Silverman explains, is the ultimate goal for many RA patients

because there is no "cure" for RA. *Id.*, ¶¶ 169-70. It confers a greater therapeutic benefit than an ACR70 response and is likewise more difficult to achieve. *Id.*; *see also* Ex. 1009 (*1999 FDA Guidance*) at 7. In fact, as Dr. Silverman observes, many early RA therapies were unable to induce remission to any appreciable extent. Ex. 2036 (*Silverman Decl.*), ¶ 170; Ex. 2065 (*Paulus 2004*) at 1, 3.

The complete data from CHARISMA was reported in *Maini 2006* (Ex. 1039). Analysis of that data demonstrates that "the rate of remission was 34% among those assigned to 8 mg/kg of tocilizumab plus MTX, 17% among those receiving 8 mg/kg of tocilizumab as monotherapy, and 8% among those receiving placebo plus MTX." *Id.* at 6; Ex. 2036 (*Silverman Decl.*), ¶ 170. In other words, the remission rate observed with the claimed combination regimen was synergistic as it was greater than the additive remission of rate of tocilizumab and MTX monotherapy. *Id.* Dr. Silverman opines that this result is "remarkable" not only because of the synergistic effects observed, but also because, as discussed above, of the difficulty in achieving any significant remission rate. *Id.*

3. The ACT-RAY Study Confirms the Value of the Invention.

Notwithstanding the publication of the '201 Patent's clinical trial results in the leading journal for the treatment of RA (*Maini 2006*, Ex. 2068), Petitioners criticized the CHARISMA trial at length in their petition, suggesting that such

results are an "anomaly" and that any the alleged benefit of the combination therapy "cannot plausibly be correct." Pet. at 50-58.

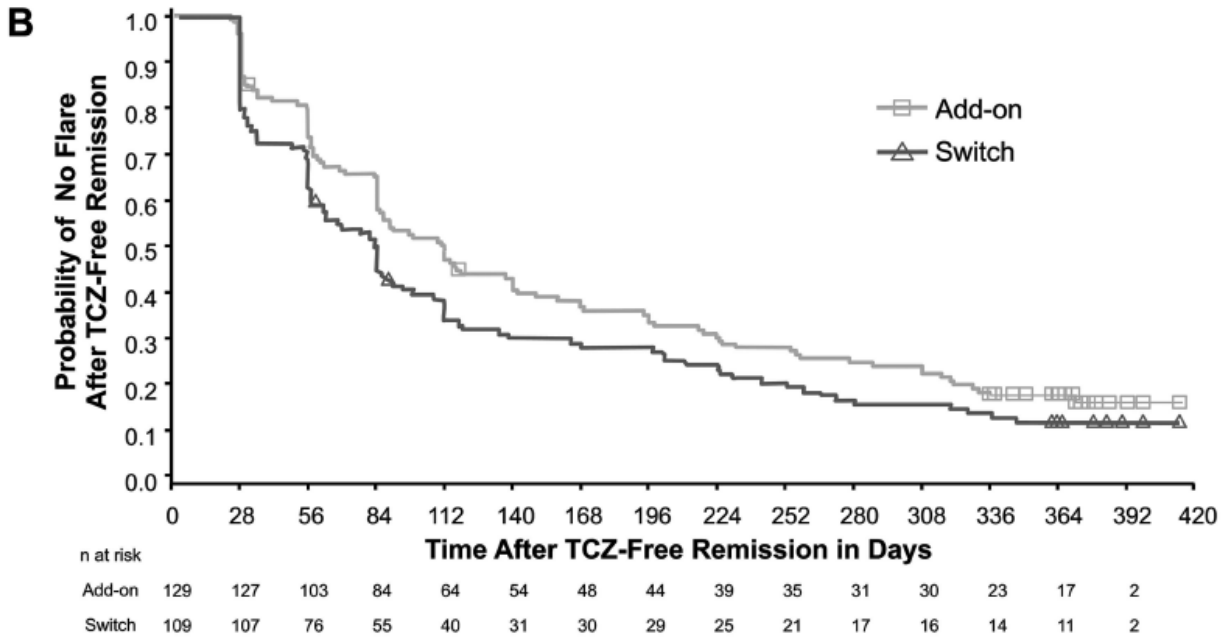
The centerpiece of Petitioner's argument is *Dougados 2012* (Ex. 1040), a publication reporting on the ACT-RAY study that compared 8 mg/kg MRA and MTX combination therapy with MRA monotherapy. As an initial matter, the ACT-RAY clinical trial discussed in *Dougados 2012* was a two-armed study and thus cannot be used to measure synergy. Ex. 2036 (*Silverman Decl.*), ¶ 179. As Dr. Silverman explains, only three-armed studies like the one disclosed in the specification of the '201 patent and in *Maini 2006* (Ex. 1039) are designed to assess whether synergy exists. Ex. 2036 (*Silverman Decl.*), ¶ 180.

Putting aside the fact that ACT-RAY was not designed to support the contention Petitioners advance, Petitioner's criticisms based on ACT-RAY are misplaced because Petitioners' argument is based on *Dougados 2012*, a report of the ACT-RAY study's data as of 24 weeks. But ACT-RAY was not a 24-week study. It was a *104*-week study. The Petition nowhere presents the ACT-RAY clinicians' final verdict on the value of the MRA + MTX combination. *See* Ex. 2036 (*Silverman Decl.*), ¶ 181.

Even at the interim 24-week mark, there were signs of this value. Ex. 2036 (*Silverman Decl.*), ¶ 181. As Dr. Silverman explains, the *Dougados 2012* paper reported a statistically significant proportion of patients with low disease activity

(DAS28-ESR < 3.2) treated with MRA and MTX combination therapy versus MRA monotherapy. Ex. 1040 at Figure 2B; Ex. 2036 (*Silverman Decl.*), ¶ 181. This interim report also disclosed a trend towards slightly higher response rates with the combination therapy compared with the monotherapy (e.g., a 5.6% difference in DAS28 remission and 3.3% difference in patients with no radiological progression). Ex. 1040 (*Dougados 2012*) at 6. As the authors of the interim report recognized, "*longer term observation* of the patients recruited for this study" is "required." *Id.* at 7 (emphasis added). Ex. 2036 (*Silverman Decl.*), ¶ 182.

The 104-week results from ACT-RAY were subsequently reported in *Huizinga 2015* (Ex. 2061). As Dr. Silverman explains, this reference demonstrates that the 8 mg/kg MRA and MTX combination provides a clinically significant improvement over the two-year period. Ex. 2036 (*Silverman Decl.*), ¶ 183. Specifically, "[a] significantly higher proportion of patients in the add-on [combination] arm achieved drug-free remission compared with patients in the switch [monotherapy] arm." Ex. 2061 (*Huizinga 2015*) at 4. These data are displayed in Figure 3B, reproduced below, which shows the clear improvement in remission between the combination arm ("Add-on") and the monotherapy arm ("Switch"):



Id. at 7.

The combination therapy arm of the trial showed statistically significant benefits compared to the monotherapy arm across a variety of parameters. Ex. 2036 (*Silverman Decl.*), ¶¶ 184-85. Based on such results, the authors of *Huizinga 2015* concluded that "combination therapy is preferred." Ex. 2061 (*Huizinga 2015*) at 7.

The inference urged by the Petition—that MRA + MTX combination therapy is not useful—is wrong. As shown above, the combination therapy yields a tangible, unexpected improvement over monotherapy. The inventors'

development of the claimed methods has improved the lives of countless RA patients and should be recognized.[7]

V. CONCLUSION

For the foregoing reasons, the Board should find claims 1-15 of the '201 Patent valid.

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[7] The Petition's criticism of CHARISMA ends with a citation to Exhibit 1041, *Chin 2015*, a "Patent Evaluation." Petitioners quote the paper as suggesting that "it has not been shown that synergistic effects can be achieved by the combination of anti-IL-6R antibody with immunosuppressants." Pet. at 58. The Petition quotes *Chin 2015* out of context. The author makes clear in the summary of the "Expert Opinion" that this comment is premised on the fact that CHARISMA was limited to RA patients and that "more diverse diseases related to IL-6 and tocilizumab therapy, not limited to rheumatoid arthritis, have to be evaluated" to ascertain the complete extent of synergy from use of tocilizumab and MTX. Ex. 1041 (*Chin 2015*) at 1. To the extent the Board puts any weight on *Chin 2015*'s analysis, it should note its conclusion regarding the patent's results: "the combination use of tocilizumab + MTX seemed to be valid as pointed out by this patent." Ex. 1041 (*Chin 2015*) at 3.

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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 13,072 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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