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Paper 10
Date: August 31, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

CHUGAI SEIYAKU KABUSHIKI KAISA,
GENENTECH, INC., and HOFFMANN LA ROCHE INC.,
Patent Owner.

IPR2022-00578
Patent 8,580,264 B2

Before ERICA A. FRANKLIN, JOHN G. NEW, and TINA E. HULSE, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 8,580,264 B2 (Ex. 1001, "the '264 Patent"). Paper 2 ("Pet."). Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc., and Hoffmann-La Roche Inc. (collectively, "Patent Owner") waived the filing of a Preliminary Response to the Petition. Paper 9.

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). Upon considering the argument and evidence presented in the papers, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1–12 of the '264 Patent.

A. Real Parties-in-Interest

Petitioner identifies itself along with Celltrion Healthcare Co. Ltd. and Celltrion Healthcare U.S.A., Inc. as real parties-in-interest. Pet. 32. Patent Owner identifies Chugai Seiyaku Kabushiki Kaisha (also called Chugai Pharmaceutical Co., Ltd.), Genentech, Inc., and Hoffmann-La Roche Inc. as real parties-in-interest. Paper 4, 1.

B. Related Proceedings

The parties state that claims of the '264 Patent were challenged in two pending *inter partes* review proceedings: *Fresenius Kabi USA, LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2021-01288 ("IPR1288"), Paper 30 (PTAB February 23, 2022) (institution decision) and *Fresenius Kabi USA,*

LLC v. Chugai Seiyaku Kabushiki Kaisha, IPR2021-01542 ("IPR1542"), Paper 25 (PTAB March 3, 2022) (institution decision). Pet. 32; Paper 4, 1.

Petitioner also filed concurrently a petition for *inter partes* review of related U.S. Patent No. 10,874,677 B2 ("the '677 patent") in IPR2022-00579. Pet. 32; Paper 4, 3. The '677 patent is also the subject of IPR2021-01336, which was instituted on February 23, 2022. Pet. 32–33; Paper 4, 3.

Patent Owner also identifies a list of U.S. patent applications and issued patents that relate to the '264 patent, including U.S. Patent No. 9,750,752, which is the subject of pending *inter parties* review, *Fresenius Kabi USA, LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2022-00201, Paper 23 (PTAB June 3, 2022) (institution decision). Paper 4, 1–3.

C. The '264 Patent

The '264 Patent, entitled "Subcutaneously Administered Anti-IL-6 Receptor Antibody" was filed on November 7, 2011, and claims the benefit of several provisional applications, the earliest of which was filed on November 8, 2010. Ex. 1001, code (54), 1:4–9.

The '264 Patent states rheumatoid arthritis ("RA") is a progressive, systemic autoimmune disease that damages the joints and is accompanied by fatigue, anemia, and osteopenia. Ex. 1001, 1:29–32. According to the Specification, the cause of RA is unknown. *Id.* at 1:37–38. Disease-modifying anti-rheumatic drugs ("DMARDs"), such as methotrexate and tumor necrosis factor ("TNF") inhibitors, are the "cornerstone of RA treatment throughout all stages of the disease." *Id.* at 1:42–44, 14:22–27.

Interleukin-6 ("IL-6") is a proinflammatory cytokine that has been implicated in the pathogenesis of autoimmune diseases, including RA. *Id.* at 1:54–2:11. Antibodies have been developed to bind to the interleukin-6 receptor ("IL-6R") and prevent IL-6 from binding to the receptor. *See id.* at

3:48–4:29, 8:35–38. These antibodies are referred to as anti-IL-6R antibodies. *See id.* Tocilizumab ("TCZ") is an example of a known immunoglobulin G1-kappa ("IgG1κ") anti-IL-6R antibody. *Id.* at 8:39–46. TCZ is characterized by a light chain amino acid sequence of SEQ ID NO. 1 and a heavy chain amino acid sequence of SEQ ID NO. 2. *Id.*

The Specification states that clinical efficacy and safety studies of intravenous TCZ have been completed. *Id.* at 2:12–18. For example, TCZ has been approved for treating RA by intravenous administration (4 mg/kg and 8 mg/kg). *Id.* at 2:19–24. The Specification also describes clinical studies for administering a fixed dose of 162 mg TCZ subcutaneously every week ("SC QW") in RA patients. *See id.* at 28:56–35:5. A fixed dose is a dosage of a drug "administered without regard to the patient's weight or body surface area (BSA), i.e., it is not administered as either a mg/kg or mg/m^2 dose." *Id.* at 14:64–67. The studies show that disease activity "appears to decrease from baseline more rapidly and to a greater magnitude with the 162 mg SC QW as compared to the other SC dose regimens tested." *Id.* at 30:48–51.

D. Illustrative Claim

Petitioner challenges claims 1–12 of the '264 Patent, of which claims 1, 10, and 12 are independent. Claim 1 is illustrative and 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 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.

Ex. 1001, Certificate of Correction, claim 1. Independent claim 10 differs from claim 1 in that it recites administering tocilizumab instead of anti-IL-6-

recepter antibody, and it does not recite the SEQ ID amino acid sequences. *Id.*, Certificate of Correction, claim 10. Independent claim 12 differs from claim 1 in that it recites "a method of inhibiting the progression of structural joint damage" in an RA patient, "wherein structural joint damage at week 24 or week 48 is found to be inhibited." *Id.*, Certificate of Correction, claim 12.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–12 would have been unpatentable on the following grounds:

Claims Challenged	**32 U.S.C. §[1]**	**Reference(s)**
1–3, 6–12	102	NCT '653[2]
1–3, 6–11	103	NCT '653, Morichika[3]
4	103	NCT '653, Morichika, Emery[4]
5	103	NCT '653, Morichika, Maini[5]

[1] 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.

[2] U.S. National Library of Medicine, *Study NCT00965653, A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis* (August 21, 2009), available at https://clinicaltrials.gov/ct2/history/NCT00965653?V_1. Ex. 1004 ("NCT '653").

[3] Morichika et al., WO 2009/084659 A1, published July 9, 2009 (certified English translation). Ex. 1110 ("Morichika").

[4] P. 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 randomised placebo-controlled trial*, 67 ANN. RHEUM. DIS. 1516–1523 (2008). Ex. 1043 ("Emery").

[5] R. N. 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 2817–2829 (2006). Ex. 1040 ("Maini").

Claims Challenged	32 U.S.C. §[1]	Reference(s)
12	103	NCT '653, Morichika, Kremer[6]
1–11	103	NCT '653, Morichika, Ng,[7] Nishimoto,[8] FDA Review,[9] SC PK Prior Art[10]
4	103	NCT '653, Morichika, Ng, Emery, Nishimoto, FDA Review, SC PK Prior Art
5	103	NCT '653, Morichika, Ng, Maini, Nishimoto, FDA Review, SC PK Prior Art

[6] J. Kremer et al., *LITHE: Tocilizumab Inhibits Radiographic Progression and Improves Physical Function in Rheumatoid Arthritis (RA) Patients (Pts) at 2 Yrs with Increasing Clinical Efficacy Over Time*, AM. COLLEGE OF RHEUMATOLOGY ABSTR. SUPPL. (2009). Ex. 1029 ("Kremer").

[7] C. M. Ng et al., *Pharmacokinetic-Pharmacodynamic-Efficacy Analysis of Efalizumab in Patients with Moderate to Severe Psoriasis*, 22 PHARMA. RES. 1088–1100 (2005). Ex. 1007 ("Ng").

[8] N. Nishimoto et al., *Mechanisms and pathological significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease*, 112 BLOOD 3959–64 (2008). Ex. 1008 ("Nishimoto").

[9] Food and Drug Administration, *Clinical Pharmacology and Biopharmaceutics Review(s) for IV Actemra Application No. 125276*, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000ClinPharmR.pdf. Ex. 1010 ("FDA Review").

[10] Petitioner's citation of "SC PK Prior Art" refers to several references for teaching bioavailability and rate of absorption values for various IgG1-κ-subtype antibodies. *See* Pet. 61–62 (citing Ex. 1007, 1012–1016, 1018–1022).

Claims Challenged	32 U.S.C. §[1]	Reference(s)
1–11	103	NCT '653, Morichika, Ng, Nishimoto, EMA Report,[11] Chernajovsky,[12] SC PK Prior Art
4	103	NCT '653, Morichika, Ng, Emery, Nishimoto, EMA Report, Chernajovsky, SC PK Prior Art
5	103	NCT '653, Morichika, Ng, Maini, Nishimoto, EMA Report, Chernajovsky, SC PK Prior Art
12	103	NCT '653, Morichika, Ng, Kremer, Nishimoto, FDA Review, SC PK Prior Art
12	103	NCT '653, Morichika, Ng, Kremer, Nishimoto, EMA Report, Chernajovsky, SC PK Prior Art

Petitioner also relies upon the Declarations of Dr. Dhaval K. Shah (Ex. 1032), Dr. Maarten Boers (Ex. 1034), and Dr. Paul A. Dalby (Ex. 1036).

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art "would in fact have been a team of individuals possessing the different skill sets typically employed on such a project." Pet. 27. Petitioner asserts that the "team would have included individuals skilled in the relevant area(s) of

[11] Europe Medicines Agency, *Assessment Report for RoActemra*, Doc. Ref.: EMEA/26276/2009 (2009). Ex. 1006, Ex. B ("EMA Report").
[12] N. Nishimoto et al., *Humanized Antihuman IL-6 Receptor Antibody, Tocilizumab*, *in Therapeutic Antibodies* 151–60 (Y. Chernajovsky & A. Nissim eds., 2008). Ex. 1009 ("Chernajovsky").

clinical medicine (e.g., rheumatologists), pharmacokineticists, formulators and project leads" working together as needed. *Id.* (citing Ex. 1034 ¶ 48; Ex. 1032 ¶ 27; Ex. 1036 ¶¶ 25–26).

Although Petitioner's definition of the level of ordinary skill in the art is uncontested on this record, defining a "person" of ordinary skill in the art as a "team of individuals" (Pet. 27) is not conventional. We note that Petitioner's experts provide an alternative definition for a person of ordinary skill in the art as someone who "would have had access to individuals skilled in clinical medicine, pharmacokinetics and formulation." Ex. 1034 ¶ 49; Ex. 1032 ¶ 27; Ex. 1036 ¶ 27. We also note that in the currently pending related cases, IPR1288 and IPR1542, the Board found in its Decision on Institution 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." IPR2021-01288, Paper 30 at 6–7; *see also* IPR2021-01542, Paper 25 at 7–8.

At this stage of the proceeding, we adopt our prior definition, with the further clarification that a person of ordinary skill in the art may alternatively (or also) have a Ph.D. and would have access to individuals skilled in clinical medicine, pharmacokinetics and formulation. We find this definition to be consistent with the prior art of record, which is sufficient to demonstrate the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not

shown" (*quoting Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))). The parties are invited to address this issue further during trial if the definition of the level of ordinary skill is in dispute.

B. Claim Construction

In an *inter partes* review, the Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

Petitioner proposes constructions of several terms. Pet. 35–40. At this stage of the proceeding and on this record, we need only address Petitioner's proposed construction of a "method of treating rheumatoid arthritis" as recited in the preambles of independent claims 1 and 10. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed to the extent necessary to resolve the controversy." (internal quotes omitted)).

Petitioner argues that "[t]he preamble in claims 1 and 10 is not limiting because it does not—and cannot—alter the active steps of the claims, which are to 'subcutaneously administer' the fixed dose QW or Q2W." Pet. 36. Petitioner alternatively argues that even if the preamble were limiting, the "method of treating rheumatoid arthritis" would merely require an intent to treat without any particular degree of efficacy. *See id.* (citing Ex. 1034 ¶¶ 121–122). Petitioner argues that the "plain meaning of 'treating' is to give a treatment," regardless of efficacy. *Id.* at 36–37 (citing Ex. 1034 ¶¶ 119–121; Ex. 1061, 2434–2435; Ex. 1062, 838). Petitioner also argues that this plain meaning is consistent with the '264 Patent Specification, which refers to treatment as both effective and ineffective administration. *See id.* at 37 (citing Ex. 1011, 14:46–63). For example, Petitioner argues that the Specification describes a clinical study with an efficacy endpoint of 85% indicating that "treatment was not efficacious in at least some of the patients." *Id.* at 37–38 (citing Ex. 1001, 47:35–52). Finally, Petitioner argues that even if the claimed treatment were interpreted to be "effective against RA, that efficacy is not limited to any particular threshold or degree." *Id.* at 38.

We note that in the Decisions on Institution in related cases IPR1288 and IPR1542, the Board previously determined that it was unnecessary to determine whether the preamble is limiting because the Board found that even if the preamble were limiting, "the plain and ordinary meaning of the phrase 'treating rheumatoid arthritis . . . in a patient' is 'attempting to cause a therapeutic improvement in a rheumatoid arthritis in a patient,' and does not require actually causing a therapeutic benefit in a particular patient." IPR2021-01288, Paper 30, 8; IPR2021-01542, Paper 25 at 9. Thus, our prior construction is consistent with Petitioner's proposed construction here.

On this record at this stage of the proceeding, we find that if the preamble is limiting, we agree with Petitioner's proposed construction and adopt that construction for the reasons stated in the Petition. Pet. 36–38. That is, if the preamble is limiting, we find the intrinsic evidence supports construing "method of treating" as "giving treatment, regardless of efficacy." *See* Ex. 1001, 14:46–63 (describing "inadequate efficacy" to various "treatment"). We further note that the Specification defines "treatment" as referring "to both therapeutic treatment and prophylactic or preventative measures." Ex. 1001, 15:1–2. The Specification then defines the term "effective amount" as "an amount of the antibody that is *effective for treating* the IL-6 disorder." *Id.* at 15:3–4 (emphasis added). If "treating" the IL-6 disorder required efficacy, it would not be necessary for the Specification to define an "effective amount" for treating the disorder, as efficacy would be implicit in the "treatment."

Thus, although we need not address whether the preamble is limiting at this stage of the proceeding, we determine that if it is, the claimed "method of treating rheumatoid arthritis" need not be effective to fall within the scope of the claims.

C. Ground 1: Alleged Anticipation by NCT '653

Petitioner argues that NCT '653 anticipates claims 1–3 and 6–12. Pet. 40–50. On this record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing that claims 1–3 and 6–11 are anticipated by NCT '653, but not claim 12.

1. NCT '653 (Ex. 1004)

NCT '653 describes a clinical trial study entitled "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis." Ex. 1004, 1. The summary states "[t]his open-label randomized

2arm study will investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of subcutaneously administered tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate." *Id.* at 6. The summary explains further that "[p]atients will be randomized to receive tocilizumab 162 mg sc [subcutaneously] either weekly or every other week, in combination with methotrexate, for 12 weeks." *Id.*

Petitioner asserts NCT '653 is a printed publication that was available on ClinicalTrials.gov before November 2009 and is therefore prior art under 35 U.S.C. § 102(b). Pet. 40. Petitioner explains that the posting renders NCT '653 publicly available because "the very purpose of ClinicalTrials.gov is to make such trials as widely and promptly available to the public as possible." *Id.* (citing Ex. 1035 ¶¶ 13–19, 23). At this stage of the proceeding, and absent a response from Patent Owner, we find Petitioner has shown sufficiently that NCT '653 qualifies as prior art.

2. Analysis

Anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citation omitted). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *Id.* (citation omitted). Moreover, to anticipate, a prior art reference must "disclose[] within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

Petitioner provides a detailed explanation of how NCT '653 discloses each limitation of independent claims 1 and 10. Pet. 42–47. That is, Petitioner asserts that NCT '653's disclosure of subcutaneously administering to RA patients 162 mg TCZ either weekly or every other week discloses each limitation of claims 1 and 10. *Id.* (citing Ex. 1004, 6). At this stage of the proceeding, we are persuaded that Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that NCT '653 anticipates claims 1 and 10. Regarding claim 10 specifically, wee find, on this record, that Petitioner has shown sufficiently that a person of ordinary skill in the art would have understood that TCZ comprises the light chain and heavy chain amino acid sequences of SEQ ID Nos. 1 and 2, respectively. *See* Pet. 45–47 (citing Ex. 1001, 6:60–62; Ex. 1032 ¶¶ 151–186; Ex. 1034 ¶¶ 132–137).

Regarding claims 2, 3, 6–8, and 9, which depend directly or indirectly from claim 1 and claim 11, which depends from claim 10, Petitioner asserts NCT '653 discloses the additional limitations of those claims. Pet. 47–48. We have considered the argument and evidence presented by the Petition and find Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that NCT '653 anticipates those claims, as well, for the reasons stated in the Petition. *See id.*; *see also* Ex. 1034 ¶¶ 139–42.

Regarding independent claim 12, which recites a "method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient" and "wherein structural joint damage at week 24 or week 48 is found to be inhibited," Petitioner asserts that a person of ordinary skill in the art would have understood that the method of treating RA in NCT '653 encompasses treating the symptoms of RA, including structural joint

damage, and therefore anticipates claim 12. Pet. 48–50. And, to the extent the claim requires the step of actually finding inhibition, Petitioner asserts that NCT '653 discloses examining patients at regular intervals to determine efficacy. *Id.* at 49 (citing Ex. 1004, 6). Moreover, Petitioner notes that although NCT '653 does not expressly identify structural joint damage as a symptom to be measured as a secondary outcome, it does teach assessing plasma levels of TCZ and other factors that would indicate inhibition of joint damage. *Id.* at 49–50 (citing Ex. 1004, 8; Ex. 1034 ¶ 146).

On this record, we are not persuaded that Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that NCT '653 anticipates claim 12. Petitioner admits that NCT '653 does not "expressly identify structural joint damage as a symptom to be measured." *Id.* at 49. Thus, Petitioner must show that NCT '653 inherently discloses the limitation that "structural joint damage at week 24 or week 48 is found to be inhibited." On this record, we are not persuaded that Petitioner has made that showing. Specifically, it appears the study described in NCT '653 extends for only 15 weeks (i.e., 12 weeks of treatment and 3 weeks of follow-up). *See* Ex. 1004, 6 (stating patients will "receive tocilizumab 162 mg sc either weekly or every other week . . . for 12 weeks. Assessments will be made at regular intervals during treatment and on the 3 weeks of follow-up"). Thus, even if the assessments that Petitioner relies on were a measure of structural joint damage, it is not clear on this record that NCT '653 necessarily discloses making those assessments at 24 or 48 weeks, as required by the claims. Ex. 1001, Certificate of Correction, claim 12.

Accordingly, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing claims 1–3 and 6–11 are anticipated by NCT '653, but not claim 12.

D. Ground 2: Alleged Obviousness over NCT '653 and Morichika

Petitioner argues claims 1–3 and 6–11 of the '264 Patent are unpatentable as obvious over NCT '653 and Morichika. Pet. 50–52. On this record, we determine Petitioner has shown a reasonable likelihood that it would prevail in showing the challenged claims would have been unpatentable as obvious over the cited art. We incorporate here our earlier findings and discussion regarding NCT '653.

1. Morichika (Ex. 1110)

Morichika is a certified English translation of an international patent application published on July 9, 2009, thereby making it prior art to the challenged claims. Ex. 1001, 1, 3. Morichika relates to antibody-containing formulations for subcutaneous administration. Ex. 1001, 1, Abstract. Morichika explains that most known antibody formulations are used for intravenous injection, but there is "growing demand" for antibody-containing formulations that can be self-injected subcutaneously. *Id.* ¶ 2. Morichika further explains that the amount of antibody administered per dose is about 100–200 mg and the solution must be highly concentrated due to the small amount of injection solution. *See id.* ¶ 3.

Morichika discloses antibody-containing liquid formulations "especially suited for subcutaneous injection." *Id.* ¶ 53. Specific examples

include antibody formulations containing an anti-IL-6R antibody referred to as "MRA."[13] *Id.* ¶ 61.

2. Analysis

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness when presented.[14] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Petitioner argues that a person of ordinary skill in the art would have combined NCT '653 with Morichika, because Morichika's subcutaneous formulation would have been suitable for use in NCT '653's clinical trial. Pet. 50–51 (citing Ex. 1034 ¶ 149). Petitioner argues that the person of ordinary skill would have been motivated to do so due to the well-known advantages of subcutaneous administration over the intravenous route. *Id.* (citing Ex. 1034 ¶¶ 62–65, 149; Ex. 1110 ¶ 53). Petitioner further argues that a person of ordinary skill would have had a reasonable expectation of

[13] Petitioner asserts that MRA refers to TCZ. Pet. 14 ("*Morichika* discloses a high-concentration formulation of tocilizumab (referred to as 'MRA' in the reference)"; *see also* Ex. 1034 ¶ 78; Ex. 1040, 2817 ("tocilizumab (previously known as MRA)").

[14] At this stage of the proceeding, Patent Owner has not presented objective evidence of nonobviousness.

success in the combination because using Morichika's formulations in the NCT '653 protocol "would have involved only routine skill." *Id.* at 51 (citing Ex. 1034 ¶ 150; Ex. 1036 ¶ 37).

As explained above, we find Petitioner has shown a reasonable likelihood of succeeding on its assertion that NCT '653 anticipates claims 1–3 and 6–11 of the '264 Patent. Thus, for the same reasons we find NCT '653 anticipates claims 1–3 and 6–11, we find Petitioner has shown a reasonable likelihood of succeeding on its assertion that the combination of NCT '653 and Morichika renders those claims obvious. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) ("[I]t is well settled that a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for anticipation is the epitome of obviousness.") (internal quotations and citations omitted). That said, to the extent Morichika's teachings bolster the use of subcutaneous TCZ to treat RA, we also find Petitioner has shown sufficiently at this stage in the proceeding that a person of ordinary skill in the art would have had a reason to combine Morichika's subcutaneous TCZ formulation and NCT '653's clinical protocol with a reasonable expectation of success for the reasons stated by the Petition. *See* Pet. 50–52 (Ex. 1034 ¶¶ 148–156; Ex. 1036 ¶ 37).

E. Grounds 3–5: Alleged Obviousness of Claims 4, 5, and 12

Petitioner asserts that claim 4 would have been obvious over NCT '653, Morichika, and Emery (Pet. 53–54); claim 5 would have been obvious over NCT '653, Morichika, and Maini (*id.* at 55); and claim 12 would have been obvious over NCT '653, Morichika, and Kremer (*id.* at 55–56). On this record, we determine Petitioner has shown a reasonable likelihood that it would prevail in showing claims 4 and 5 would have been

unpatentable as obvious over the cited art, but not claim 12. We incorporate here our earlier findings and discussion regarding NCT '653 and Morichika.

1. Emery (Ex. 1043)

Emery is a journal article that appears to have been published in 2008, thereby making it prior art to the challenged claims. Ex. 1043. Emery describes a clinical trial study relating to IL-6 receptor inhibition in RA patients who failed to respond or did not tolerate one or more tumor necrosis factor ("TNF") antagonists (i.e., the patients were refractory to TNF). Ex. 1043, 1516. Specifically, Emery discloses 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.*

2. Maini (Ex. 1040)

Maini is a journal article that appears to have been published in 2006, thereby making it prior art to the challenged claims. Ex. 1040. Maini describes a clinical trial study relating to the efficacy of "tocilizumab (previously known as MRA), a humanized anti-interleukin-6 (IL-6) receptor antibody, alone and in combination with methotrexate (MTX), for the treatment of rheumatoid arthritis (RA)." Ex. 1040, 2817. Maini states that TCZ "was used either as monotherapy (by discontinuation of MTX) or concomitantly with MTX therapy." *Id.* at 2818. Maini discloses that a "20% response (improvement) according to the American College of Rheumatology criteria (ACR20 response) was achieved by 61% and 63% of patients receiving 4 mg/kg and 8 mg/kg of tocilizumab as monotherapy, respectively, and by 63% and 74% of patients receiving those doses of tocilizumab plus MTX." *Id.* Maini states that "[t]he results of this study clearly show that infusions of tocilizumab every 4 weeks, with or without

background MTX therapy, can produce marked and dose-related improvement in RA disease activity." *Id.* at 2826.

3. Kremer (Ex. 1029)

Kremer discloses an abstract that appears to have been published in October 2009 from the 73rd Annual Scientific Meeting of the American College of Rheumatology (October 16–21, 2009), thereby making it prior art to the challenged claims. Ex. 1029. Kremer "report[s] the results of a 2-yr planned analysis of a double-blind, randomized controlled, phase 3 trial of TCZ in [patients] with moderate to severe RA who remained on MTX despite inadequate response." *Id.* at 516.

Kremer discloses that patients in the clinical trial received "TCZ + MTX (4 mg/kg [TCZ4] or 8 mg/kg [TCZ8]) or placebo + MTX (control [CON]) every 4 wks." *Id.* Kremer discloses that "clinically significant improvements in SJC [swollen joint count] occurred [] that were maintained through [week] 104" in patients treated with TCZ. *Id.* Additionally, Kremer discloses "significantly less radiographic progression (81% inhibition)" in the TCZ8 group. *Id.* Kremer explains that "TCZ + MTX continues to inhibit radiographic progression and improve physical function with a clinical effect, as evidenced by improving DAS28 [disease activity score] remission, LDAS [low disease activity state], and SJC at 2 yrs and with a manageable safety profile." *Id.*

4. Analysis

Claim 4 depends from claim 1 and further recites that the patient be a "TNF-inhibitor-inadequate responder." Ex. 1001, Certificate of Correction, claim 4. Petitioner asserts that Emery teaches that the combination of TCZ and MTX was effective in treating RA in TNF-non-responders. Pet. 53–54 (citing Ex. 1043, 1522; Ex. 1034 ¶¶ 61, 159–160). Petitioner argues that the

known efficacy of TCZ and MTX in TNF inhibitor-inadequate responders, as well as the commercial approval of its use, "would have motivated a POSA to treat such patients with the fixed-dose SC regimen" of NCT '653. *Id.* at 54 (citing Ex. 1006, 55; Ex. 1034 ¶ 161). Petitioner adds that a person of ordinary skill in the art would have been further motivated by the known advantages of subcutaneous formulations over IV formulations. *Id.* (citing Ex. 1034 ¶ 161).

Claim 5 depends from claim 1 and further recites that the patient be "methotrexate (MTX) naïve or has discontinued MTX." Ex. 1001, Certificate of Correction, claim 5. Petitioner asserts that Maini describes the results of a study in which TCZ was used as monotherapy "by discontinuation of MTX" or together with MTX, and reports that both treatments were safe and efficacious. Pet. 55 (citing Ex. 1040, 2818, 2821; Ex. 1034 ¶¶ 61, 166–167). Petitioner argues that in light of this known efficacy, and for the same reasons asserted for claim 4, claim 5 would have been obvious. *Id.*

On this record, we are persuaded that Petitioner has shown sufficiently at this stage in the proceeding that Emery and Maini teach the additional limitations of claims 4 and 5, respectively, and that a person of ordinary skill in the art would have had a reason to combine the references with a reasonable expectation of success for the reasons stated by the Petition. *See* Pet. 53–55; Ex. 1034 ¶¶ 158–167.

Regarding claim 12, Petitioner asserts that Kremer teaches administering 4 mg/kg or 8 mg/kg IV TCZ every four weeks for 12 months and found that patients receiving 4 mg/kg had almost the same inhibition of structural joint damage as those receiving 8 mg/kg IV TCZ. Pet. 55–56 (citing Ex. 1029, Table A). Petitioner argues that in light of this known

efficacy, and for the same reasons explained with respect to claims 1–11, claim 12 would have been obvious over the cited art. *Id.* at 56 (citing Ex. 1034 ¶¶ 171–172, 190).

We are not persuaded. Petitioner relies on Kremer's results in Table A to show inhibition of structural joint damage. Pet. 56. But Table A shows results after two years. Ex. 1029, Table A. Kremer appears to be silent as to whether the patients' joints were examined at week 24 or 48, as required by the claims, and what those results were. *See id.* at 516. Thus, at this stage of the record, we find Petitioner has not shown sufficiently that Kremer teaches or suggests the limitation of "wherein structural joint damage at week 24 or week 48 is found to be inhibited."

Accordingly, on this record, we determine Petitioner has shown a reasonable likelihood of succeeding on its assertion that claims 4 and 5 would have been obvious over the cited art, but not claim 12.

F. Remaining Grounds

In the remaining grounds of the Petition, Petitioner asserts claims 1–12 of the '264 Patent would have been unpatentable as obvious over the same combinations of art as the previous grounds (i.e., NCT '653 and Morichika alone (claims 1–3, 6–11) or in combination with Emery (claim 4), Maini (claim 5), or Kremer (claim 12)), but adds references to bolster its argument that a person of ordinary skill in the art would have had a reasonable expectation that a 162 mg SC fixed dose of TCZ weekly or twice weekly would have been effective against RA. Pet. 56–73. Specifically, Petitioner adds Ng, Nishimoto, FDA Review, and SC PK Prior Art in one set of grounds (identified as Grounds 6 and 8 in the Petition) and Ng, Nishimoto, EMA Report, Chernajovsky, and SC PK Prior Art in another set of grounds (identified as Grounds 7 and 9 in the Petition). The grounds are

substantively similar, but, if it is found that FDA Review is not prior art, Petitioner relies on EMA Report and Chernajovsky for the same teachings. Pet. 67–68.

For these grounds, Petitioner argues that a person of ordinary skill in the art would have known that 1 μg/ml of TCZ is the minimum effective concentration ("MEC") at which TCZ would effectively block the activity of IL-6, as taught by Nishimoto. Pet. 56–57 (citing Ex. 1032 ¶¶ 105–107; Ex. 1034 ¶¶ 175–178; Ex. 1008, 3961–63). Moreover, Petitioner asserts that a person of ordinary skill in the art would have understood that they could "simply plug[] the [SC dosage regimen of NCT '653] and known PK [pharmacokinetic] parameters of tocilizumab into a suitable PK/PD [pharmacodynamic] model and then observe whether the regimen would produce efficacious mean blood plasma levels of antibody." Pet. 59–60 (citing Ex. 1032 ¶ 5; Ex. 1034 ¶¶ 179–183).

According to Petitioner, a person of ordinary skill in the art would have used a two-compartment model, as Ng did for efalizumab, a humanized monoclonal IgG1-*kappa* antibody that is structurally similar to TCZ. Pet. 60 (citing Ex. 1007, 1088; Ex. 1032 ¶¶ 47, 81, 81, 84–86). Moreover, Petitioner argues that a person of ordinary skill in the art would have used the "plug and play" software programs available at the time to create a two-compartment model using the PK data from FDA Review, regarding Roche's IV TCZ product Actemra and from SC PK Prior Art regarding structurally similar compounds as TCZ. Pet. 60–63 (citing Ex. 1010, 114; Ex. 1032 ¶¶ 92–98, Table 4). In FDA Review, Roche published its two-compartment PK/PD model and the PK parameters used to generate the model. Ex. 1010, 110–24. Alternatively, Petitioner asserts that a person of ordinary skill in the art would have looked to Chernajovsky and EMA

Report for PK/PD data associated with TCZ. Pet. 67–70 (citing Ex. 1032 ¶¶ 87, 90; Ex. 1006; Ex. 1009). According to Petitioner's expert, Dr. Shah, a person of ordinary skill in the art would have recognized that plugging the PK parameters into the prior art ADAPT software program available at the time demonstrates that NFT '653's 162 mg fixed dose of TCZ administered once weekly or every other week results in a plasma concentration at or above the 1 μg/ml MEC for TCZ. Pet. 63–66 (citing Ex. 1032 ¶¶ 115–123). Accordingly, Petitioner asserts that from the modeling results, a person of ordinary skill in the art would have had a reasonable expectation that both the once-weekly and every other week dosage regimens of NCT '653 would have substantial efficacy. Pet. 66 (citing Ex. 1034 ¶¶ 179–183).

On this record, and without a response from Patent Owner, we find Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing that claims 1–11 of the '264 Patent would have been obvious over the cited art for the reasons stated by the Petition. That is, at this stage of the proceeding, we are persuaded that Petitioner has shown sufficiently for institution that a person of ordinary skill in the art would have been able to use known PK parameters for TCZ and known modeling software to determine that the dosage regimen of NCT '653 could be combined with the additional cited art to treat RA patients as recited by the claims with a reasonable expectation of success. *See* Pet. 56–73; Ex. 1034 ¶¶ 173–195. Because the additional references do not cure the deficiency of Kremer, however, we find Petitioner has not shown a reasonable likelihood that it would prevail in showing that claim 12 would have been obvious over the prior art for the reasons stated above. *See* Section II.E.4.

Accordingly, we determine Petitioner has shown a reasonable likelihood that it would prevail in its assertion that claims 1–11 of the '264 Patent would have been obvious over the cited art, but not claim 12.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one of the challenged claims of the '264 Patent is unpatentable. Accordingly, we institute an *inter partes* review of claims 1–12 of the '264 Patent on each of the grounds raised in the Petition.

Our determination in this Decision is not a final determination on the construction of any claim term or the patentability of any challenged claim and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner's contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that "there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial") (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–12 of U.S. Patent No. 8,580,264 B2 is instituted with respect to all challenged claims and all 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, which will commence on the entry date of this decision.

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