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Paper 25
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

CHUGAI SEIYAKU KABUSHIKI KAISHA, GENENTECH, INC., and
HOFFMAN-LA ROCHE INC.,
Patent Owner.

IPR2021-01542
Patent 8,580,264 B2

Before ERICA A. FRANKLIN, JOHN G. NEW, and ZHENYU YANG,
Administrative Patent Judges.

YANG, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH (collectively, "Petitioner") filed a Petition (Paper 4 ("Pet.")), seeking an *inter partes* review of claims 4, 5, and 12 of U.S. Patent No. 8,580,264 B2 (Ex. 1001, "the '264 patent"). Chugai Seiyaku Kabushiki Kaisha ("Chugai"), Genentech, Inc., and Hoffmann-La Roche Inc. (collectively, "Patent Owner") filed a Preliminary Response (Paper 20 ("Prelim. Resp.")). With our authorization (Ex. 3001), Petitioner filed a Reply to the Preliminary Response (Paper 23, "Reply"), and Patent Owner filed a Sur-reply (Paper 24, "Sur-reply").

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). The Federal Circuit has interpreted the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition." *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018).

For the reasons provided below, we determine Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. Thus, based on the information presented, we institute an *inter partes* review of claims 4, 5, and 12 of the '264 patent on all grounds.

A. Related Matters

According to Petitioner, the '264 patent is not currently the subject of any litigation or post-grant proceedings. Pet. 5.

Petitioner explains that the '264 patent originally issued with nine claims, corresponding to claims 1–3 and 6–11 challenged here. Paper 3, 1. Petitioner previous filed IPR2021-01288 ("the first Petition"), seeking an *inter partes* review of the original nine claims. *Id.* According to Petitioner, just one day before the first Petition was filed, a Certificate of Correction issued, adding claims 4, 5, and 12. *Id.* Petitioner filed the instant Petition "about a month after the Certificate of Correction issued." *Id.* at 2.

Petitioner also has filed IPR2021-01336, seeking *inter partes review* of the claims of U.S. Patent No. 10,874,677, which is in the same family as the '264 patent. Pet. 6.

B. The '264 Patent and Related Background

The '264 patent "relates to identification of a fixed dose of [anti-interleukin-6 receptor] anti-IL-6R antibody, e.g. tocilizumab ["TCZ"], which is safe and effective for subcutaneous administration in patients with [interleukin-6] IL-6-mediated disorders," including rheumatoid arthritis ("RA"). Ex. 1001, 1:13–23.

RA is a systemic autoimmune disease. *Id.* at 1:29–30. Disease-modifying antirheumatic drugs ("DMARDs"), such as methotrexate ("MTX"), are the cornerstone of RA treatment. *Id.* at 1:42–43. Other biological compounds, including those that target tumor necrosis factor ("TNF") alpha, also have been used successfully to treat RA. *Id.* at 1:47–49.

Some RA patients, however, fail to respond to these treatments. *Id.* at 1:49–50; *see also* Ex. 1025, 3.[1,2]

IL-6 is a proinflammatory cytokine that is abundantly expressed in RA patients. Ex. 1025, 3. IL-6 binds to its soluble and membrane-bound receptors. *Id.* TCZ is a recombinant humanized monoclonal antibody that binds to human IL-6R. *Id.* In the '264 patent, the amino acid sequences of TCZ light chain and heavy chain comprise SEQ ID Nos. 1 and 2, respectively. *Id.* at 6:60–62; FIGs. 7A, 7B.

Before the '264 patent, intravenous ("IV") administration of TCZ at 4 mg/kg and 8 mg/kg had been approved in the U.S. for use in RA patients who had an inadequate response to anti-TNF agents. *Id.* at 2:20–23. TCZ has been marketed by Patent Owner under the tradename ACTEMRA. *Id.* at 2:28–29; Prelim. Resp. 1.

The '264 patent discloses a method of treating RA in a patient "comprising subcutaneously ["SC"] administering tocilizumab to the patient, wherein the tocilizumab is administered as a fixed dose of 162 mg per dose every week or every two weeks." Ex. 1001, 4:42–46.

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[1] Maini et al., *Double-Blind Randomized Controlled Clinical Trial of the Interleukin-6 Receptor Antagonist, Tocilizumab, in European Patients with Rheumatoid Arthritis Who Had an Incomplete Response to Methotrexate*, 54(9) Arthritis & Rheumatism 2817–29 (2006) (Ex. 1025, "Maini 2006"). Maini 2006 is one of the prior art asserted by Petitioner in the Petition.

[2] Unless otherwise noted, we cite to the page numbers provided by the parties.

C. Challenged Claims

Petitioner challenges claims 4, 5, and 12. Each of claims 4 and 5 depends from claim 1. Claims 1, 4, 5, and 12 are reproduced below:

> 1. A method of treating rheumatoid arthritis (RA) in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient, wherein the anti-IL-6R antibody is administered as a fixed dose of 162 mg per dose every week or every two weeks, and wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID Nos. 1 and 2, respectively.
>
> 4. The method of claim 1 wherein the RA patient is a TNF-inhibitor-inadequate responder.
>
> 5. The method of claim 1 wherein the RA patient is a methotrexate (MTX) naive or has discontinued MTX.
>
> 12. A method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient comprising subcutaneously administering a fixed dose of 162 mg of tocilizumab to the patient every two weeks, wherein structural joint damage at week 24 or week 48 is found to be inhibited.

Ex. 1001, 59–60 (Certificate of Correction).

D. Asserted Challenge to Patentability

Petitioner asserts the following challenges to patentability:

Claims Challenged	35 U.S.C. §[3]	Reference(s)
4	103(a)	NCT00965653,[4] Emery[5]
4	103(a)	Ohta 2010,[6] Emery
5	103(a)	NCT00965653, Maini 2006
5	103(a)	Ohta 2010, Maini 2006
12	102	Ohta 2010
12	103(a)	Ohta 2010, Nishimoto 2007[7]
12	103(a)	NCT00965653, Nishimoto 2007

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the '264 patent has an effective filing date before March 16, 2013, the pre-AIA version of §§ 102 and 103 applies.

[4] ClinicalTrials.gov, *A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis*, NCT00965653, available at https://clinicaltrials.gov/ct2/show/NCT00965653 (first posted August 21, 2009 (Ex. 1038), last update posted Nov. 2, 2016 (Ex. 1028)) (collectively, "NCT00965653").

[5] Emery et al., *IL-6 Receptor Inhibition with Tocilizumab Improves Treatment Outcomes in Patients with Rheumatoid Arthritis Refractory to Anti-Tumour Necrosis Factor Biologicals: Results from a 24-Week Multicenter Randomized Placebo-Controlled Trial*, 67 Ann. Rheum. Dis. 1516–23 (2008) (Ex. 1014, "Emery").

[6] Ohta et al., *Optimal Dose Prediction by Pharmacokinetic and Biomarker Response of Subcutaneous Tocilizumab Treatment – A Phase I/II Study Evaluating the Safety, Pharmacokinetics and Clinical Response in Patients with Rheumatoid Arthritis*, 62(10) Arthritis & Rheumatism S467–68 (2010) (Ex. 1034, "Ohta 2010").

[7] Nishimoto et al., *Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab*, 66 Ann. Rheum. Dis. 1162–67 (2007) (Ex. 1089, "Nishimoto 2007").

Claims Challenged	35 U.S.C. §[3]	Reference(s)
4	103(a)	Emery, Bonilla,[8] and Wang[9]
5	103(a)	Maini 2006, Bonilla, and Wang
12	103(a)	Maini 2006, Nishimoto 2007, Bonilla, and Wang

Petitioner relies on the declarations of Thomas M. Zizic, M.D. (Ex. 1002) and Howard L. Levine, Ph.D. (Ex. 1003). Petitioner relies on the Declaration of Robert Paarlberg (Ex. 1004) to support contentions regarding the prior art status of NCT00965653. Patent Owner relies on the Declarations of Kimio Terao (Ex. 2005), Masayuki Nishiyama (Ex. 2006), and Amy Zhang (Ex. 2007) to support contentions regarding reduction to practice.

II. ANALYSIS

A. Level of Ordinary Skills

Petitioner argues that an ordinarily skilled artisan "would have been an individual with an M.D. specializing in the treatment of autoimmune disorders and having several years of experience treating patients with such disorders, including rheumatoid arthritis, or having several years of experience researching treatments for autoimmune disorders, including rheumatoid arthritis." Pet. 17 (citing Ex. 1002 ¶ 35). For purposes of its Preliminary Response, Patent Owner does not dispute this definition of the

[8] Bonilla, *Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes*, 28 Immun. and Allergy Clinics of N. America 803–19 (2008) (Ex. 1021, "Bonilla").
[9] Wang et al., *Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials*, 49 J. of Clin. Pharm. 1012–24 (2009) (Ex. 1022, "Wang").

ordinary skill level. Prelim. Resp. 13 n.4. For purposes of this Decision, we adopt Petitioner's definition as it is consistent with the disclosures of the '264 patent and the prior art of record.

B. Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b) (2020). Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Petitioner proposes the constructions of several terms. Pet. 18–22. Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record, only the phrase "a method of treating rheumatoid arthritis in a patient" needs express construction.

Each of claims 4 and 5 depends from claim 1. In claim 1, the preamble recites "[a] method of treating rheumatoid arthritis (RA) in a patient." The parties dispute whether the preamble of claims 1 and 10 is limiting: Petitioner argues it is not (Pet. 18–19); whereas Patent Owner contends it is (Prelim. Resp. 13–17). The parties also disagree over whether "treating" or "treats" requires efficacy: Petitioner argues it does not (Pet. 19–20); whereas Patent Owner contends it does (Prelim. Resp. 17–23).

We do not need to address whether preamble of claim 1 is limiting, because, as explained below, we agree with Petitioner that "[e]ven if the preamble was limiting," "the plain and ordinary meaning of the phrase 'treating rheumatoid arthritis . . . in a patient' is 'attempting to cause a therapeutic improvement in rheumatoid arthritis in a patient,' and does not require actually causing a therapeutic benefit in a particular patient." Pet. 19 (citing Ex. 1002 ¶ 105; Ex. 1027, 3; Ex. 1080, 3–4).

We start by noting that the Board previously addressed the same claim limitation in another proceeding between the parties. In that case, Petitioner challenged the claims of U.S. Patent No. 7,521,052 ("the '052 patent"), also owned by Chugai. IPR2021-01024, Paper 23, 1. The only claim of the '052 patent is directed to "[a] method for treating rheumatoid arthritis." *Id.* at 4. Based on the record there, the Board stated that "the plain and ordinary meaning of the phrase reciting '[a] method for treating rheumatoid arthritis . . . in a patient' does not require achieving a recognizable therapeutic benefit in the patient, but instead only requires attempting to cause such a therapeutic improvement in the patient's disease." *Id.* at 6–7. In other words, Petitioner's proposed construction for the preamble in this case is consistent with the Board's construction of the same phrase in IPR2021-01024.

Of course, we recognize that we have a different record here. For one, unlike in IPR2021-01024, where Chugai did not contest Petitioner's proposed construction for the preamble (*see id.* at 6), Patent Owner does so here (Prelim. Resp. 13–23). More importantly, the intrinsic evidence here is different from that in IPR2021-01024. And that intrinsic evidence is what we focus on in our analysis.

Looking at the claims of the '264 patent, we note that they each recites a fixed dose with the dosing frequency, but do not require the treatment to be effective, even though there are clear standards, such as ACR20, DAS28, and ACR-hybrid, to assess efficacy. Ex. 1001, 33:11–42.

The facts in the cases Patent Owner relies on are distinguishable. In those cases, the claim language includes the built-in element of efficacy, requiring "an effective amount." *See, e.g.*, *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH,* 8 F.4th 1331, 1335 (Fed. Cir. 2021) (the claims-at-issue recite "treating headache," or "treating at least one vasomotor symptom," comprising "administering to the individual an effective amount of" an anti-CGRP antagonist antibody); *see also Merck Sharp & Dohme Corp. v. Teva Pharms. USA, Inc.*, No. CV-176921, 2019 WL 943532, at *1 (D.N.J. Feb. 26, 2019) (the claim-at-issue "recites a method of treating or preventing ileus by administering to a patient an effective amount of alvimopan").

Dependent claims of the '264 patent further support our conclusion. Patent Owner points out that claim 6 recites the further method step of "administering to the RA patient one or more additional drug which *treats* the RA." Prelim. Resp. 20. According to Patent Owner, "[b]y its plain language, this claim requires that this additional drug 'treats the RA'—*i.e.*, achieves the result that the patient's RA is treated." *Id.* We disagree.

Claim 7, which depends from claim 6, further specifies "the additional drug is selected from the group consisting of: immunosuppressive agents, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), methotrexate (MTX), anti-B-cell surface marker antibodies, anti-CD20 antibodies, rituximab, TNF-inhibitors,

corticosteroids, and co-stimulatory modifiers." *See also* claim 11 (reciting "further comprising administering one or more additional drug which treats the rheumatoid arthritis, wherein the additional drug is selected from the group consisting of non-biological DMARDS, NSAIDs, and corticosteroids").

The '264 patent explains that DMARDs are "the cornerstone of RA treatment throughout all stages of the disease." Ex. 1001, 1:42–44. Yet, it is undisputed that some patients are DMARD-inadequate responders. *See id.*, claim 3 (reciting "the RA patient is a DMARD-inadequate responder"). The '264 patent defines a "DMARD inadequate responder" as "one who has experienced an inadequate response to previous or current treatment with one or more DMARDs (including one or more TNF inhibitors) because of toxicity or inadequate efficacy." *Id.* at 14:46–50.

Similarly, the '264 patent states that "biological compounds that target tumor necrosis factor alpha (TNF-α), B-cells, or T-cells have been used successfully to treat RA, but ~30% to 40% of patients fail to respond to these therapies." *Id.* at 1:47–50; *see also id.*, claim 4 (reciting "the RA patient is a TNF-inhibitor-inadequate responder"). According to the '264 patent, a TNF inhibitor inadequate responder "has experienced an inadequate response to previous or current treatment with one or more TNF inhibitors because of toxicity or inadequate efficacy." *Id.* at 14:51–54.

The '264 patent specifically refers to several exemplary TNF inhibitors, including etanercept and infliximab. *See id.* at 14:39–45. As Patent Owner acknowledges, both etanercept and infliximab were approved for treating RA before 2002. Prelim. Resp. 2; Ex. 2011, 1. Yet, the '264

patent states that a TNF inhibitor inadequate responder includes a patient who has received "etanercept for ≥3 months at 25 mg twice a week or at least 4 infusions of infliximab at ≥3 mg/kg but had an inadequate response thereto." *Id.* at 14:54–57.

Thus, according to the claims and the Specification of the '264 patent, DMARDs and TNF inhibitors, including etanercept and infliximab, are drugs that "have been used successfully to treat RA," even though some patients "fail to respond," or have "inadequate response" to these therapies. *Id.* at 1:47–50, 14:46–57. As a result, the term "treats the rheumatoid arthritis," as used in claims 6 and 11, does not require that the administration result in an effective treatment for a particular patient.

Because the same term in the same patent generally carries the same construed meaning (*Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003)), we similarly adopt Petitioner's proposed construction for the preamble of claim 1, that is, "treating rheumatoid arthritis . . . in a patient" does not require actually causing a therapeutic benefit in a particular patient. Pet. 19.

C. Alleged Obviousness of Claim 4 over Emery, Bonilla, and Wang

Petitioner asserts that claim 4 would have been obvious over the combination of Emery, Bonilla, and Wang. Pet. 48–55. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

1. Prior Art Disclosures

a. Emery

Emery reports a phase III RADIATE study that "examined the efficacy and safety of tocilizumab, an anti-IL-6 receptor monoclonal antibody in patients with rheumatoid arthritis (RA) refractory to tumour necrosis factor (TNF) antagonist therapy." Ex. 1014, 3.

According to Emery, "[n]inety-five per cent of previous TNF antagonist failures were due to inadequate efficacy." *Id.* at 6. In Emery, patients who previously received, but had inadequate response to, one or more TNF antagonists, including adalimumab, etanercept, or infliximab, "were randomly assigned to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo (control) intravenously every 4 weeks with stable methotrexate for 24 weeks." *Id.* at 3.

Based on the results of that study, Emery concludes that "[t]ocilizumab plus methotrexate is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile." *Id.*

b. Bonilla

Bonilla compares administering polyclonal human immunoglobulin (Ig) via the IV and the SC routes. Ex. 1021, 4. According to Bonilla, "IVIG is usually administered every 3 to 4 weeks," whereas "SCIG is usually given weekly," and "a 2-week interval is also practical." *Id.* at 15, 18. Despite the different frequencies of the IV and SC administrations, Bonilla teaches "the amount of IgG administered over time is generally equivalent." *Id.* at 15.

Bonilla states that, when administering Ig via the SC route, because "[t]he dose is absorbed slowly and redistributed slowly," and because the amount administered each time is smaller and the interval is shorter, "the fluctuations in IgG level that are characteristic of IVIG dosing are expected to be much smaller." *Id.*; *see also id.* at 18 ("SCIG leads to more physiologic IgG levels because the peaks and nadirs between infusions are blunted by slow absorption and maintenance of closer equilibrium between intra- and extravascular compartments.").

c. Wang

Wang states that "without clear scientific rationale, body size-based dosing is often used for administering monoclonal antibodies (mAbs)." Ex. 1022, 7. After comparing fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials, Wang concludes that the two dosing approaches "perform similarly across the mAbs investigated." *Id.* Based on this finding, Wang "recommend[s] fixed dosing as the preferred approach because it offers advantages in ease of dose preparation, reduced cost, and reduced chance of dosing errors." *Id.* at 18 ("[W]hen there is no advantage of one dosing approach over another from a PK and PD perspective, fixed dosing is the approach of choice.").

2. Analysis

Petitioner relies on Emery for teaching TCZ was safe and effective for treating RA in patients who previously failed treatment with TNF-inhibitors. Pet. 48–49 (citing Ex. 1014 at 3). According to Petitioner, the only difference between claim 4 of the '264 patent and Emery is that claim 4 recites "a subcutaneous fixed dose of 162 mg for tocilizumab administered

every week or every other week," whereas Emery teaches "an intravenous dose of tocilizumab of 4 mg/kg to 8 mg/kg administered every four weeks." *Id.* at 49. Petitioner relies on Wang for teaching that "a fixed dose would be preferable to a weight-based dose in the absence of a reason to the contrary." *Id.* at 52 (citing Ex. 1022, 18). Additionally, Petitioner relies on Bonilla for teaching that antibodies are preferably administered via SC route every other week instead of every four weeks by IV. *Id.* at 51 (citing Ex. 1002 ¶ 194). An ordinarily skilled artisan, Petitioner continues, "would have looked to Bonilla to determine an equivalent subcutaneous fixed dose of the 4 mg/kg every four week intravenous regimen." *Id.* at 52 (citing Ex. 1002 ¶ 198). Petitioner contends an ordinarily skilled artisan would have been motivated to combine Emery with Bonilla and Wang to arrive at the claimed methods with a reasonable expectation of success. *Id.* at 51–55.

Patent Owner counters that Petitioner has not established a motivation to create an SC fixed dose of TCZ, and has not shown an ordinarily skilled artisan would have had a reasonable expectation of success in arriving at the claimed dosing regimen. Prelim. Resp. 60–65. For the reasons explained below, based on the current record, we find Petitioner has made a sufficient showing on these issues for institution purposes.

a. Reason for SC Administration

Petitioner argues that an ordinarily skilled artisan "would have been motivated to substitute an equivalent every other week subcutaneous dose" for the IV doses in Emery, because Bonilla teaches that "antibodies were preferably administered subcutaneously every two weeks rather than intravenously every four weeks," and because other prior art teaches SC

administration offers significant advantages over IV administration. Pet. 51 (citing Ex. 1002 ¶¶ 194–195; Ex. 1016, 12–13; Ex. 1017, 7; Ex. 1070, 2). Pointing to a PCT publication as evidence, Petitioner argues that "Chugai had itself announced that subcutaneous was the 'preferred' form of tocilizumab." *Id.* (citing Ex. 1011,[10] 4).

Citing Haller,[11] Patent Owner argues that Petitioner "ignores 'several well-known *disadvantages* associated with SC injections." Prelim. Resp. 60 (quoting Ex. 2032, 2). Patent Owner is correct that Haller discusses certain issues of SC administration; Patent Owner, however, fails to mention that Haller also points out solutions to the problems. *See* Ex. 2032, 2.

More importantly, Haller touts the advantages of SC injections. *Id.* According to Haller, "[f]rom many perspectives, including reduced pain, improved patient quality of life, reduced cost of patient care, and reduced risk of infection, SC represents a preferred route for administering a drug by self-injection." *Id.* Despite the disadvantages associated with SC injections that Patent Owner emphasizes, Haller reports that in a survey of oncology practices across the country, "there is a conscious shift to SC administration." *Id.* "Compared with IV drugs, the majority of participants in the survey considered SC drugs clinically safer and more cost-effective, resulting in higher patient satisfaction." *Id.*

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[10] WO2009/041621 A1, published April 2, 2009 (Ex. 1011).
[11] Haller, *Converting Intravenous Dosing to Subcutaneous Dosing with Recombinant Human Hyaluronidase*, 31 Pharm. Tech. 118–32 (2007) ("Haller").

Perhaps more relevant to our case here, Haller also discusses "the relative desirability of SC versus IV administration" using "anti-TNF-alpha treatments for rheumatoid arthritis" as examples. *Id.* Two of those examples, infliximab and adalimumab, both monoclonal antibodies against TNF-α, were approved for treating RA before 2002. Prelim. Resp. 2; *see also* Ex. 1001, 14:39–44 (listing infliximab and adalimumab as examples of TNF inhibitor). Haller explains that infliximab is administered intravenously, whereas adalimumab is given subcutaneously. Ex. 2032, 2. According to Haller, efficacy differences between the two drugs when administered with MTX are "considered minimal." *Id.* Interestingly, Haller points out that

> A broad indicator, such as revenues . . . shows that IV- and SC-delivered agents were essentially equal in 2001, and both have been growing at healthy rates. The relative growth rate of the SC agent, however, is approximately 50% higher than that of the IV drug (a 33% compound annual growth rate for IV versus 50% for SC), translating into 2006 revenues for the SC agent that are almost double that of the IV agent. This increase occurred despite reimbursement dynamics for SC injectables that were unfavorable until recently.

Id.

Although these revenue numbers may be not be of concern to an ordinarily skilled artisan, they appear to reflect the patients' preference for SC over IV administration, which seemingly would be at least a part of the consideration for developing RA treatments. Thus, Haller does not support Patent Owner's argument that the reason to shift from IV to SC administration is "pure hindsight." *See* Prelim. Resp. 60.

In sum, based on this record, Petitioner has shown sufficiently, for purposes of institution, that an ordinarily skilled artisan would have been motivated to administer TCZ via the SC route.

b. Reason for Fixed Dose

Patent Owner also challenges Petitioner's reliance on Wang for teaching the fixed dose. Prelim. Resp. 62–63. According to Patent Owner, Wang advises that "[a] full population PK and PD analysis should be conducted, including covariate analysis," and if "body size is identified as a covariate of PK or PD parameters, population and individual performances of both dosing approaches should be evaluated." *Id.* (quoting Ex. 1022, 18). Patent Owner argues that because data on the pharmacokinetics ("PK") or pharmacodynamics ("PD") of TCZ administered via the SC route in humans was not publicly available before the priority date of the '264 patent, Wang would not have motivated an ordinarily skilled artisan to pursue fixed dosing for TCZ. *Id.* at 63.

Again, Patent Owner's characterization of Wang is not incorrect, but incomplete. Yes, Wang suggests determining the dosing route based on PK and PD analyses, but only for phase 3 studies. Ex. 1022, 18. Patent Owner, however, omits to mention Wang's teaching that

> When an mAb is first tested in humans, the effect of body size on PK and/or PD parameters in humans is unknown. Because no obvious advantage has been identified for one approach over the other in terms of reducing variability in PK/PD measurements, either dosing approach may be used in FIH [first-in-human] and other early stage trials before the effect of body size on PK and PD in humans can be evaluated. However, we recommend using fixed dosing approach because it offers

> advantages in ease of preparation, reduced cost, and reduced chance of dosing errors.

Id.

Moreover, as Petitioner points out, "several IgG antibodies and other biologics" including etanercept, adalimumab, certolizumab, and golimumab, "were approved in the prior art that were used in a subcutaneous fixed dose." Pet. 55; *see also id.* at 13 (listing approval date, dosage, and indications). Among them, adalimumab and golimumab are monoclonal antibodies approved for treating RA before the priority date. Prelim. Resp. 5. Each is administered SC with a fixed dose, every other week for adalimumab, and once a month for golimumab. Ex. 1023, 14; Ex. 1084, 4.

Thus, on this record and for purposes of institution, Petitioner has shown sufficiently that, at the relevant time, when the PK and PD data for TCZ allegedly were not publicly available, an ordinarily skilled artisan would have been motivated to administer TCZ using a fixed dose.

c. 162 mg Per Dose

Petitioner argues that an ordinarily skilled artisan "would have looked to Bonilla to determine an equivalent subcutaneous fixed dose of the 4 mg/kg every four week intravenous regimen." Pet. 52 (citing Ex. 1002 ¶ 198). According to Petitioner, the equivalent amount of an antibody administered via the SC route may be as low as the amount administered via the IV route, and as high as the amount necessary to account for the potential impact of reduced bioavailability of the SC administration. *Id.* at 34–35 (citing Ex. 1002 ¶¶ 140; Ex. 1016, 6–7). Petitioner asserts that the reported bioavailability of TCZ administered via the SC route was 72%, "which means administering 139% (1/0.72 = 1.39) of the intravenous dosage

subcutaneously would provide the same amount of tocilizumab over time." *Id.* at 34 (citing Ex. 1002 ¶ 140; Ex. 1019,[12] 18); *see also id.* at 52 ("[A] POSA would have understood from Bonilla that the equivalent amount of an antibody administered subcutaneously would be somewhere between 100% and 139% of the intravenous dose.") (citing Ex. 1002 ¶ 198).

Petitioner argues that, starting from the 4 mg/kg every four week IV dose, as Emery teaches, and assuming the body weight of a typical patient is 70 kg, 140 mg TCZ would be administered via the SC route every other week.[13] *Id.* at 53 (citing Ex. 1002 ¶ 199). According to Petitioner, accounting for the potential 39% increase, "a POSA would have understood that an equivalent subcutaneous every other week regimen would require administering a fixed dose of between 140 mg and 195 mg." *Id.* (citing Ex. 1002 ¶ 199). Thus, Petitioner concludes that an ordinarily skilled artisan "would have arrived at the claimed 162 mg every other week subcutaneous regimen through routine optimization as 162 mg falls squarely within the range, and there is no evidence that the particular amount is critical." *Id.* (citing Ex. 1002 ¶ 199).

Patent Owner points out that Bonilla discusses polyclonal immunoglobulins, not monoclonal antibodies like TCZ. Prelim. Resp. 40 (citing Ex. 1021, 4). Patent Owner also argues that the patients in Bonilla suffer from immunodeficiencies requiring Ig infusions to supplement

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[12] European Medicines Agency, Assessment Report for RoActemra (2009) (Ex. 1019, "EMA Assessment Report").

[13] Petitioner calculates the dose as follows: "70 kg x (4 mg/kg every four weeks) = 280 mg every four weeks, or 140 mg every two weeks, for a 70 kg patient." Pet. 53 n.14.

immune responses, whereas RA patients suffer from an overactive immune system requiring immunosuppression. *Id.* Patent Owner appears to suggest the differences between a polyclonal antibody and a monoclonal antibody, or between the different patient populations, would affect an ordinarily skilled artisan's understanding of Bonilla's teaching, specifically that, over time, the amount of immunoglobulins administered, whether via IV or SC route, is generally equivalent. Patent Owner, however, has not produced evidence to support this attorney argument. Thus, based on the current record, we accord it little weight.

Patent Owner also points out that Bonilla describes "the results of just a single study in which immunodeficient participants were subcutaneously administered a product called Vivaglobin® at between 1.02 and 1.92 times the IV dosage." *Id.* (citing Ex. 1021, 17). According to Patent Owner, Bonilla "never states or even suggests that its results would apply to other immunoglobulins or indications." We disagree, because Bonilla teaches that "any product suitable for IV administration with concentration of 10% or more . . . may be administered SC." *See* Ex. 1021, 17.

Patent Owner further challenges Petitioner's reliance on the 72% relative SC/IV bioavailability. Prelim. Resp. 42. Patent Owner points out that number was from "one study in *monkeys*." *Id.* (citing Ex. 1019, 18). Patent Owner dismisses that data as "irrelevant" because of "the widespread knowledge that monoclonal antibodies exhibited dramatic interspecies variation in subcutaneous bioavailability." *Id.* (citing Ex. 2028, 7). Thus, Patent Owner concludes that an ordinarily skilled artisan would not have

assumed the 72% bioavailability reported in monkeys would remain the same in humans. *Id.* at 42–43.

We recognize, as Patent Owner emphasizes, that "interspecies variation makes it challenging to predict human bioavailability from animal data." *Id.* at 43 (citing Ex. 2029, 8; Ex. 2030, 2) (quotation marks and bracket omitted). On the other hand, the EMA Assessment Report, which Petitioner refers to for reporting the 72% bioavailability, states:

> The cynomolgus monkey was chosen as the pharmacologically relevant species because tocilizumab cross-reacts with monkey IL-6R under *in vitro* and *in vivo* conditions. In a cynomolgus monkey model of collagen-induced arthritis (CIA), tocilizumab was shown to prevent both the local joint and the systemic inflammatory disease manifestations.

Ex. 1019, 17. Thus, on this record, and for purposes of institution, we find it is reasonable for Petitioner to rely on the bioavailability data from monkeys.

On the dose amount, Patent Owner contends that the range of potential dosing options is "far broader" than Petitioner presents. Prelim. Resp. 64. This is because, Patent Owner explains, multiple studies had shown TCZ administered via the SC route is safe and effective at both 4 mg/kg and 8 mg/kg every four weeks. *Id.* Thus, following Petitioner's way of calculation, Patent Owner contends that the potential SC dosage ranges from 70 mg every week to 389 mg every two weeks.[14] *Id.*

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[14] Patent Owner calculates the dose as follows: 70 kg x (4 mg/kg every four weeks) = 70 mg every week. 70 kg x (8 mg/kg every four weeks) = 560 mg every four weeks, or 280 mg every two weeks. Adjusting 280 mg to account for the alleged 72% relative SC/IV bioavailability, the upper limit would be 389 mg (280/0.72 = 382). Prelim. Resp. 64 n.22.

Based on this record, we agree with Patent Owner that the potential SC dosage ranges from 70 mg to 389 mg. This, however, does not change the fact the claimed dose of 162 mg still falls within that range. Where, as here, the prior art suggests a range, and the claimed invention falls within that range, there is a presumption of obviousness. *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). Patent Owner may rebut this presumption by showing unexpected results or criticality of the claimed dosage, that the prior art taught away from the claimed dosage, or other pertinent objective indicia indicating that the claimed invention would not have been obvious in light of the prior art. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018). Patent Owner has not come forward with such evidence, but may do so during trial.

Patent Owner also criticizes Petitioner for relying on the "typical 70 kg" body weight. Prelim. Resp. 43–44. Patent Owner points out that Wang reports results of an experiment assuming 75 kg and 90 kg median body weights.[15] *Id.* at 44 (citing Ex. 1022, 16–17, Figure 8). Patent Owner asserts that the potential SC dosing range for 90 kg median body weight would be between 180 and 250 mg, "well *above* the 162 mg amount claimed." *Id.* We are not persuaded by Patent Owner's analysis.

We note that, in Wang's simulation, the median body weight is 75.7 kg. Ex. 1022, 9. This number is close to the 70 kg "typical" weight Petitioner uses for calculating the dosing amount. Patent Owner explained in the related IPR2021-01288 that, for 75 kg median body weight, the potential

[15] Although not statisticians ourselves, we understand "median" and "average" are different measures of central tendency.

SC dosing range would be between 150 and 208 mg. *See* IPR2021-01288, Paper 10, 56 n.22. Thus, even with Patent Owner's calculation, the proper range, using Patent Owner's model, would be from 150 to 250 mg. *See* Prelim. Resp. 64 n.22 (presenting the range as from between the lowest and highest). Thus, with the claimed 162 mg within the range, there is a presumption of obviousness, which Patent Owner may rebut during trial. *See Iron Grip*, 392 F.3d at 1322.

d. Reasonable Expectation of Success

Petitioner argues that an ordinarily skilled artisan would have reasonably expected a 162 mg fixed dose of TCZ administered via the SC route every other week to be successful for treating TNF-inhibitor-inadequate responders because Emery teaches that 4 mg/kg of TCZ administered by IV every four weeks was safe and effective, and Bonilla teaches that an equivalent SC dose would provide equivalent results. Pet. 53–54 (citing Ex. 1002 ¶ 201).

In addition, Petitioner asserts that "a POSA would also have understood that the efficacy of tocilizumab depended upon maintaining trough concentrations above a minimum threshold." *Id.* at 54 (citing Ex. 1033, 9). In view of Bonilla's teaching that the trough concentrations would be higher for a SC dose administered every other week than an equivalent IV dose administered every four weeks, Petitioner continues, an ordinarily skilled artisan would have reasonably expected the trough concentration in the SC dosing regimen (162 mg fixed dose administered via the SC route every other week) to be higher than that in the IV dosing

regimen (4 mg/kg administered via the IV route every four weeks). *Id.* at 54 (citing Ex. 1002 ¶ 200; Ex. 1021, 17).

Further, Petitioner contends that an ordinarily skilled artisan would have reasonably expected a fixed dose of 162 mg TCZ "to be successful over a wide range of patient weights." *Id.* Petitioner argues that TCZ "was known in the prior art to be safe and effective over a wide range of doses, from 4 mg/kg to 8 mg/kg, despite the AUC for the 8 mg/kg dose being more than double the AUC of the 4 mg/kg dose." *Id.* at 52 (citing Ex. 1025, 2; Ex. 1033, 7). Petitioner points out that, when TCZ was administered as a weight-based dose, an "almost two-fold" increase in AUC "did not affect efficacy or safety parameters in a clinically relevant manner." *Id.* (citing Ex. 1002 ¶ 197; Ex. 1019, 23–24).

Lastly, Petitioner points out that "several IgG antibodies and other biologics" including etanercept, adalimumab, certolizumab, and golimumab, "were approved in the prior art that were used in a subcutaneous fixed dose." *Id.* at 55; *see also id.* at 13 (listing approval date, dosage, and indications). Petitioner asserts that "[t]hese approvals would have further reinforced to a POSA that a subcutaneous fixed dose of tocilizumab would have reasonably been expected to be successful." *Id.* at 55 (citing Ex. 1002 ¶ 202).

Patent Owner argues "Petitioners' Invocation of 'Routine Optimization' Does Not Satisfy their Burden of Establishing a Reasonable Expectation of Success." Prelim. Resp. 63. Specifically, Patent Owner contends that Bonilla "never actually teaches" the IV to SC dosage calculation. *Id.* We disagree.

Bonilla teaches the amount of immunoglobulin administered over time, whether via IV or SC route, "is generally equivalent," despite the different frequencies of administrations. Ex. 1021, 15. Bonilla explains, for example, in one study,

> patients were switched from IVIG to SCIG under a protocol that called for dose adjustment of the SC product to give a time-averaged area under the curve that was equivalent to what had been obtained previously with IVIG. This change required administration of an average of 1.37 times (range 1.02–1.92) the IV dose by the SC route.

Id. at 17. Thus, for purposes of institution, we find it is reasonable for Petitioner to rely on Bonilla's teaching to calculate the SC dosage for TCZ.

In addition, Patent Owner asserts that the range of potential dosing option is "far broader" than Petitioner's calculation, and should be from 70 mg to 389 mg. Prelim. Resp. 64. As explained above, although we agree with Patent Owner on this point, the claimed dose of 162 mg still falls within the broader range, and thus, there is a presumption of obviousness. *see supra* Section II.C.2.c.

In sum, based on the current record and for purposes of this Decision, we find Petitioner has made a sufficient showing of reasonable expectation of success.

e. Summary

In sum, based on this record, Petitioner has shown a reasonable likelihood that it would prevail on its obviousness challenge of claim 4 over the combination of Emery, Bonilla, and Wang. Thus, we institute an *inter partes* review as to all challenges raised in the Petition. *See* Patent Trial and

Appeal Board Consolidated Trial Practice Guide, 64 (Nov. 2019)[16] ("The Board will not institute on fewer than all claims or all challenges in a petition.").

D. Alleged Obviousness of Claim 5 over Maini 2006, Bonilla, and Wang

Petitioner asserts that claim 5 would have been obvious over the combination of Maini 2006, Bonilla, and Wang. Pet. 48–56. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

1. Maini 2006

Maini 2006 reports a double-blind randomized controlled clinical trial of TCZ. Ex. 1025, 2. There, patients with "an inadequate response to MTX or a disease flare while receiving MTX (at a dosage of 10–25 mg weekly) during a minimum of 6 months of therapy" were recruited for the study. *Id.* at 4. In that trial, all patients received a total of four IV infusions of TCZ or TCZ placebo every four weeks, together with 10–25 mg MTX or MTX placebo each week. *Id.* at 3–4. TCZ was administered at a dose of 2 mg/kg, 4 mg/kg, or 8 mg/kg. *Id.* at 3.

Maini 2006 shows that IV infusions of TCZ every four weeks, with or without MTX therapy, were safe and effective for treating RA. *Id.* at 11–13. According to Maini 2006, TCZ monotherapy at the dose of 4 mg/kg or 8 mg/kg generated the highest responses, and "those doses are proposed for use in future clinical studies." *Id.* at 12.

[16] Available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf

2. Analysis

Petitioners relies on Maini 2006 for teaching TCZ was safe and effective for treating RA in patients who had discontinued MTX. Pet. 49. According to Petitioner, the only difference between challenged claim 5 and Maini 2006 is that claim 5 recites "a subcutaneous fixed dose of 162 mg for tocilizumab administered every week or every other week," whereas Maini 2006 teaches "an intravenous dose of tocilizumab of 4 mg/kg to 8 mg/kg administered every four weeks." *Id.*

Similar to its challenge of claim 4, Petitioner relies on Wang and Bonilla for teaching a fixed dose of 162 mg TCZ administered via the SC route every week or every two weeks. *Id.* at 51–53 (citing Ex. 1002 ¶¶ 190–202). Petitioner contends an ordinarily skilled artisan would have been motivated to combine Maini 2006 with Bonilla and Wang to arrive at the claimed methods with a reasonable expectation of success. *Id.* at 51–55.

Patent Owner advances the same counter-arguments here as it does to address the challenge to claim 4. Prelim. Resp. 60–65. For the same reason explained above (*see supra*, Section II.C.2), we find Petitioner's arguments sufficiently persuasive for institution purposes.

E. Alleged Obviousness of Claim 12 over Maini 2006, Nishimoto 2007, Bonilla, and Wang

Petitioner asserts that claim 12 of the '264 patent would have been obvious over the combination of Maini 2006, Nishimoto 2007, Bonilla, and Wang. Pet. 48–58. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

1. Nishimoto 2007

Nishimoto 2007 states that the objective of its study is to "evaluate the ability of tocilizumab (a humanised anti IL 6 receptor antibody) monotherapy to inhibit progression of structural joint damage in patients with RA." Ex. 1089, 1.

According to Nishimoto 2007, inhibiting joint damage is an important therapeutic endpoint. *Id.* In Nishimoto 2007, patients received either 8 mg/kg TCZ intravenously every 4 weeks, or conventional DMARDs, for 52 weeks. *Id.* Radiographs of hands and feet were taken at week 28 and week 52. *Id.* at 1, 2.

Nishimoto 2007 reports that patients treated with TCZ monotherapy performed better than the DMARD group. *Id.* Nishimoto 2007 concludes that TCZ monotherapy "was generally well tolerated and provided radiographic benefit in patients with RA." *Id.*

2. Analysis

Claim 12 requires inhibiting progression of structural joint damage at week 24 or week 48. Petitioner relies on Nishimoto 2007 for teaching "the importance of finding structural joint damage to be inhibited between weeks 28 and 52 when treating RA patients, which includes week 48." Pet. 48 (citing Ex. 1089, 1); *see also id.* at 56–57 (arguing Nishimoto 2007 teaches administering TCZ inhibits structural joint damage "beginning as early as week 28 and through at least week 52, which means that such inhibition would be found at week 48") (citing Ex. 1002 ¶¶ 210–211).

According to Petitioner, an ordinarily skilled artisan would have been motivated to "combine Nishimoto 2007 and Maini 2006 with Bonilla and

Wang to administer a fixed dose of 162 mg every other week to treat an RA patient (for the reasons set forth above) and to also find structural joint inhibition at week 48." *Id.* at 57 (citing Ex. 1002 ¶¶ 210–211). Petitioner contends that "[a] POSA would also have expected this regimen to be successful." *Id.* at 57–58 (citing Ex. 1002 ¶¶ 212–213).

Patent Owner emphasizes that, in Nishimoto 2007, inhibiting progression of structural joint damage was achieved by administering TCZ at not 4 mg/kg, but 8 mg/kg, via the IV route every four weeks. Prelim. Resp. 50–51 (citing Ex. 1089, 1). Patent Owner contends that, by Petitioner's way of calculation, this mount corresponds to the higher SC dosage of 162 mg every week, not every two weeks, as claim 12 requires. *Id.* at 51. We are not persuaded.

As Patent Owner acknowledges, "[m]ultiple studies had shown that IV tocilizumab was safe and effective when dosed from 4 mg/kg to 8 mg/kg every four weeks." *Id.* at 64. Maini 2006, which Petitioner relies on for this challenge, is one of such studies. *See* Ex. 1025, 12 (stating both 4 mg/kg and 8 mg/kg IV TCZ are efficacious). Moreover, relying on Kremer,[17] Petitioner argues that "a POSA would have known that an intravenous dose of 4 mg/kg administered every four weeks . . . inhibited progression of structural joint damage to a similar extent as Nishimoto's 8 mg/kg regimen." Pet. 57 (citing

[17] Kremer at al., *Tocilizumab Inhibits Joint Structural Damage in Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate: The LITHE Study*, 58(12) Arthritis & Rheumatism 4031 (L14) (2008) (Ex. 1093, "Kremer").

Ex. 1002 ¶¶ 212–213; Ex. 1093, 6). Based on the current record, we find Petitioner's argument persuasive.

Patent Owner's other counter-arguments here are as the same as those asserted to address the challenge to claim 4. Prelim. Resp. 60–65. For the same reason explained above (*see supra*, Section II.C.2), we find Petitioner's arguments sufficiently persuasive for institution purposes.

F. Other Challenges

Petitioner argues that claims 4, 5, and 12 would have been obvious over the combination of NCT00965653 and Emery, Maini 2006, and Nishimoto 2007, respectively. Pet. 23–36, 40–41, 47–48. Petitioner also asserts that Ohta 2010 anticipates claim 12, and that the combination of Ohta 2010 and Emery, Maini 2006, and Nishimoto 2007 renders obvious claims 4, 5, and 12, respectively. *Id.* at 36–40, 42–47. Because we determine Petitioner has met its burden in three other challenges, we do not address these challenges.

We institute an *inter partes* review as to all challenges raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S.Ct. 1348, 1357–58 (2018). Thus, the parties are encouraged to further address the relevant issues of all challenges, including these other grounds, to fully develop the record during trial.

III. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. We, thus,

institute an *inter partes* review of all challenged claims on all asserted grounds.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing could change upon further development of the record during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted on all challenged claims of the '264 patent based on all the asserted grounds set forth in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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