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 KAISA
Patent Owner.

IPR2021-01024
Patent No. 7,521,052

Title: METHOD FOR TREATING INTERLEUKIN-6 RELATED DISEASES

PETITIONERS' REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

Chugai's Patent Owner's Response ("POR") (Paper 35) relies on a semantic argument about the phrase "conventional treatment" and mischaracterizes several prior art references in an effort to rebut Petitioners' strong arguments that the '052 patent is anticipated and obvious. Chugai's effort fails. The '052 patent's single claim requires administering a combination of two drugs—MRA and MTX—at an unspecified "effective amount" to treat rheumatoid arthritis. Regardless of whether the Board adopts its preliminary construction, Chugai's proposed construction, or some combination of the two,[1] the fact remains that the "effective amount[s]" of MRA and MTX claimed by the patent were well known in the prior art, as was treatment of RA with a combination of effective amounts of those drugs. The Board should reject Chugai's arguments to the contrary and find that the '052 patent is either anticipated by Yoshizaki and/or obvious over Nishimoto in view of Weinblatt 2003.

II. CLAIM CONSTRUCTION

A. "an effective amount of an anti-IL-6 receptor antibody (anti-IL-6r antibody)" / "an effective amount of methotrexate (MTX)"

In its POR, Chugai rehashes its attempt to import limitations into the term

[1] Petitioners agree with the Board's preliminary construction and propose that it be adopted as the Board's final construction.

"effective amount," (POR at 18), which the Board properly rejected in its Institution Decision. As the Board correctly explained, the issue with Chugai's proposed construction is that it morphs the "distinct[]" and "separate[]" limitations of an "effective amount" of MRA and an "effective amount" of MTX into a "combined effectiveness amount" requirement that is inconsistent with the claim language and not supported by the Specification. Paper 23 at 11.

Chugai's position is based on the erroneous premise that "[c]laim 1 **requires that the claimed combination is 'effective'** for 'treating RA' in a 'patient in need thereof.'" POR at 16 (emphasis added). But, that is not what claim 1 says. The term "effective" explicitly modifies the amounts of the individual drugs, not the "claimed combination." Ex. 1001 at 22:31-35. This same faulty assumption pervades Dr. Silverman's, Chugai's expert's, interpretation of the term, which should be discounted for that reason alone. Ex. 2036, ¶54 ("Claim 1 of the '052 Patent requires that the claimed combination is 'effective' for 'treating RA' in 'a patient in need thereof.'"). Chugai's attempt to bolster its position by arguing that Dr. Zizic, Petitioners' expert, agreed that a "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" should be rejected because Dr. Zizic did not take that position. POR at 16 (citing Ex. 2037 at 144:14-145:6). An amount of a drug can, of course, be effective and be toxic. As Dr. Zizic explained

at his deposition, some drugs can be very successful in treating RA but cannot be used as a treatment option given their toxicity. *See, e.g.*, Ex. 2037 at 43:22-44:7.

None of the limitations Chugai seeks to import (e.g., combined effectiveness, acceptable toxicity) are present in the claims, nor is there adequate support for these limitations in the Specification. For the reasons set out in the Petition, (Paper 3 at 18-21), as well as those articulated by the Board, (Paper 23 at 9-14), Petitioners submit that the Board's preliminary construction is correct and should be adopted as its final construction.

III. THE '052 PATENT IS ANTICIPATED BY YOSHIZAKI

Yoshizaki anticipates the '052 patent because it discloses a method of treating an RA patient with an effective amount of MRA and an effective amount of MTX. Ex. 1005.11. Specifically, Yoshizaki discloses the treatment of a patient with severe RA with rhPM-1.[2] *Id.* Yoshizaki discloses that the patient with severe RA "received 50 mg rhPM-1 twice a week or once a week **combined with the conventional treatment**," which a POSA would have understood to include MTX. *Id.* (emphasis added). And, Yoshizaki discloses that "clinical and laboratory abnormalities improved after the rhPM-1 therapy." *Id.*

[2] The parties agree that rhPM-1 was an early designation for the anti-IL-6 receptor antibody that later became known as MRA or tocilizumab. *See, e.g.*, POR at 19.

A. Yoshizaki Discloses a MRA/MTX Combination Regimen

A POSA would have understood "the conventional treatment" in Yoshizaki to include MTX because Yoshizaki discloses that in the same sentence. Ex. 1005.11. Yoshizaki states that the patient with severe RA was given "NSAIDs, DMARDs, **MTX**, and 15 mg [prednisolone]" and received MRA "combined with **the** conventional treatment." *Id.* (emphasis added). As Dr. Zizic explains, a POSA would have understood that "**the** conventional treatment" referred to the treatment that had just been recited by Yoshizaki. Ex. 1064, ¶22.

Consistent with this disclosure, Chugai's expert, Dr. Silverman, admitted that treating an RA patient with MTX was part of conventional treatments at the time of Yoshizaki's publication. In his declaration, Dr. Silverman states that "a conventional initial treatment [at the time of Yoshizaki] would have included an NSAID and perhaps a glucocorticoid along with one of the traditional DMARDs available." Ex. 2036, ¶64. And, at his deposition, Dr. Silverman admitted that MTX was considered one of the "traditional DMARDs available," as he used that phrase in his declaration. Ex. 1065 at 190:3-6 (**Q**: Was MTX considered one of the "traditional DMARDs available," as you used that phrase, as of this time? **A**: Yes.). Thus, not only does Yoshizaki specifically disclose that the patient's conventional treatment included MTX, Chugai's expert admits that was consistent with the standard practice at the time.

Given the above, a POSA would undoubtedly have understood that Yoshizaki discloses administering a MRA/MTX combination to a patient when it discloses that a patient received "50 mg rhPM-1 twice a week or once a week combined with the conventional treatment," (Ex. 1005.11). Ex. 1064, ¶¶20-22.

Chugai nevertheless argues that Yoshizaki's conventional treatment may not have included MTX because: (1) conventional treatments did not **always** include MTX; (2) a "conventional treatment" would not have included administering "NSAIDs, DMARDs, MTX, and 15 mg [prednisolone]" as part of the same regimen; and (3) "common practice" was to administer a new RA drug by itself, rather than in combination. POR at 20-30. None of these arguments withstand scrutiny, nor do they justify ignoring the plain language of Yoshizaki.

As explained above, a POSA would have understood that when Yoshizaki discloses combining rhPM-1 with "the conventional treatment," that includes treatment with MTX, not just because MTX was **a** conventional treatment for RA at that time, but because Yoshizaki explicitly discloses that **the** conventional treatment this particular RA patient received **did** include MTX. Ex. 1064, ¶22. Chugai's argument that conventional treatments did not always include MTX thus entirely misses the point.

Chugai's argument that conventional treatment did not involve administering NSAIDs, DMARDs, MTX, and prednisolone as part of the same treatment regimen

also fails. POR at 23-24. The 1996 ACR Guidelines instruct using such a regimen. The 1996 Guidelines disclose that a patient with Refractory RA should be treated with: the most effective NSAID; the most effective DMARD (single **or combination**); and possible local or oral steroids.[3] Ex. 1022.02. That is exactly the same treatment regimen disclosed in Yoshizaki.[4] Thus, there is no reason for a POSA to have questioned that the combination of drugs identified by Yoshizaki was part of the patient's "conventional treatment." Ex. 1064, ¶¶20-25. Indeed, other physicians at that time administered this same combination to RA patients. *See, e.g.*, Ex. 1058 (studying a combination of MTX, two other DMARDs, and permitting concomitant administration of corticosteroids and NSAIDs)

Chugai appears to take issue only with Yoshizaki's description of "the

[3] Dr. Silverman agreed that a patient who has Refractory RA could also have severe RA, confirming that the 1996 ACR Guidelines apply to the patient described in Yoshizaki. Ex. 1065 at 193:9-194:11.

[4] Dr. Silverman acknowledged that prednisolone was "a common steroid used in the treatment of RA patients," (Ex. 2036, ¶60 n.2; Ex. 1065 at 183:12-18), and that combinations of multiple DMARDs, including MTX, were "conventional," (Ex. 2036, ¶66 n.3). And, the 1996 ACR guidelines identify MTX as one of the DMARDs that may be used in combination. Ex. 1022.06-07.

conventional treatment" as containing "NSAID**s**" instead of "an NSAID." POR at 23 ("a rheumatologist would never prescribe multiple NSAIDs at once"). But, as Dr. Silverman admitted at his deposition, the term "NSAID**s**" is often used to refer to a single NSAID. Ex. 1065 at 191:13-22, 195:11-19, 196:20-197:6. In fact, both the ACR guidelines and Dr. Silverman use the term "NSAIDs" in this way. Ex. 1010.05-06 ("Pharmacologic therapy for RA often consists of combinations of NSAIDs, DMARDs, and/or glucocorticoids."); Ex. 2036, ¶21 ("Clinicians treating RA patients often prescribed a single DMARD either by itself – what is referred to as a 'monotherapy' – or with one or more NSAIDs and/or a steroid."). A POSA would therefore have understood that the conventional treatment with which MRA was combined included, at least MTX, prednisolone, and an NSAID, an entirely common combination regimen. Ex. 1064, ¶22.

Chugai's "common practice" argument is similarly unavailing because, while some physicians may have preferred to administer experimental RA drugs as monotherapies, others preferred to administer them in combination. Ex. 1064, ¶22; *see, e.g.*, Ex. 2018.01 ("With the initial trials evaluating an agent never previously used as a therapy for RA, it was felt that treatment with cM-T412 for 6 months as the only therapeutic agent would not be appropriate. Therefore, the decision was made by the sponsoring pharmaceutical company and the US Food and Drug Administration to have the first study with cM-T412 in a cohort of patients with RA

who were taking stable doses of MTX."). Thus, even if Chugai were correct that it was common to administer a new DMARD as a monotherapy, there was certainly precedent for administering it in combination with other DMARDs, including MTX. There would therefore have been no reason for a POSA to doubt Yoshizaki's express disclosure.[5]

B. Yoshizaki Discloses an Effective Amount of MRA and MTX

In addition to disclosing the treatment of a patient with the MRA/MTX combination, Yoshizaki also discloses administering an effective amount of those drugs to a patient in need thereof.

As discussed above, the Board's preliminary construction was correct, and under that construction, Yoshizaki discloses administering an effective amount of each of MRA and MTX. With regard to MRA, Yoshizaki discloses that the patient was administered 50 mg once or twice weekly, which a POSA would understand

[5] Chugai notes that MTX was not approved in Japan at the time of Yoshizaki's study, but the purported relevance of that fact is unclear. POR at 28-29. To the extent Chugai is suggesting that, because it was unapproved, MTX was not a conventional treatment, that is incorrect. MTX had been used to treat RA for years by the time of Yoshizaki's study, and Yoshizaki itself identifies it as a "conventional treatment." Ex. 1064, ¶22; Ex. 1005.06.

falls within the range described in the Specification. *Compare* Ex. 1005.11 *with* Ex. 1001 at 3:55-62. With regard to MTX, a POSA would have understood that Yoshizaki discloses administering an effective amount of MTX because conventional MTX dosing was somewhere between 7.5 and 25 mg per week, which falls within the MTX dosage described in the specification. *Compare* Ex. 1065 at 105:4-18, 107:11-20 *with* Ex. 1001 at 2:60-67.

That said, even if the Board were to adopt Chugai's proposed construction and require that an "effective amount" of MRA and MTX were amounts "that relieve RA symptoms without undue toxicity when administered in the same treatment regimen," Yoshizaki would nonetheless anticipate the claim at issue for two simple reasons. First, Yoshizaki discloses that the combined MRA/MTX treatment in fact resulted in relief of RA symptoms. Ex. 1005.11 ("the clinical and laboratory abnormalities improved"). Second, at no point does Yoshizaki report that the administered regimen had undue toxicity. To the contrary, Yoshizaki discloses that "the results of this open study suggest that rhPM-1 is effective, safe and useful for the treatment of RA." *Id.*

Finally, regardless of which construction is adopted, it is telling that Chugai spends three pages arguing its claim construction position, (POR at 15-18), and nearly twelve pages arguing that Yoshizaki does not anticipate the '052 patent, (POR at 18-30), and yet it never argues that either the MRA dose or MTX dose disclosed

in Yoshizaki is not an "effective amount."[6] That fact alone should confirm that the MRA and MTX doses disclosed in Yoshizaki constitute "effective amounts" of the drugs. *See* Ex. 1005.11 (disclosing the MRA dosage amount); Ex. 1065 at 105:4-18, 107:11-20 (discussing known effective doses of MTX).

Accordingly, because Yoshizaki discloses the treatment of a RA patient with the MRA/MTX combination using an effective amount of each drug, Yoshizaki anticipates the '052 patent.

IV. THE '052 PATENT IS OBVIOUS OVER NISHIMOTO IN VIEW OF WEINBLATT 2003

A. A POSA Would Have Been Motivated to Combine Nishimoto and Weinblatt 2003 to Arrive at the Clamed Regimen

Nishimoto discloses that MRA was successful in treating patients with RA, and that MRA is used in combination with MTX. Ex. 1006.04-05. Weinblatt discloses that while MTX was the treatment of choice for RA in 2003, "MTX is

[6] At most, Chugai contends that because MTX was eventually approved at a dose of 8 mg/week in Japan a POSA would "not assume that the dose given to this Japanese patient was th[e] same as the dose assumed to be 'effective' by Dr. Zizic." POR at 29. However, a MTX dose of 8 mg/week falls squarely within the "preferabl[e]" range of doses disclosed by the '052 specification, and is therefore still an "effective amount" within the meaning of the claim. *See* Ex. 1001 at 2:60-67.

frequently combined with one or more other traditional [DMARDs]" in order to "enhance the [patient's] clinical response." Ex. 1008.02; Ex. 1002, ¶155. Thus, taken in combination, a POSA would have been motivated to add the 8 mg/kg every four week MRA dose recommended by Nishimoto to a patient's existing 10-25 mg MTX regimen, as disclosed by Weinblatt 2003. Ex. 1002, ¶156. Chugai does not dispute that a POSA would have been motivated to administer this combined regimen to an RA patient. *See* POR at 32-51.

B. A POSA Would Have Reasonably Expected the Claimed Regimen to be Successful

MRA and MTX were each known to be independently safe and effective for treating RA. Ex. 1002, ¶¶36-42. And it was commonplace to add biologics to the treatment regimens of patients who had not adequately responded to MTX. *Id.* at ¶¶43-45. Thus, a POSA would have reasonably expected that the MRA/MTX combination regimen arrived at by combining Nishimoto and Weinblatt 2003 would be successful—*i.e.*, safe and effective—for treating RA. Ex. 1002, ¶161. Chugai attempts to avoid this simple, straightforward, conclusion by mischaracterizing prior art combination therapies as failures and manufacturing concerns of "overlapping toxicities."

1. A POSA Would Have Reasonably Expected the Claimed Combination to Demonstrate Increased Efficacy

While Weinblatt is just one example of a DMARD being added to a patient's

existing MTX regimen and demonstrating improved efficacy—it is an illustrative one. In Weinblatt, a biologic DMARD (adalimumab) was added to the treatment regimens of patients who had continued to exhibit RA symptoms, despite having been titrated to a stable MTX dose between 10 and 25 mg. Ex. 1008.02; Ex. 1002, ¶155. The patients in Weinblatt maintained their existing MTX regimens when the adalimumab dose was added. Ex. 1008.01 ("patients with active RA were randomly assigned to receive injections of adalimumab . . . or placebo every other week while continuing to take their long-term stable dosage of MTX"). After the 24-week study concluded, Weinblatt found that the "addition of adalimumab to MTX therapy substantially and rapidly improve standard measures of disease activity . . . and quality of life scores in RA patients not adequately responding to therapy with MTX alone." Ex. 1008.09.

Given Nishimoto's disclosure that MRA was effective for treating patients with RA, and Weinblatt's demonstration of improved efficacy in combining a biologic DMARD with patients' existing MTX therapy, a POSA would have reasonably expected that adding MRA to a patient's existing MTX therapy would result in improved efficacy. Ex. 1002, ¶161.

While Chugai alleges that "developing successful combination therapies in RA is highly unpredictable," the evidence shows precisely the opposite. POR at 36. In fact, Chugai has failed to identify even a single prior art combination trial where

a safe and effective DMARD was added to a patient's existing MTX regimen and did not result in increased efficacy.

In its attempt to rebut this evidence, Chugai first relies on Williams and Willkens, as reported by Felson. POR at 36-37 (citing Ex. 2010). But Felson recognized that studies failed to show improved efficacy because "the individual agents tended to be prescribed at the minimal effective therapeutic dosage." Ex. 2010.04. Indeed, both Williams and Willkens involved MTX-naïve patients who were given a 7.5 mg MTX dose. Ex. 2024.08; Ex. 2072.02. While 7.5 mg MTX was the typical starting dose, it was well-known that it often failed to provide sufficient therapeutic benefit, and patients would be titrated up to between 10 and 25 mg before the response would be deemed inadequate. Ex. 1065 at 105:4-18, 107:11-20; Ex. 1051.06 ("methotrexate doses of more than 10 mg per week are generally needed"); Ex. 1008.02 (study of RA patients "with active RA despite long-term therapy with MTX" required participants to be "treated with MTX for a minimum of 6 months and . . . taking a stable weekly dose (12.5-25 mg, or 10 mg if intolerant to higher doses)"); Ex. 1007.02 ("The initial dosage is usually 7.5 to 10.0 mg/wk, titrated upward to an average dosage of 12.5 to 15.0 mg/wk"). Unsurprisingly, subsequent literature identified this low MTX dose as a likely cause for the lack of increased efficacy observed in these clinical trials. Ex. 2042.05 (attributing Williams' and Willkens' "disappointing results" to MTX doses being "lower-than-optimal"). As

discussed above, a POSA combining Nishimoto with Weinblatt would have used a higher dose of MTX—somewhere between 10 and 25 mg.

Chugai also cites Boers (Ex. 2056) and Tugwell (Ex. 2057) as evidence that a POSA would not have expected the claimed regimen to be successful. POR at 37-38. But neither of these references would have suggested that adding MRA to a patient's MTX regimen would fail to increase efficacy. Boers did not even consider any MTX combinations. As explained by Dr. Zizic, MTX was considered the "treatment of choice," (Ex. 1008.02), and the "anchor therapy," (Ex. 1007.02), for RA, precisely because of its "favorable efficacy and toxicity profile," (*id.*), so combinations not including MTX are far less probative. Ex. 1064, ¶15. And the only MTX combinations evaluated by Tugwell were Williams and Willkens, which used too low of a MTX dose, as discussed above. *See also* Ex. 1064, ¶39.

Chugai next cites Verhoeven (Ex. 2022) and claims five of the seven studies evaluating MTX combinations found no difference in efficacy or "merely" a positive trend. POR at 38-39. But, two of those five studies were Williams and Willkens (discussed above). Ex. 2022.03. One of the studies (O'Dell) exhibited a "positive trend" for the combination as compared to MTX alone, which Verhoeven defines as "significantly greater improvement in at least 25% of the measures" of clinical outcome. *Id.* at 2. Another (Moreland) involved a combination of MTX and an antibody (cM-T412), which other studies showed was ineffective even as a

monotherapy agent. Ex. 1064, ¶44; Ex. 2022.03; Ex. 1055.01. And while Verhoeven reports the sulfasalazine/MTX combination in the fifth study (Haagsma) showed no increase in efficacy over MTX alone, Haagsma involved administering 7.5 mg to MTX-naïve patients, and Haagsma's authors noted that when sulfasalazine is instead added to MTX as part of a "step-up strategy," "increased efficacy without additional toxicity" is shown. Ex. 2040.06; Ex. 1064, ¶45; Ex. 2022.03. Notably, the "step-up" strategy – *i.e.*, adding a new RA drug to a patient's existing regimen – is the approach a POSA would have used when combining Nishimoto and Weinblatt. Ex. 1064, ¶46; Ex. 1002, ¶154.

A review of MTX combination trials that employed the "step-up" approach confirms that a POSA would have believed adding MRA to a patient's existing MTX regimen would be successful. Ex. 1064, ¶46; Ex. 1060.03. Each combination Hochberg evaluated demonstrated improved efficacy, leading the authors to conclude that "several agents are efficacious in a step-up strategy when given to patients with an incomplete response to methotrexate." *Id.* Yet, despite Hochberg "update[ing] and extend[ing] the results of . . . Verhoeven," (Ex. 1060.03), Hochberg is tellingly absent from Chugai's analysis.

Chugai also attempts to discount successful biologic/MTX combinations based on mechanistic differences (POR at 40-43), but this ignores the fact that multiple DMARDs, having multiple mechanisms of action, demonstrated increased

efficacy when combined with MTX. *See, e.g.*, Ex. 1060.03; Ex. 1064, ¶¶48-50.

Finally, Chugai also claims that a POSA would not have had a reasonable expectation of success based on Yoshizaki. POR at 43. As detailed above (§ III), a POSA would have understood that Yoshizaki treated a patient with a MRA/MTX combination and observed that "the clinical and laboratory abnormalities improved after the rhPM-1 therapy." Ex. 1005.11. Given Yoshizaki's disclosure, a POSA would understand that at least one person was successfully treated with a MRA/MTX combination, and as such, the POSA would have a reasonable expectation of success in treating other patients with the same combination.

Simply put, when almost any effective DMARD was added to a patient's existing MTX regimen, efficacy improved, regardless of its mechanism of action. Ex. 1064, ¶51. Despite Chugai's arguments to the contrary, the bottom line is simple: a POSA, when evaluating the art as a whole, would have reasonably expected that when an effective DMARD, such as MRA, was added to a patient's existing MTX regimen, the combination would have increased efficacy.

2. A POSA Would Have Reasonably Expected the Claimed Combination to be Safe

a. There Was No Concern About Overlapping Toxicities

Chugai claims a POSA would not have expected the combination of MRA and MTX to have acceptable toxicity because MRA and MTX were purportedly both known to be hepatotoxic and a POSA would have been concerned about

"overlapping toxicities" if the two drugs were administered together. POR at 45-51. But nothing in the prior art suggested any type of "overlapping toxicities." Ex. 1064, ¶¶10-13. In fact, as of the priority date, **there was no evidence that MRA was hepatotoxic**. Ex. 1064, ¶¶10-13. And while MTX was known to have some hepatotoxicity, the risk was understood to be acceptable for an efficacious RA drug. Ex. 1064, ¶¶14-16.

Chugai provides no prior art citations for its assertion that MRA had "known" hepatotoxicity. *See* POR at 47 (providing no citation for the statement "one of the adverse drug reactions that tocilizumab was known to cause is hepatotoxicity"). The only document Chugai can point to that even suggests that MRA might be hepatotoxic is a non-prior art[7] Chugai slide deck (Ex. 2020, Okuda). Even if it were prior art, however, Okuda merely discloses that some patients' liver enzymes were

[7] Chugai refers to Okuda as a "prior art reference" in a related proceeding, but provides no support for this assertion. IPR2021-01025, Paper 35 at 21. To qualify as prior art, a reference must have been publicly accessible to a POSA. *Samsung Elecs. v. Infobridge Pte.*, 929 F.3d 1363, 1368-69 (Fed. Cir. 2019). Not only does Okuda itself contain no indicia that it was published or available to a POSA, Chugai does not even **allege** it was publicly accessible, much less provide any explanation for how a POSA could have located it.

elevated to an unspecified extent when administered MRA. Ex. 2020.24. As Dr. Zizic explains, without knowing the extent to which these patients' liver enzymes were elevated, a POSA would have had no basis to suspect hepatotoxicity. Ex. 1064, ¶11. In fact, Okuda expressly discloses that "**treatment with MRA was well tolerated**." Ex. 2020.26 (emphasis added).

Okuda's disclosure that MRA was "well tolerated" echoes the prior art. The published abstract disclosing the results of the same study as Okuda says absolutely nothing about elevated liver enzymes or hepatotoxicity, despite its stated objective to "**evaluate the** efficacy and **safety of MRA**." Ex. 1017.02 (emphasis added). The fact that Nishimoto Abstract B disclosed that the Okuda data demonstrated that MRA was "well tolerated" (Ex. 1017.02) without even mentioning the possibility of hepatotoxicity is telling. Other prior art also touted MRA's favorable safety profile with no mention of any potential hepatotoxicity. *See, e.g.*, Ex. 1016.02 ("[r]epetitive therapy with MRA appeared considerably safe"); Ex. 1006.05 (no mention of hepatotoxicity and recommending an 8 mg/kg MRA dose "[o]n the basis of" the results of the same study described by Okuda).

While Chugai asserts that "[i]t is undisputed that MTX is a toxic drug that poses serious dangers to liver health," (POR at 46), it conveniently fails to acknowledge that the prior art clarified that this "risk of liver toxicity is low," (Ex. 1010.10), and avoidable through standard patient monitoring. Ex. 1064, ¶¶14, 16;

see also Ex. 1022.06 ("The risk of liver toxicity is small."); Ex. 1051.06 ("Careful monitoring of blood counts, creatinine, hepatic aminotransferases, and pulmonary symptoms generally keep serious toxic effects resulting from therapy to a minimum."). In fact, MTX was considered the "anchor therapy" for RA patients receiving combination therapy precisely "**[b]ecause of its favorable** efficacy and **toxicity profile**." Ex. 1007.02 (emphasis added); *see also* Ex. 1064, ¶15; Ex. 1054.01.

Thus, while a POSA would have been aware of MTX's potential toxicity, a POSA would have also understood that the possibility of such toxicity was remote and could easily be avoided through routine liver enzyme monitoring. Ex. 1064, ¶¶14, 16. This was understood to be true even when MTX was administered in combination with RA drugs known to be hepatotoxic (unlike MRA), such as leflunomide. Ex. 1064, ¶¶17-18; *see, e.g.*, Ex. 1010.10 ("Leflunomide is also beneficial as combination therapy with MTX"); Ex. 2037 at 261:20-262:4 (testifying with respect to MTX and leflunomide that, while "I don't usually use the two of them together[, . . .] some people do").

Chugai's assertion that a POSA would have been concerned with overlapping hepatotoxicity between MRA and MTX is therefore not only baseless, it is directly contradicted by numerous prior art references that are exhibits in this proceeding. Ex. 1064, ¶¶17-26.

b. Chugai Mischaracterizes Prior Combination Trials as Failures.

In addition to its unsupported "overlapping toxicities" theory, Chugai also mischaracterizes four combination therapies – MTX/Cytoxan, MTX/sulfasalazine; infliximab/leflunomide, and MTX/leflunomide – as "failure[s]" due to elevated toxicities in an effort to suggest a POSA would not have expected the combination of MRA and MTX to be safe. POR at 45-49. But none of the examples provided by Chugai supports its position. Ex. 1064, ¶¶27-32.

Chugai's argument that the MTX/Cytoxan combination failed is not based on any prior art disclosure, but allegedly on Dr. Zizic's deposition testimony. POR at 46 (citing Ex. 2037 at 43:22-44:22). However, Dr. Zizic was discussing the treatment of RA with Cytoxan as a **monotherapy**, not as a combination therapy. *See* Ex. 2037 at 43:6-44:22; Ex. 1064, ¶31; Ex. 1065 at 18:21-28:4. As a thorough reading of Dr. Zizic's deposition transcript makes clear, when Dr. Zizic was discussing Cytoxan, he was discussing its use a monotherapy, not as part of a MTX/Cytoxan combination therapy. Ex. 2037 at 42:1-44:22.

Chugai's remaining examples fare no better. Ex. 1064, ¶¶27-32. The safety profile of the MTX/sulfasalazine combination was described as "acceptable" by the authors of the study, despite additive toxicity. Ex. 1064, ¶28; Ex. 2041.06. The infliximab/leflunomide combination is irrelevant because it includes neither MRA nor MTX. Nonetheless, the authors did not consider it a "failure." Ex. 1064, ¶29;

Ex. 2066.06; *see also* Ex. 1067.03 (characterizing the infliximab/leflunomide combination as "an effective combination"). And, while Chugai characterizes its last example, a leflunomide/MTX combination as "a textbook example of overlapping hepatotoxicity concerns" and notes there was some elevated toxicity, (POR at 48-49), the authors of the study explicitly considered the combination "generally well tolerated" and having "therapeutic potential for RA," (Ex. 2042.01, 04). Ex. 1064, ¶30; *see also* Ex. 1010.10 (describing a leflunomide/MTX combination as "beneficial").

The fact that these studies reported some elevated risk of toxicity does not mean that they were **unacceptably** toxic, as shown by the authors' and others' analysis of the results. Ex. 1064, ¶32. Chugai's argument that these combinations were failures is not credible in light of the contemporaneous reaction of POSAs to the same results. *See, e.g.*, Ex. 2064.02 (describing the "increasing use of [the leflunomide/MTX] combination in the management of RA").

Despite Chugai's rhetoric, it has failed to provide any relevant example of two safe and effective RA monotherapies being unsuccessfully combined due to elevated toxicities. This is unsurprising given that MTX has been combined with nearly every RA drug and has had acceptable toxicity. Ex. 1064, ¶32. Thus, a POSA would have reasonably expected that the MRA/MTX combination would be safe for the treatment of patients with RA.

V. CONCLUSION

Petitioners submit they have established that the ’052 patent is anticipated by Yoshizaki because Yoshizaki discloses the successful—i.e., safe and effective—treatment of a patient by administering an effective amount of MRA and an effective amount of MTX. Petitioners further submit that the ’052 patent is obvious over Nishimoto, in view of Weinblatt 2003, because Nishimoto discloses that MRA is a safe and effective DMARD, Weinblatt 2003 discloses that successful DMARDs can be safely and effectively combined with patients’ existing MTX regimens, and as a result, a POSA would have had a reasonable expectation of success in combining MRA with MTX to achieve a safe and effective treatment regimen. The claims of the ’052 patent should therefore be cancelled.

* * *

Dated: July 15, 2022

By: */Elizabeth J. Holland/*

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CERTIFICATE OF WORD COUNT

The undersigned certifies that *Petitioners' Reply to Patent Owner's Response* contains 4,940 words (as calculated by the word processing system used to prepare this document), excluding the parts exempted by 37 C.F.R. § 42.24(c)(1).

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CERTIFICATE OF SERVICE

The undersigned certifies that a true and correct copy of *Petitioners' Reply to Patent Owner's Response* has been caused to be served on the Patent Owner by email to lead counsel for Patent Owner at tfletcher@wc.com with a courtesy copy to Genentech-actemra@wc.com, pursuant to Patent Owner's agreement to accept electronic service by email as set forth in Patent Owner's Second Updated Mandatory Notices (Paper No. 38).

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