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.

IPR2021-01025
Patent No. 10,744,201

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

PETITIONERS' REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

Chugai's Patent Owner's Response ("POR") (Paper 35) attempts to interject a number of inapplicable complexities into what is a simple obviousness case. In short, the claims require administering a combination of two drugs—MRA and MTX—at specific doses to treat RA. Both the drugs, and the claimed dosage amounts, were indisputably disclosed in the art as being useful for treating RA. It is also undisputed that the prior art not only disclosed that RA drugs were generally administered in combination to improve efficacy, but the specific MRA/MTX combination had been administered for that purpose. As a result, it would have been obvious to a POSA to administer both of these known drugs together, in their known dosage amounts, to treat an RA patient, and the Board should reject Chugai's arguments to the contrary.

II. ALL CLAIMS ARE OBVIOUS OVER NISHIMOTO IN VIEW OF WEINBLATT 2003

Chugai makes several fundamental misstatements that pervade its response. Specifically, Chugai's argument that the challenged claims would not have been obvious is based on its assertions that: (1) MRA and MTX have overlapping toxicities; (2) a 4 mg/kg dose of MRA would have equal or greater efficacy than an 8 mg/kg dose; and (3) the same 7.5 mg dose of MTX initially administered to MTX-naïve patients would have been administered to RA patients who have had an inadequate response to MTX. None of these assertions has any basis in the prior art.

A. A POSA Would Not Have Been Concerned about Overlapping Toxicities Between MRA and MTX

According to Chugai, both MRA and MTX were known to be hepatotoxic, and there were therefore "well-founded" concerns that they would exhibit "overlapping toxicities" if administered together. POR at 31-36. But nothing in the prior art suggested such "overlapping toxicities." In fact, as of the priority date, **there was no evidence that MRA was hepatotoxic**. And, while MTX was known to have some hepatotoxicity, the risk was understood to be acceptable for an efficacious RA drug.

Chugai provides no prior art citations for its assertion that MRA had "known" hepatotoxicity. *See* POR at 28 (providing no citation for the statement "it was known that both [MRA and MTX] were individually hepatotoxic"), 32 (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 [1] Chugai

[1] Chugai refers to Okuda as a "prior art reference," but provides no support for this assertion. POR 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). Okuda contains no indicia that it was published or available to a

slide deck (Ex. 2020, Okuda). Even if it were prior art, however, Okuda merely discloses that some patients' liver enzymes were 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, Nishimoto Abstract B, 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

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POSA, and Chugai does not even **allege** it was publicly accessible, much less explain how a POSA could have located it.

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 31), it fails to acknowledge that the prior art clarified that this "risk of liver toxicity is low" and avoidable through standard patient monitoring. Ex. 1010.10; *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. 1050.09; 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. 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. *See, e.g.*, Ex. 1010.10 ("Leflunomide is also beneficial as combination therapy with MTX"); Ex. 2037 at 261:20-262:4 (Dr. Zizic 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. 8 mg/kg MRA was the Most Efficacious Known Dose

Chugai also alleges that the prior art taught that a 4 mg/kg dose of MRA was "equally if not more effective in achieving an ACR70 response in patients" than an 8 mg/kg dose. POR at 20-21. This is incorrect, and, again, directly refuted by the prior art. Nishimoto (Ex. 1006.05) and Nishimoto Abstract B (Ex. 1017.02) – the two most recent prior art reports on the safety and efficacy of MRA for treating RA – unequivocally disclosed that 8 mg/kg was the more efficacious dose.[2]

[2] Chugai relies on Okuda (Ex. 2020) for its supposed disclosure of equivalent or increased efficacy of the 4 mg/kg dose, and asserts that Dr. Zizic "inexplicably" ignored these data in his analysis. POR at 21. However, there is nothing "inexplicable" in Dr. Zizic not having considered Okuda. As discussed above, there is no evidence Okuda is prior art, a fact Dr. Zizic explained at his deposition. Ex. 2037 at 272:13-273:6. Furthermore, as Chugai acknowledges, the very same data was disclosed in Nishimoto Abstract B (Ex. 1017), which Dr. Zizic previously discussed at length. Ex. 1002, ¶¶80-83, 157.

Nishimoto Abstract B describes a phase II clinical study evaluating the safety and efficacy of MRA at 4 mg/kg and 8 mg/kg. Ex. 1017.02. The primary endpoint of the study was "the percentage of patients with ACR20 response at week 12," and it reported that the 4 mg/kg dose provided an ACR20 response in just 57.4% of patients while the 8 mg/kg dose provided an ACR20 response in 78.2% of patients. *Id.* The study also found that this difference was statistically significant (p=0.020), leading the authors to conclude that MRA "significantly reduced the disease activity in patients with RA in a dose-dependent manner." *Id.* Expressly based on the results of this study, Nishimoto recommended using the 8 mg/kg dose when treating RA patients. Ex. 1006.05. Chugai's assertion that these data would have taught a POSA that the 4 mg/kg dose was preferred cannot be reconciled with the authors' own contemporaneous disclosure to the contrary.

In addition to reporting data for the ACR20 response, Nishimoto Abstract B also reported data for the ACR70 response. Ex. 1017.02. Although both MRA groups had a greater ACR70 response than the placebo group, there was no statistical difference between the two MRA groups (p=0.589). *Id.* Consequently, the study was unable to draw any conclusions about the differences in ACR70 responses between the 4 mg/kg and 8mg/kg arms. Ex. 1064, ¶59. Given that, it would make no sense for a POSA to interpret these data as suggesting that the 4 mg/kg dose would provide an equal or greater likelihood of achieving an ACR70 response,

particularly when it had already been established that the 8 mg/kg dose provided a greater ACR20 response – which embraces the same efficacy criteria as ACR70 – and the study described the reduction in disease activity as "dose-dependent." Ex. 1017.02; Ex. 1009.06 ("'ACR 70,' which is defined entirely parallel to the ACR 20, except 70 percent improvement, rather than 20 percent, is needed for the component assessed"); *see also* Ex. 1064, ¶59.

Rather, a POSA would have understood that, in light of its demonstrated superiority at the ACR20 level, the 8 mg/kg dose would be more likely to provide a greater ACR70 response. Ex. 1064, ¶¶59-60.

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

While MTX was the most widely prescribed DMARD, it was often inadequate as a monotherapy to fully control a patient's symptoms and thus, other DMARDs would typically be added once the dose had been escalated to between 10 and 25 mg. Ex. 1064, ¶¶14-16; *see also* Ex. 1008.02; Ex. 1051.05-06. A POSA would therefore have understood that when a second DMARD was added to a patient's therapy, the patient would already be taking a weekly MTX dose between 10 and 25 mg and that the standard practice was to continue this MTX regimen, as exemplified by Weinblatt 2003 and others. Ex. 1064, ¶¶52-55; Ex. 1008.10; *see also* Ex. 2042; Ex. 1059.04.

Furthermore, given that the goal of adding a DMARD to a patient's MTX

regimen was to enhance the clinical response, standard practice was to administer the second DMARD at that DMARD's typical dose. Ex. 1064, ¶63; *see, e.g.*, Ex. 1033.09, 14; Ex. 2021.18-20; Ex. 2043.02; Ex. 2060; Ex. 1052; Ex. 1053; Ex. 1065 at 165:16-18. Thus, because the 8 mg/kg MRA was **recommended** by the prior art for treating RA, a POSA would have selected that dosage when adding MRA to a patient's MTX regimen. Ex. 1064, ¶¶57-63.

1. A POSA Would Have Selected the 8 mg/kg MRA Dose When Combining MRA with MTX

Chugai claims a POSA would have selected a 4 mg/kg MRA dose rather than an 8 mg/kg dose because "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." POR at 20. This misstates the prior art. A correct reading of the prior art makes clear that a POSA would have selected the most effective, safe, dose for use in combination with a patient's current MTX regimen.

First, Chugai mischaracterizes the 8 mg/kg dose in Nishimoto as being "'recommended' **for monotherapy use**." *See, e.g.*, POR at 20 (emphasis added). Nishimoto states, with no monotherapy caveat, that "treatment with 8 mg/kg of body weight of MRA every 4 weeks was **recommended**." Ex. 1006.05. Indeed, the very next sentence of Nishimoto describes an ongoing clinical trial combining MRA with MTX. *Id*. Had Nishimoto intended to limit the recommended dose to monotherapy,

it would have said that—it did not. A POSA would therefore have understood Nishimoto's recommendation to be applicable to both a monotherapy and a combination therapy. Ex. 1064, ¶58.

Second, Dr. Zizic did not "concede[]" RA drugs are not generally administered at their typical amounts when given in combination. POR at 20 (citing Ex. 2037 at 264:9-265:11). Chugai's citation not only fails to provide the proper context for the exchange between Chugai's counsel and Dr. Zizic (they were discussing leflunomide, not MRA), it does not even include Dr. Zizic's complete response to Chugai's counsel's question. Dr. Zizic explicitly stated that leflunomide is "[u]nlike, let's say, tocilizumab [i.e., MRA]," and "so I would not have the same concerns there that I would with leflunomide and methotrexate." Ex. 2037 at 265:13; 265:19-266:2. Dr. Zizic's testimony clearly distinguished this leflunomide study from the general rule of using standard dosages when combining RA therapies.

Third, Chugai's claim that Felson (Ex. 2010) reviewed 214 RA combination therapy trials before supposedly pronouncing a practice of using lower dosing in combination therapy misreads Felson. POR at 21. While Felson's initial search returned 214 potentially relevant trials, Felson ultimately analyzed just 5 of those trials. Ex. 2010.02-03. And the recommended monotherapy dose was actually used in the majority of those studies. Ex. 1064, ¶¶67-70; Ex. 2010.04 (Table 2); Ex. 1061.02; Ex. 1062.01; Ex. 1063.01-02.

In fact, the only examples Felson identifies as having used lower doses are Williams (Ex. 2024) and Wilkens (Ex. 2072). Ex. 2010.04-05. As Dr. Zizic explains, a POSA would not have interpreted Felson as describing a "common practice," but rather would have understood Felson was criticizing previous clinical trials for using suboptimal doses. Ex. 1064, ¶66. Indeed, the American College of Rheumatology ("ACR") similarly criticized these early combination trials for using "suboptimum dosages," (Ex. 1010.12), and contrasted them with subsequent combination trials that employed full doses of the individual drugs and "were found to be beneficial." *Id.*; *see also* Ex. 1064, ¶66. Simply put, Felson does not reflect a "common practice" as of the priority date.

Finally, Chugai also tries to analogize the MRA/MTX combination to a handful of trials that purportedly employed lower than standard doses when administering a combination. POR at 23-25. As detailed below, none of these trials support Chugai's position.

In one such example, Chugai alleges that Weinblatt 2003's use of every-other-week dosing of adalimumab was less frequent than the dose used for monotherapy. POR at 23-24. That is incorrect. While an early adalimumab study tested the drug weekly, (Ex. 2071.01), the prior art subsequently reported that there was "a plateau in dose-response at a dose of 1 mg/kg **biweekly**," (Ex. 1066.02 (emphasis added)). In other words, by the time of Weinblatt 2003's study, every other week dosing –

the frequency used in Weinblatt 2003 – was considered the optimal dosing regimen. Ex. 1064, ¶¶73-79; *see also* Ex. 1033.14 (recommending administration of adalimumab every other week).[3]

Chugai makes a similarly flawed argument with respect to etanercept in combination with MTX. POR at 24-25. While etanercept was tested at both 25 mg and 50 mg, Chugai suggests that its approval at 25 mg shows that a lower dose is selected "where two dosages offered comparable efficacy." *Id*. at 25. But as discussed above, MRA did not have "comparable efficacy" at the 4 mg/kg and 8 mg/kg doses; the higher dose was more efficacious, and was explicitly recommended by the prior art. Ex. 1006.05. Therefore, a POSA would have used the 8 mg/kg MRA dose recommended by Nishimoto when combining MRA with MTX.

Chugai also relies on a leflunomide/MTX combination trial as an example of using a reduced dose to minimize the risk of overlapping toxicities. POR at 22-23 (citing Weinblatt 1999). While this study used a lower dose of leflunomide than was typical for monotherapy, it does not suggest a POSA would do the same with MRA.

[3] Chugai is also incorrect that the Humira label recommends using a lower dose when combined with MTX. POR at 23. The Humira label expressly recommends the same 40 mg every other week dose whether administered with or without MTX. Ex. 1033.03, 14; Ex. 1064, ¶¶23, 73-75.

As discussed, a POSA would not have believed there was any overlapping toxicity between MRA and MTX. *See* § II.A. Furthermore, other DMARD/MTX combination studies administered the standard dose of a DMARD known to have an overlapping toxicity with MTX. *See, e.g.*, Ex. 1059.02. This confirms Weinblatt 1999 is a cherry-picked example and not reflective of the "common practice." Ex. 1064, ¶¶83-84.

As explained above, and in Dr. Zizic's declaration, it was standard practice to select the recommended dose for a combination therapy RA trial. And, while there may be isolated instances where lower doses were used, these are exceptions to the standard practice and do not detract from Nishimoto's unequivocal recommendation of the 8 mg/kg MRA dose, whether administered alone or in combination.

2. A POSA Would Have Selected the 10-25 mg MTX Dose When Combining MRA with MTX

As it did in arguing against the selection of the 8 mg/kg MRA dose, Chugai relies on a handful of trials to support its assertion that a POSA would have used a MTX dose lower than 10 mg when combining MRA with MTX. None of these examples, however, suggest that a POSA would have used a lower dosage amount of MTX when combining it with MRA.

As an initial matter, most of the examples Chugai cites are irrelevant because they involve MTX-naïve patients. By contrast, a POSA would have been motivated to combine Nishimoto's 8 mg/kg MRA dose with MTX "to treat RA patients **who**

had inadequately responded to methotrexate alone," (Ex. 1002, ¶152 (emphasis added)), *i.e.*, patients who were already receiving a stable MTX dose. Ex. 1064, ¶¶52-84. It was well known that while 7.5 mg was the typical starting dose, it generally failed to provide sufficient therapeutic benefit, and would be titrated up to between 10 and 25 mg before the response would be deemed inadequate. 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"). Thus, at the time MRA would be added to a patient's MTX regimen, the patient would already be taking a MTX dose between 10 and 25 mg. Ex. 1008.02. Ex. 1064, ¶¶52-55.

Nearly every clinical study conducted in or around 2003 that evaluated the addition of a DMARD to a patient's existing MTX regimen maintained that patient's MTX dosage amount. *See, e.g.*, Ex. 1008.02; Ex. 2042.02; Ex. 1059.02. As Dr. Zizic explains, this is known as the "step-up" approach, and studies that used this approach, almost without exception, required patients to continue their previously stable MTX dosing regimen. Ex. 1064, ¶¶52-54; *see also* Ex. 2022.01. In fact, the only exception to this general practice that Chugai identifies is Maini (Ex. 1015).

But, not only is Maini an outlier, subsequent literature disparaged the use of "suboptimum dosages" of MTX, (Ex. 1010.12), or "lower-than-optimal dosing of methotrexate," (Ex. 2042.05), in clinical studies.[4]

Thus, regardless of whether a POSA would have given MTX-naïve patients a starting dose of 7.5 mg, the prior art makes clear that if a POSA wanted to **add MRA to a patient's existing MTX regimen** (i.e., the "step-up" strategy exemplified by Weinblatt 2003) the POSA would have maintained the patient's existing MTX dosing regimen, which would have been between 10 and 25 mg at the time MRA was added. Ex. 1064, ¶¶52-55.

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

1. A POSA Would Have Reasonably Expected the Claimed Regimen to be Safe

MRA and MTX were each known to be safe and effective for treating RA. Ex. 1002, ¶¶36-42. And it was commonplace to add biologics to the treatment

[4] Chugai alleges that reducing the patients' MTX dose when adding a new RA drug was typical for any first trial testing the combination. POR at 26-28. Not so. Other first studies of combinations of new RA drugs with MTX employed the standard approach of maintaining the patients' existing MTX dose, rendering Maini merely an exception to the general practice. *See, e.g.*, Ex. 2018.01; Ex. 1064, ¶¶52-56.

regimens of patients who had not adequately responded to MTX. *Id.* at ¶¶43-45. Thus, a POSA would have reasonably expected that a MRA/MTX combination therapy would be successful—i.e., safe and effective—for treating RA. Chugai attempts to avoid this simple, straightforward, conclusion by manufacturing concerns of "overlapping toxicities" and mischaracterizing prior art combination therapies as failures.

As discussed, Chugai's allegation concerning overlapping hepatotoxicity between MRA and MTX is unfounded. *See* § II.A. Even if Chugai's allegation were correct (it is not), not only would the POSA have been aware that other hepatotoxic drugs (*e.g.*, leflunomide), had nevertheless been successfully combined with MTX, they would also have known that at least one patient had been successfully treated with a MRA/MTX combination. Ex. 1006.11.[5] Thus, this alleged concern is merely

[5] Yoshizaki discloses an RA patient "given NSAIDs, DMARDs, MTX, and 15 mg [prednisolone]" who received 50 mg MRA "combined with the conventional treatment." Ex. 1005.11. Yet, Chugai characterizes this unambiguous disclosure as "strained," arguing that: (1) not all conventional treatments included MTX; (2) no rational physician would administer all these drugs concomitantly; (3) "common practice" was to administer a new RA drug by itself, rather than in combination; and (4) since neither MTX nor MRA were approved in Japan at the time, a POSA would

a red herring; a POSA would have reasonably expected the combination to be sufficiently safe to be successful. Ex. 1064, ¶¶6-32.

In addition to its "overlapping toxicities" theory, Chugai also suggests that a POSA would not have expected the combination of MRA and MTX to be safe by mischaracterizing four specific prior art combination therapies – MTX/Cytoxan, MTX/sulfasalazine; infliximab/leflunomide, and MTX/leflunomide – as "failures"

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not have administered both in combination. POR at 40-42. None of these arguments withstand scrutiny. First, Yoshizaki refers to "the" conventional treatment it had just defined. It does not refer to "a" conventional treatment. Ex. 1005.11. Second, administering NSAIDs, MTX, prednisolone, and DMARDs concomitantly to treat RA was recommended by the ACR. *See, e.g.*, Ex. 1022.02 ("The majority of patients with active RA receive an NSAID and at least 1 DMARD, with or without low-dose oral glucocorticoids"). Third, while some physicians may have preferred to administer experimental RA drugs as monotherapies, others, like Yoshizaki, preferred to administer them in combination. *See, e.g.*, Ex. 1005.11; 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.") Fourth, MTX had an extensive history of use as an RA treatment at the time. Ex. 1064, ¶22.

due to elevated toxicities. POR at 29-36. None of the examples provided by Chugai supports its position.

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 30-31 (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. Ex. 2037 at 43:22-44:22); 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. 2041.06. The infliximab/leflunomide combination is irrelevant because it includes neither MRA nor MTX. In any event, the authors did not consider it a "failure." 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," (POR at 32-34), the authors of the study explicitly considered the combination "generally well tolerated" and having "therapeutic

potential for RA," (Ex. 2042.01, 04). *See also* Ex. 1010.10 (finding the leflunomide/MTX combination "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, ¶¶27-30. 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 failed to provide a 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 had acceptable toxicity. Ex. 1064, ¶¶14-26.

2. A POSA Would Have Reasonably Expected the Claimed Regimen to be Effective

Chugai's contention that a POSA would not have reasonably expected the MRA/MTX combination to be efficacious is similarly unavailing. While Chugai alleges that "developing successful combination therapies in RA is highly unpredictable" (POR at 39), the evidence shows precisely the opposite. 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.

Chugai first relies on Williams and Willkens, as reported by Felson, in support of this argument. 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. Subsequent literature identified this low dose as a likely cause for the lack of increased efficacy. Ex. 2042.05 (characterizing Williams' and Willkens' MTX doses as "lower-than-optimal").

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 Boers is irrelevant because it did not consider any MTX combinations, and the only MTX combinations evaluated by Tugwell were Williams and Willkens (discussed above). 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. But, two of the 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 indicated increased efficacy. Ex. 1064, ¶43; Ex. 1058; Ex. 2022.03. Another (Moreland) involved a MTX/antibody combination, but other studies found that the antibody (cM-T412) was ineffective as

a monotherapy agent. Ex. 1064, ¶44; Ex. 2022.03; Ex. 1057; 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 (a suboptimal dose), and Haagsma's authors noted that when sulfasalazine is added to MTX as part of a "step-up strategy," "increased efficacy without additional toxicity" is shown. Ex. 1064, ¶45; Ex. 2022.03; Ex. 2040.06. Notably, the step-up strategy is the approach a POSA would have used when combining Nishimoto and Weinblatt 2003. 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.

Finally, Chugai attempts to discount successful biologic/MTX combinations based on mechanistic differences (POR at 42-45), but this ignores the fact that multiple DMARDs, having multiple mechanisms of action, demonstrated increased efficacy when combined with MTX. Ex. 1064, ¶¶48-50; *see, e.g.*, Ex. 1060.03. In

fact, when almost any effective DMARD was added to MTX, efficacy improved, regardless of its mechanism of action. Ex. 1064, ¶51.

The bottom line is simple: a POSA, when evaluating the art as a whole, would have reasonably expected that when a successful DMARD, such as MRA, was added to MTX, the combination would have demonstrated increased efficacy.

E. A POSA Would Have Reasonably Expected to Achieve the Claimed ACR70 Results

Claim 1 requires increasing the likelihood of achieving an ACR70 response with MRA/MTX as compared to MTX alone. As Dr. Zizic explained, the 8 mg/kg MRA dose had demonstrated an ACR70 response in a greater percentage of patients than the 10-25 mg MTX dose, (Ex. 1002, ¶157), and Chugai identified no reason why a POSA would have expected MTX alone to be more likely to induce an ACR70 response than the MRA/MTX combination.

Claim 6 requires achieving an ACR70 response with MRA/MTX in a patient who would not have had such a response to either drug alone. As just stated, a POSA would have reasonably expected that a MRA/MTX combination would induce an ACR70 response in patients that would not have had such a response to MTX alone. Additionally, biologic DMARDs that had similar ACR70 responses to MRA monotherapy demonstrated greater ACR70 responses when combined with MTX. *See, e.g.*, Ex. 1033.04; *see also* Ex. 1017.02.

Chugai asserts that claim 11 requires "synergy." It does not. Claim 11

requires only a greater than additive ACR70 response "in a tested population of rheumatoid arthritis patients." Ex. 1001 at 23:7-20. As Dr. Zizic explained, (Ex. 1002, ¶¶168-169), this distinction is important because in a small population of subjects, the natural variability of clinical responses makes it reasonably likely a POSA would observe a greater than additive response, even in the absence of synergy. Thus, whether a POSA would have expected MRA and MTX to have synergy is irrelevant.

F. The Results of the Claimed Regimen Were Not Unexpected

1. Closest Prior Art

Chugai claims the closest prior art is Okuda (Ex. 2020). Okuda, however, is not prior art. *See supra* n.1. Even if it were, the data disclosed in Okuda was disclosed in Nishimoto Abstract B (Ex. 2017), and, as Chugai concedes, the latter provides more precise values for these data. *See* POR at 52, n.6.

2. The Prior Art Taught that 8 mg/kg MRA Was More Effective than 4 mg/kg

Okuda and Nishimoto Abstract B disclose that 8 mg/kg MRA provided a statistically significantly greater response in ACR20 achievement than 4 mg/kg. Ex. 2020.23; Ex. 1017.02. These references also disclose that both MRA doses provided statistically significantly greater ACR70 responses than placebo. *Id.* Because 8 mg/kg induced a greater ACR20 response than 4 mg/kg, and an ACR70 response just requires a more pronounced improvement in the same efficacy criteria, a POSA

would have expected that a sufficiently powered study would find that 8 mg/kg would induce a greater ACR70 response than 4 mg/kg. Ex. 1064, ¶59; Ex. 1017.02.

3. The Prior Art Taught that Combining a DMARD with MTX Provided Increased Efficacy Compared to the DMARD Alone

As discussed, (*see* § II.D.2), a POSA would have been aware that combining a DMARD with MTX would result in greater efficacy (including a greater ACR70 response) as compared to the DMARD alone. *See, e.g.*, Ex. 1033.04; Ex. 1012.04; Ex. 1015.04-06.

4. 8mg/kg MRA with MTX Would Have Been Expected to Provide Greater Efficacy than 4 mg/kg MRA with MTX

Chugai claims it was "surprising" that a clinical study showed a greater ACR70 response for 8 mg/kg MRA plus MTX than 4 mg/kg plus MTX (POR at 51-56), but this is precisely what a POSA would have expected based on the prior art disclosure that MRA "reduced disease activity **in a dose-dependent manner**." Ex. 1017.02 (emphasis added). Chugai ignores this unambiguous statement and instead relies on non-prior art data in the patent to claim a POSA would have believed "there was no dose-dependent response." POR at 53. But, as Chugai acknowledges, "the issue of unexpected results requires a comparison against what was known." POR at 50 (citing *Millennium Pharms. v. Sandoz*, 862 F.3d 1356, 1368 (Fed. Cir. 2017)).

5. There is No Evidence that 8mg/kg MRA Plus MTX Results in Synergistic Efficacy

Chugai also alleges that 8 mg/kg MRA plus MTX resulted in unexpected

synergy. But, as Dr. Zizic explained, (Ex. 1002, ¶¶181-185), and Chugai fails to refute, the data relied upon does not establish synergy; it merely reflects a meaningless nominal difference in outcomes. Ex. 1064, ¶¶88-90. Instead, Chugai recasts Petitioners' position as alleging "that MRA + MTX combination therapy is not useful," and only rebuts this strawman by showing that the combination had some benefits over MRA alone. POR at 56-59. As discussed throughout, a POSA would have expected a MRA/MTX combination to have increased efficacy over MRA alone. Ex. 1007.04 ("To improve disease control, therapies that contain combinations of DMARDs are often used.")

6. Even if the Results Were Unexpected, they are Insufficient to Overcome Petitioners' *Prima Facie* Showing of Obviousness

Finally, even if the Board were to find the results Chugai relies on were unexpected, such a finding would be insufficient to overcome Petitioners' strong *prima facie* case of obviousness. *See, e.g.*, *Becton, Dickinson & Co. v. Baxter Corp.*, 998 F.3d 1337, 1345 (Fed. Cir. 2021).

III. CONCLUSION

Petitioners submit they have established that a POSA would have been motivated to combine Nishimoto and Weinblatt 2003 to arrive at the claimed regimen, and would have had a reasonable expectation that the claimed regimen would be successful. The claims of the '201 patent should therefore be cancelled.

* * *

Dated: July 15, 2022

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CERTIFICATE OF WORD COUNT

The undersigned certifies that *Petitioners' Reply to Patent Owner's Response* contains 5,597 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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