Trials@uspto.gov
571-272-7822

Paper 30
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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.

IPR2021-01288
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 3 ("Pet.")), seeking an *inter partes* review of claims 1–3 and 6–11 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 10 ("Prelim. Resp.")). With our authorization (Ex. 3001), Petitioner filed a Reply to the Preliminary Response (Paper 15, "Reply"), and Patent Owner filed a Sur-reply (Paper 26, "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 1–3 and 6–11 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. 4.

Petitioner explains that the ’264 patent originally issued with nine claims, corresponding to claims 1–3 and 6–11 challenged here. Paper 9, 1. Just one day before this Petition was filed, however, a Certificate of Correction issued, adding claims 4, 5, and 12. *Id.* Petitioner has filed IPR2021-01542, seeking *inter partes review* of the newly added claims 4, 5, and 12 of the ’264 patent. *Id.* at 2.

Petitioner also has filed IPR2021-01336, seeking an *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. 4.

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. Illustrative Claims

Among the challenged claims, claims 1 and 10 are independent. Claim 1 is illustrative and is 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.

Ex. 1001, 63:17–25.

Claim 10 is similar to claim 1, except that, instead of the SEQ ID NOs., it recites TCZ by name. *Id.* at page 60, Certificate of Correction.

D. Asserted Challenge to Patentability

Petitioner asserts the following challenge to patentability:

Claims Challenged	35 U.S.C. §[3]	Reference(s)
1–3, 6–11	102	NCT00965653[4]
1–3, 6–11	103(a)	NCT00965653
1, 2, 9, 10	102	Ohta 2010[5]

[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] 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*

Claims Challenged	35 U.S.C. §[3]	Reference(s)
1–3, 6–11	103(a)	Ohta 2010, Maini 2006
1–3, 6–11	103(a)	Maini 2006, Bonilla,[6] and Wang[7]

Petitioner relies on the Declarations of Thomas M. Zizic, M.D. (Ex. 1002) and Howard L. Levine, Ph.D. (Ex. 1003). Petitioner also 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. 20 (citing Ex. 1002 ¶ 33). For purposes of its Preliminary Response, Patent Owner does not dispute this definition of the

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with Rheumatoid Arthritis, 62(10) Arthritis & Rheumatism S467–68 (2010) (Ex. 1034, "Ohta 2010").

[6] Bonilla, *Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes*, 28 Immun. and Allergy Clinics of N. America 803–19 (2008) (Ex. 1021, "Bonilla").

[7] 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. 27 n.10. 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. 21–25. 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 and for purposes of this Decision, only the phrases "[a] method of treating rheumatoid arthritis in a patient"/"treats the rheumatoid arthritis" need express construction.

In each of independent claims 1 and 10, the preamble recites "[a] method of treating rheumatoid arthritis (RA) in a patient." Each of claims 6 and 11 requires administering to the RA patient one or more additional drug that "treats the rheumatoid arthritis."

The parties dispute whether the preamble of claims 1 and 10 is limiting: Petitioner argues it is not (Pet. 21–22); whereas Patent Owner contends it is (Prelim. Resp. 28–31). The parties also disagree over whether

"treating" or "treats" requires efficacy: Petitioner argues it does not (Pet. 22–25); whereas Patent Owner contends it does (Prelim. Resp. 31–37).

We do not need to address whether preamble of claims 1 and 10 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. 22 (citing Ex. 1002 ¶ 97; 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. 27–37). More importantly, the intrinsic evidence here is

different from that in IPR2021-01024. And that 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. CV176921, 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. 34. 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, we agree with Petitioner that 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. Pet. 24–25.

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 claims 1 and 10, that is, "treating rheumatoid arthritis . . . in a patient" does not require actually causing a therapeutic benefit in a particular patient. Pet. 22.

C. Alleged Anticipation by NCT00965653

Petitioner asserts that claims 1–3 and 6–11 are anticipated by NCT00965653. Pet. 25–36. 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. Disclosure of NCT00965653

NCT00965653 is a clinic trial study, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis." Ex. 1028, 1; Ex. 1038, 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." Ex. 1028, 2; Ex. 1038, 3–4. 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." Ex. 1028, 2; Ex. 1038, 4.

2. Analysis

Petitioner maps each limitation of the challenged claims to the disclosures in NCT00965653. Pet. 30–36. Specifically, Petitioner refers to NCT00965653 for disclosing SC administration of 162 mg TCZ to RA patients. *Id.*

Patent Owner argues that NCT00965653 does not anticipate the challenged claims for two reasons: (a) NCT00965653 is not prior art; (b) NCT00965653 does not enable the claimed SC dosing regimen; and (c) NCT00965653 describes a prospective Phase I study, and thus, does not meet the efficacy requirement of the challenged claims. Prelim. Resp. 14–40. Below, we address each of Patent Owner's contentions and explain why we find them unsupported based on the current record.

a. Prior Art Status of NCT00965653

Petitioner argues that NCT00965653 is prior art because it is a printed publication publicly available before the priority date of the challenged claims. Pet. 27–30. Patent disagrees. Prelim. Resp. 14–21. Based on this record and for purposes of this Decision, we determine that Petitioner has shown sufficiently that NCT00965653 is prior art.

Petitioner has the burden to prove NCT00965653 qualifies as prior art. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016). "[A]t the institution stage, the petition must identify, with particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication." *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 ("*Hulu*") at 13 (PTAB Dec. 20, 2019) (precedential).

"Public accessibility" is considered to be "the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. §102(b)." *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

A determination whether a particular reference qualifies as a printed publication "is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis." *Hall*, 781 F.2d at 899. In a proceeding before the Board, there is no presumption in favor of finding that a reference is a printed publication. *Hulu*, 16.

Petitioner asserts that NCT00965653 is a prior art printed publication, which was "publicly available on ClinicalTrials.gov before November 2009, or more than one year before the earliest claimed priority date of the '264 patent." Pet. 25, 27. To support that assertion, Petitioner relies on the declaration of Mr. Paarlberg[8] for the background information regarding the ClinicalTrials.gov website. *Id.* at 28–29 (citing Ex. 1004 ¶¶ 12, 13, 15, 16, 23). According to Mr. Paarlberg, pursuant to the FDA Modernization Act, The National Library of Medicine, under the National Institutes of Health ("NIH"), launched ClinicalTrials.gov in February 2000 to provide the public with access to information on clinical studies conducted in the United States for drugs for serious or life-threatening diseases and conditions. Ex. 1004 ¶¶ 12–13; *see also* Pet. 28 (quoting Ex. 1029, 1, an NIH press release explaining that the database published on ClinicalTrials.gov "is intended to provide 'patients, families and members of the public ***easy access to information***'").

Petitioner also asserts that "[t]he FDA Amendments Act of 2007 later expanded the database by requiring additional submission information,

[8] Mr. Paarlberg is the founder of and a principal at "a consultancy specializing in regulatory policy, regulatory intelligence, and global clinical trial disclosure strategy and operations." Ex. 1004 ¶ 3.

mandating searchable categories in the database, and imposing a fine for failure to submit information within 21 days of first patient enrollment" in a trial. Pet. 28 (citing Ex. 1004 ¶¶ 15–16). Referring to the ClinicalTrials.gov Glossary, Petitioner asserts that the NIH explains that the "First Posted" date identified for a particular study is "[t]he date on which the study record was first available on ClinicalTrials.gov." *Id.* (quoting Ex. 1030, 7). Petitioner additionally asserts that the NIH tracks all subsequent versions of the study and identifies those versions for the public in a "History of Changes" feature on the website. *Id.* at 28–29 (citing Ex. 1004 ¶ 23).

Regarding NCT00965653, Petitioner asserts that study record was "First Posted" on ClinicalTrials.gov on August 25, 2009, and available to the public on that date. *Id.* (citing Ex. 1028, 1; Ex. 1004 ¶ 28). Petitioner asserts that the History of Changes indicates each of the subsequent updates to the study record. *Id.* at 29 (citing Ex. 1004 ¶¶ 29, 30, 33); *see also* Ex. 1037 ("History of Changes" showing all updates to the original NCT00965653 study record through November 1, 2016). According to Petitioner, ClinicalTrials.gov confirms that those changes have not involved changes to the protocol itself, which has remained the same since it was published in the "First Posted" version. *Id.*; Ex. 1004 ¶¶ 34, 35; Ex. 1038 ("History of Changes" showing original, August 2009 version NCT00965653 study record). Based on the foregoing, Petitioner asserts that "[t]he totality of the evidence, including the indicia on the face of [the relied upon] documents and the testimony of Mr. Paarlberg, establishes that NCT00965653 (Ex. 1028) was publicly accessible more than one year before the earliest claimed priority date." *Id.* at 29–30.

Patent Owner argues that the particular document submitted as Exhibit 1028 was published on November 2, 2016, which is the date identified as the "last update[d]" on the document. Prelim. Resp. 15. Patent Owner argues that because that publication date was several years after the '264 patent's priority date, Exhibit 1028 is not prior art. *Id.* Additionally, Patent Owner argues that Exhibit 1028 contains information not disclosed until after the priority date, as "[s]everal different 'versions' of the *NCT00965653* webpage have been published on Clinicaltrials.gov between August 2009 and November 2016," wherein each version is updated with new information. *Id.* (citing Ex. 1037).

Patent Owner acknowledges that Petitioner also cites to Exhibit 1038, "which purportedly corresponds to the original version of the webpage published in August 2009." *Id.* at 16. Patent Owner argues that Petitioner, however, does not make that exhibit the basis of its grounds relying on the NCT00965653 study. *Id.* According to Patent Owner, for those grounds, institution cannot "proceed on a different basis that adds to or replaces the Ex. 1028 reference specified in the Petition." *Id.* at 18 (citing *Sirona Dental Sys. GmbH v. Institut Straumann AG*, 892 F.3d 1349, 1356 (Fed. Cir. 2018) (explaining that it would be improper for the Board to "deviate from the grounds in the petition and raised its own obviousness theory" because an inter partes review must proceed "in accordance with or in conformance to the petition")).

Further, Patent Owner argues that Petitioner fails to prove that an interested artisan could have located NCT00965653 in November 2009 with reasonable diligence. *Id.* at 19. In particular, Patent Owner alleges that

Mr. Paarlberg's testimony is insufficient because he does not explain "how clinical trials were indexed or what search allegedly would have allowed a reasonably diligent POSA to pick *NCT00965653* out of the thousands of available clinical trial records." *Id.* at 20. According to Patent Owner, "Mr. Paarlberg simply speculates that *NCT00965653* 'would have been readily accessible,'" without attesting to any personal knowledge that the record was available on the Clinicaltrials.gov website. *Id.* at 20–21 (citing Ex. 1004, 22; *Coal. for Affordable Drugs IV LLC v. Pharmacyclics, Inc.*, IPR2015-01076, Paper 33 ("*Coal. for Affordable Drugs*"), 7 (PTAB Oct. 19, 2015) (giving little to no weight to declarant's unsupported assertions that that a clinical trial document was publicly available on Clinicaltrials.gov on a certain date sufficient to establish it as a prior art printed publication).

Petitioner asserts that "Mr. Paarlberg identified precisely what information was included in the prior art version of NCT00965653" and "[i]t is that printed publication—*i.e.*, the disclosure of NCT00965653 as it existed more than one year before the claimed priority date—upon which Petitioners' invalidity challenges are based." Reply 6 (citing Pet. 29). Petitioner asserts that "[w]hile Ex. 1028 itself may not have been published until 2016, as explained by Mr. Paarlberg, it, along with the various history of change documents, evidences the information that was include in the prior art version of NCT00965653 that forms the basis of Petitioners' challenge." *Id.* at 7. Petitioner contends that, although it does not have access to the original version of NCT00965653, it has established that the original version was a printed publication, publicly available more than one year prior to the earliest claimed priority date. *Id.* at 7–8.

Petitioner responds to Patent Owner's assertion that it has not shown an interested artisan could have located NCT00965653 by November 2009 by reiterating Mr. Paarlberg's testimony that Congress mandated the ClinicalTrials.gov website to "contain searchable categories, allowing the public to search for trials by the disease or condition, name of the intervention, location, age group, study phase, sponsor, recruitment status, or identification number." *Id.* at 9 (citing Ex. 1004 ¶¶ 16, 32). Additionally, Petitioner notes that Dr. Zizic also testifies that "a POSA would routinely access ClinicalTrials.gov for up-to-date information on clinical trials." *Id.* (quoting Ex. 1002 ¶ 67).

Regarding Patent Owner's reliance on *Coal. for Affordable Drugs*, Petitioner asserts that, contrary to the record here, petitioner in that case did not submit any evidence of the website's publishing practices or offer an explanation or evidence of what the dates on the face of the document represent. *Id.* at 10.

Patent Owner argues that the "prior art version of NCT00965653" Petitioner now asserts as the basis for the grounds "is pieced together through several non-prior-art documents and other extrinsic evidence." Sur-reply 3. According to Patent Owner, that "patchwork of circumstantial evidence" was not necessary because Petitioner had access to Exhibit 1038, the purported "original version" of NCT00965653. *Id.* at 4.

Further, Patent Owner argues that Exhibit 1028 is not analogous to a version of the original document that would be available through the Internet Archive, i.e., the Wayback Machine, as alleged, because that archive provides snapshots captured before the priority date and no changes or

additions are made to the contents of the captured webpage itself. *Id.* (citing Reply 7–8).

As for public accessibility, Patent Owner reiterates its argument that Petitioner has not provided testimony from someone who had accessed the reference before the priority date, or established that the website was searchable such that a POSA could have found the reference with reasonable diligence. *Id.* at 5 (citing *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10 ("*Celltrion*"), 11–14 (PTAB Oct. 12, 2017)).

Having considered the arguments and the evidence, we determine that, for purposes of institution, and based on the totality of the evidence currently in the record, Petitioner has established a reasonable likelihood that NCT00965653 is a printed publication that was publicly accessible before the critical date of the challenged patent, and therefore, qualifies as prior art.

To begin, we recognize and accept Petitioner's clarification that it relies on the "First Posted" version of NCT00965653, that is referenced in Exhibit 1028, and is best represented in the History of Changes document submitted as Exhibit 1038. Both exhibits were submitted with the Petition (*see* Pet. v–xvii, List of Exhibits) and described by Mr. Paarlberg's testimony regarding the publication of the study on ClinicalTrials.gov (*see* Ex. 1004 ¶¶ 26–40).

In reaching our determination, we have considered Mr. Paarlberg's currently unrebutted testimony that "ClinicalTrials.gov displays the most recent version of the study record, and a history of changes is available on the ClinicalTrials.gov archive site." Ex. 1004 ¶ 23 (citing Ex. 1051, 2; Ex. 1077, 3). Indeed. Mr. Paarlberg's testimony appears be a direct quote

from the ClinicalTrials.gov "How to Edit Your Study Record" webpage. *See* Ex. 1051, 2.

It is our understanding, based on the current record, that the first posted version of the study, along with all versions of the study record posted prior to the most recent version, are no longer available on the website in the original form that they were posted. In other words, only the most recent version of the study record is available on the website in the form that it was posted. Thus, it is understandable that Petitioner—having no access to the original form of the first posted document on the ClinicalTrials.gov website—submits this most recent version, Exhibit 1028, and references it in the challenges.

Petitioner, however, does not rely on Exhibit 1028 alone. As Mr. Paarlberg explains, ClinicialTrials.gov includes its own "archive site" which makes available a history of changes that lists the first posted version of the study record, and each update to the study record, organized by its submission date and noting changes involved. Ex. 1004 ¶ 23 (citing Ex. 1051, 2). That archive site also allows a user to compare versions of the study records to view changes between those records. *See* Ex. 1037. For NCT00965653, the "History of Changes" page explains that a user may "[s]elect two study versions to compare." *Id.* at 1.

Additionally, a user may access details of the "First Posted" version of the study record by comparing that record with itself, which Mr. Paarlberg testifies that he has done. Ex. 1004 ¶ 36. Mr. Paarlberg refers to that comparison result as "NCT00965653 August 21, 2009 Study Record." *Id.* Petitioner has submitted that study record as Exhibit 1038.

Petitioner also has submitted Exhibit 1053, which Mr. Paarlberg testifies is a merged comparison of the August 21, 2009 version of the study record and the November 1, 2016 current version of the study record, that he testifies may be readily accomplished on ClinicalTrials.gov in the "History of Changes" webpage. Ex. 1004 ¶ 33. He explains that "[t]he merged comparison [in Exhibit 1053] identifies all of the changes that were made to the NCT00965653 record between the original and final postings." *Id.* (citing Ex. 1053).

On the current record, we find Mr. Paarlberg has demonstrated credibly that the changes to NCT00965653 made after August 21, 2009 did not alter the dosing regimen originally disclosed in the first posted version of the study record, i.e., 162 mg tocilizumab administered subcutaneously either weekly or every other week, in combination with 7.5–25 mg methotrexate administered weekly, or the same goal of the study to determine the efficacy and safety of the regimens in patients with rheumatoid arthritis who had inadequate responses to methotrexate. *Id.* ¶ 35 (citing Ex. 1053, 4).

Taken together, we find that the evidence relied on in the Petition, i.e., Exhibits 1028, 1038, 1053, and Mr. Paarlberg's currently unrebutted testimony, provides strong indicia that the first posted version of the NCT00965653 study record, as best represented on the current record by Exhibit 1038, is a printed publication that was published on the ClinicalTrials.gov website before the '264 patent's priority date.

Contrary to Patent Owner's contention, our recognition of Petitioner's reliance on Exhibit 1038 does not deviate from the grounds in the Petition.

See Prelim. Resp. 18–19 (citing *Sirona Dental*, 892 F.3d at 1356). Although citing to Exhibit 1028, Petitioner has identified, and thus, relied upon the disclosure of the first posted version of the NCT00965653 study record as the basis for the first two grounds. Pet. 30–42. Petitioner explicitly confirms that intention in the Reply. Reply 6–7. That we consider the Exhibit 1038 version of that study record as the best representation of the relied upon version of the NCT00965653 study record amounts only to a different, more accurate citation for the study version relied upon in the Petition and not some improper revision of the grounds for the challenges based on that study discussed in *Sirona Dental* and *SAS*.

Further, we do not find that the current record supports Patent Owner's contention that Petitioner has not shown sufficiently, for purposes of, institution that NCT00965653 was publicly accessible as of the critical date. *See* Prelim. Resp. 19–21. According to Patent Owner, Mr. Paarlberg's testimony merely amounts to speculation that NCT00965653 would have been readily accessible prior to the critical date of the '264 patent because he does not attest to having personal knowledge that the record was available on the Clinicaltrials.gov website. *See* Prelim. Resp. 20–21 (citing *Coal. for Affordable Drugs*, 7). We disagree.

The issue in *Coalition for Affordable Drugs* was not merely that the declarant did not attest to any personal knowledge of the public accessibility or dissemination of the clinical trial record. *Coal. for Affordable Drugs*, 7. Rather, the issue was that the declarant's testimony provided nothing more than a conclusory opinion that the clinical trial record constitutes prior art without disclosing any underlying facts or data supporting that testimony.

Id. Further, the Board determined in that case that the petitioner failed to explain or provide evidence regarding what the date on the clinical trial record represented and also failed to offer any evidence of the website's publishing practices. *Id.* Based on those collective deficiencies, the Board determined that the petitioner had not made a threshold showing that the clinical trial record was a prior art printed publication.

Petitioner's showing here does not suffer the deficiencies involved in *Coalition for Affordable Drugs*. Instead, Mr. Paarlberg has provided what is currently unrebutted testimony, that we determine, based on the current record, is credibly supported by disclosures on the ClinicalTrials.gov website. For example, Mr. Paarlberg explains how the records on ClinicalTrials.gov are managed and supports that testimony by referring to the webpage on that site that describes those practices. *See, e.g.*, Ex. 1004 ¶¶ 17, 20–23. He also refers to the relevant provisions of the FDA Amendments Act of 2007 to support his testimony that the website was designed to "contain searchable categories, allowing the public to search for trials by the disease or condition, name of the intervention, location, age group, study phase, sponsor, recruitment status, or identification number." *Id.* ¶ 16. Further, as discussed above, he demonstrates how a user may readily access current and archived records on the website, including records submitted by Petitioners as Exhibits 1028, 1038, and 1053. *See, e.g.*, *id.* at ¶¶ 24–36. Regarding the date relied upon in those exhibits to address the prior art status of the printed publication, Mr. Paarlberg provides the meaning of the "First Posted" date by quoting the definition for the term set forth in the ClinicalTrials.gov Glossary. *Id.* ¶ 26 (quoting Ex. 1030, 7).

Based on the foregoing testimony by Mr. Paarlberg, and the evidence that he cites, we determine on the current record that Petitioner has established sufficiently, for purposes of institution, that the "First Posted" NCT00965653 study record was sufficiently accessible to the public interested in the art and searchable on the ClinicalTrials.gov website such that a POSA could have found it with reasonable diligence. *See Voter Verified, Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2012).

In sum, based on this record and for purposes of this Decision, we determine that Petitioner has shown sufficiently that NCT00965653 is prior art.

b. Enablement of NCT00965653

Patent Owner argues that NCT00965653 does not enable the claimed SC dosing regimen. Prelim. Resp. 21–26. Specifically, Patent Owner asserts that NCT00965653 "neither discloses nor otherwise provides the POSA with any guidance whatsoever on how to make subcutaneous tocilizumab formulation necessary to practice the claimed dosing regimen." *Id.* at 22. Patent Owner's contentions are largely centered on its assertion that antibodies must be stabilized in a suitable formulation before administration to patients and arriving at such a formulation may be challenging because of the unpredictable solution behavior for various antibodies. *Id.* at 22–23. Patent Owner alleges also that experimentation and guidance to minimize antibody aggregation is required to avoid potentially serious health consequences of immunogenic antibody aggregates. *Id.* at 24–25.

Petitioner responds that prior art publications are presumed enabled, and at this stage, it is "entitled to rely upon that presumption to establish invalidity." Reply 4 (citing *Apple Inc. v. Corephotonics, Ltd.*, 861 Fed. App'x 443, 450 (Fed. Cir. 2021)). Petitioner asserts also that Patent Owner has not satisfied its burden to prove nonenablement by demonstrating that developing a tocilizumab formulation would have required undue experimentation. *Id.* (citing *Invitrogen Corp. v. Clonetech Labs., Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005)). Further, Petitioner contends that Patent Owner's allegations are directed to unclaimed subject matter, as the challenged claims do not require any particular formulation, or the formulation be shelf-stable and commercially viable. *Id.* at 4–5 (citing *In re Antor Media Corp.*, 689 F.3d 1282, 1290–91 (Fed. Cir. 2012) ("[A] prior art reference need not enable its full disclosure; it only needs to enable the portions of its disclosure alleged to anticipate the claimed invention.")).

Patent Owner appears to suggest NCT0096563 is not presumed enabled, because such a presumption is only recognized for prior art patents and for prior art publications during patent prosecution. Sur-reply 6. Patent Owner dismisses *Apple v. Corephotonics*, a case Petitioner relies on, as a non-precedential Federal Circuit decision. *Id.* Patent Owner asserts that, in any event, it has presented evidence and arguments sufficient to rebut that presumption. *Id.* at 6–7.

Based on our consideration of the arguments and evidence, we find Petitioner has the better position. As Petitioner correctly asserts, we recognize the same presumption of enablement for prior art printed publications in AIA trial proceedings as would be applied during patent

examination and in district court litigation. *See, e.g.*, *Antor*, 689 F.3d at 1287; *Apple Inc. v. Corephotonics*, 861 Fed. App'x at 450. As a result, the burden of production shifts to Patent Owner to present evidence demonstrating that NCT0096563 is not enabling.

Having reviewed Patent Owner's argument, we do not find that Patent Owner has sufficiently addressed the *Wands* factors or produced persuasive evidence to demonstrate that NCT0096563 is not enabling. *See* Prelim. Resp. 21–26; *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Thus, based on the current record, we do not find that Patent Owner has rebutted the presumption that NCT0096563 is enabling so as to shift the burden of production back to Petitioner at this stage in the proceeding.

c. Alleged Efficacy Requirement

Patent Owner argues that "A Proper Claim Construction Requires Efficacy that NCT00965653 Does Not Disclose." Prelim. Resp. 27. Patent Owner points out that the challenged claims require "treating rheumatoid arthritis (RA) in a patient." *Id.* According to Patent Owner, "[b]ecause NCT00965653 is merely a proposal to 'investigate' the recited dosing regimen . . . it does not and cannot disclose that the regimen in fact treats RA." *Id.*

As explained above, we determine the preamble of claims 1 and 10, that is, "treating rheumatoid arthritis . . . in a patient," does not require actually causing a therapeutic benefit in a particular patient. *See supra* Section II.B. Thus, we reject Patent Owner's arguments based on the alleged requirement of efficacy.

d. Summary

Based on the current record and for purposes of institution, we determine that Petitioner has shown sufficiently that NCT00965653, best represented by the "First Posted" version, as submitted in Exhibit 1038, discloses each limitation of independent claims 1 and 10.

Because there is a reasonable likelihood that Petitioner would prevail in its challenge of claims 1 and 10 as anticipated by NCT00965653, we institute an *inter partes* review as to all challenges raised in the Petition. *See* Patent Trial and Appeal Board Consolidated Trial Practice Guide ("CTPG") 64 (Nov. 2019)[9] ("The Board will not institute on fewer than all claims or all challenges in a petition.").

D. Alleged Obviousness over Maini 2006, Bonilla, and Wang

Petitioner asserts that claims 1–3 and 6–11 of the '264 patent would have been obvious over the combination of Maini 2006, Bonilla, and Wang. Pet. 49–62. 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. 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.*

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

at 3–4. 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.

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 argues that "[t]he only difference between claims 1–3 and 6–11 of the '264 patent and Maini 2006 is that the claims recite a subcutaneous fixed dose of 162 mg for tocilizumab, whereas Maini 2006 discloses an intravenous dose of tocilizumab of 4 mg/kg to 8 mg/kg." Pet. 50. 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 54 (citing Ex. 1022, 18). Petitioner relies on Bonilla for teaching that immunoglobulins are "preferably administered by subcutaneous injection of an equivalent amount every other week instead of every four weeks by IV because it leads to more stable serum concentration levels." *Id.* at 53 (citing Ex. 1021, 8, 15–18). 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 54

(citing Ex. 1002 ¶ 157). 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 50–58.

Patent Owner counters that Petitioner has not established a motivation to create an SC fixed dose of TCZ, and has not explained how an ordinarily skilled artisan would have arrived at the claimed 162 mg dose. Prelim. Resp. 57. For the reasons explained below, based on the current record, we find Petitioner has made a sufficient showing on these issues for institution purpose. We focus our analysis on independent claims 1 and 10.

a. Reason for SC Administration

Petitioner points out that before the priority date of the '264 patent, Patent Owner publicly disclosed the development of an SC form of TCZ for treating RA. Pet. 53; Ex. 1045, 12 (Subcutaneous dose form in development); Ex. 1046, 4 ("Started phase I / II study for subcutaneous injection formulation for rheumatoid arthritis in Japan and overseas"). In addition, Chugai also disclosed that, for TCZ, "[i]ts preferred form of administration in chronic autoimmune diseases is thought to be subcutaneous formulation." Ex. 1011,[10] 4. These disclosures, together with advantages of administering Ig subcutaneously every other week over intravenously every four weeks, as Bonilla teaches, Petitioner continues, would have motivated an ordinarily skilled artisan to administer TCZ via the

[10] WO2009/041621 A1, published April 2, 2009 (Ex. 1011).

SC route "every other week in an amount equivalent to the 4 mg/kg every four week dose disclosed by Maini 2006." Pet. 53–54.

Citing Haller,[11] Patent Owner argues that Petitioner "ignores 'several well-known *disadvantages* associated with SC injections." Prelim. Resp. 58 (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.*

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*

[11] Haller, Converting Intravenous Dosing to Subcutaneous Dosing with Recombinant Human Hyaluronidase, 31 Pharm. Tech. 118–32 (2007) ("Haller").

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. 58–59.

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. 60. 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 subcutaneously administered tocilizumab 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 61.

Again, Patent Owner's characterization of Wang is not incorrect, but incomplete. Yes, Wang suggests determining 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 proteins" including etanercept, adalimumab, certolizumab, and golimumab, "were approved in the prior art that were used in a subcutaneous fixed dose." Pet. 58; *see also id.* at 13–14 (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. 54 (citing Ex. 1002 ¶ 157). According to Petitioner, the equivalent amount of an antibody administered via the SC route "may be as low as the amount administered intravenously and as high as the amount necessary to account for the potential impact of reduced bioavailability of the subcutaneous mode of administration." *Id.* at 54–55 (citing Ex. 1021, 16–17). Petitioner asserts that the reported bioavailability of TCZ administered via the SC route was 72%, "which means that as much as 139% of the IV dose may be required if administered subcutaneously." *Id.* at 55 (citing Ex. 1019,[12] 18; Ex. 1002 ¶ 157).

Petitioner argues that, starting from the 4 mg/kg every four week IV dose, as Maini 2006 teaches, and assuming the body weight of a typical patient is 70 kg, 140 mg TCZ would be administered via the SC route every

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

other week.[13] *Id.* at 55–56 (citing Ex. 1002 ¶ 158). According to Petitioner, "[a]ccounting 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.* at 56 (citing Ex. 1002 ¶ 158). 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 ¶ 158).

Patent Owner points out that Bonilla discusses polyclonal immunoglobulins. Prelim. Resp. 52 (citing Ex. 1021, 4). According to Patent Owner, that is "an entirely different class of molecules," which "bear little resemblance to monoclonal antibodies" like TCZ. *Id.* Patent Owner has not produced evidence to show that the differences between a polyclonal antibody and a monoclonal antibody 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. *See* Ex. 1021, 15, 17. Thus, based on the current record, we accord little weight to this attorney argument.

Patent Owner also points out that Bonilla describes "the results of just a single study in which participants were subcutaneously administered a product called Vivaglobin® at between 1.02 and 1.92 times the IV dosage."

[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. 56 n.14.

Prelim. Resp. 52 (citing Ex. 1021, 17). According to Patent Owner, Bonilla "does not state, or even suggest, that the results it describes would be applicable to other immunoglobulins, let alone recombinant monoclonal antibodies" like TCZ. *Id.* 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. 54. Patent Owner points out that number was from "one study in *monkeys*." *Id.* (citing Ex. 1019, 18). Patent Owner contends that "[i]t was well-known that monoclonal antibodies exhibited marked 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 54–55.

We recognize, as Patent Owner emphasizes, that "interspecies variation makes it challenging to predict human bioavailability from animal data." *Id.* at 55 (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. 62. This is because, Patent Owner explains, Maini 2006 teaches TCZ administered via the SC route at both 4 mg/kg and 8 mg/kg is safe and effective. *Id.* Thus, following Petitioner's way of calculation, Patent Owner contends that the potential SC dosage ranges from 70 mg to 389 mg.[14] *Id.*

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. 55. Patent Owner points out that

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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. 62 n.23.

Wang reports results of an experiment assuming 75 kg and 90 kg median body weights.[15] *Id.* at 56 (citing Ex. 1022, 16–17). Patent Owner asserts that the potential SC dosing range would be between 150 and 208 mg for 75 kg weight and between 180 and 250 mg for 90 kg weight. *Id.* at 56 n.22. "In the latter case," Patent Owner argues, "the lowest recommended dosage would be *above* the 162 mg amount claimed." *Id.* We are not persuaded by Patent Owner's analysis.

As an initial matter, 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. Moreover, even with Patent Owner's calculation, the proper range, using Patent Owner's model, would be from 150 to 250 mg. *See* Prelim. Resp. 62 n.23 (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 because Maini 2006 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. 56–57 (citing Ex. 1002 ¶ 159).

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

In addition, Petitioner asserts that "a POSA would have understood that the efficacy of tocilizumab depended upon maintaining trough concentrations above a minimum threshold." *Id.* at 57 (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 57 (citing Ex. 1002 ¶ 160; Ex. 1021, 17).

Further, Petitioner contends that an ordinarily skilled artisan would have reasonably expected a fixed dose "to be successful over a wide range of patient weights." *Id.* (citing Ex. 1002 ¶ 161). Petitioner acknowledges that TCZ's "clearance was dependent upon body weight, and hence a fixed dose would result in heavier patients having a lower AUC than lighter patients." *Id.* at 57–58 (citing Ex. 1019, 23–24). According to Petitioner, however, AUC was known "to vary significantly" when TCZ was administered as a weight-based dose, with "as much as a two-fold increase in AUC as between light and heavy patients." *Id.* at 58 (citing Ex. 1019, 23–24). "This doubling of AUC," Petitioner continues, was found to "not affect efficacy or safety in a clinically relevant manner." *Id.* (citing Ex. 1019, 23–24). Thus, Petitioner concludes "[a] POSA would therefore have reasonably expected any AUC variation based on different clearance rates due to body weight to similarly

not affect the safety or efficacy of the 162 mg dose." *Id.* (citing Ex. 1002 ¶ 161).

Lastly, Petitioner points out that "several IgG antibodies and other proteins" including etanercept, adalimumab, certolizumab, and golimumab, "were approved in the prior art that were used in a subcutaneous fixed dose." *Id.*; *see also id.* at 13–14 (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 58 (citing Ex. 1002 ¶ 162).

Patent Owner argues "Petitioners' Invocation of 'Routine Optimization' Does Not Satisfy their Burden of Establishing a Reasonable Expectation of Success." Prelim. Resp. 61. Specifically, Patent Owner contends that Bonilla "never actually teaches" the IV to SC dosage calculation. *Id.* at 61–62. 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. 62. 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.D.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 claims 1 and 10 over the combination of Maini 2006, Bonilla, and Wang. For this independent reason, we institute an *inter partes* review as to all challenges raised in the Petition.

E. Other Challenges

Petitioner argues that if the preamble of independent claims 1 and 10 ("treating rheumatoid arthritis") is construed to require efficacy, Petitioner asserts that claims 1–3 and 6–11 would have been obvious over NCT00965653. Pet. 37–42. Because we determine the claims do not require efficacy for a particular patient, we do not reach this challenge

Petitioner also asserts that Ohta 2010 anticipates claims 1, 2, 9, and 10, and that the combination of Ohta 2010 and Maini 2006 renders claims 1–3 and 6–11 obvious. *Id.* at 43–49. Because we determine Petitioner has met its burden in two other challenges (*see supra* Sections II.C, II.D), we

do not address these challenges either. We, however, note that Patent Owner's antedation evidence tends to support its argument that Ohta 2010 is not prior art. *See* Prelim. Resp. 40–48.

Because we institute an *inter partes* review as to all challenges raised in the Petition, the parties are encouraged to further address the relevant issues of all challenges, including these other grounds, to fully develop the record during trial.

F. Analysis of Discretion under 35 U.S.C. § 314(a)

Institution of *inter partes* review is discretionary. *See* 35 U.S.C. § 314(a). The statutory language provides the Director with discretion to deny institution of a petition. *See Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 273 (2016) ("[T]he agency's decision to deny a petition is a matter committed to the Patent Office's discretion."); CTPG, 55. The Director has delegated his authority under § 314(a) to the Board. *See* 37 C.F.R. § 42.4(a) ("The Board institutes the trial on behalf of the Director.").

AIA was "designed to establish a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs." H.R. Rep. No. 112−98, pt. 1, at 40 (2011), 2011 U.S.C.C.A.N. 67, 69 (reviews were meant to be "quick and cost effective alternatives to litigation"); *see also* S. Rep. No. 110−259, at 20 (2008); CTPG 56. The Board recognized these goals, but also "recognize[d] the potential for abuse of the review process by repeated attacks on patents." *General Plastic Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 16−17 (PTAB Sept. 6, 2017) (precedential).

In *NHK Spring Co. v. Intri-Plex Technologies, Inc.*, the Board determined that the advanced state of a parallel proceeding is an additional factor weighing in favor of denying institution under 35 U.S.C. § 314(a). IPR2018-00752, Paper 8, 19–20 (PTAB Sept. 12, 2018) (precedential). In *Apple Inc. v. Fintiv, Inc.*, the Board articulated a list of factors that we consider in determining whether to exercise discretion to deny institution based on an advanced stage of a parallel proceeding:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
>
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
>
> 3. investment in the parallel proceeding by the court and the parties;
>
> 4. overlap between issues raised in the petition and in the parallel proceeding;
>
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

IPR2020-00019, Paper 11, 5–6 (PTAB Mar. 20, 2020) (precedential).

The *Fintiv* factors "relate to whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding." *Id.* In evaluating these factors, we take "a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* (citing CTPG 58).

Patent Owner asserts that we should decline to institute under *NHK Spring/Fintiv*. Prelim. Resp. 63–67. But as Patent Owner acknowledges, there is no pending litigation between the parties. *Id.* at 64. Nevertheless,

Patent Owner urges that we could deny institution under *Fintiv* because of "the near-certainty of parallel, duplicative proceedings." *Id.* In particular, Patent Owner asserts that "[t]he absence of any currently pending litigation between the parties does not mean they do not have a dispute." *Id.* According to Patent Owner, the statutory scheme governing biosimilars like Petitioner's copy of Patent Owner's tocilizumab product, Actemra, "all but guarantees" patent litigation between the parties, and Petitioner's refusal "to hold off serving its notice of intent to market until this proceeding concludes . . . virtually guarantee[s] that the trial court and the Board will be addressing the '264 patent in parallel. *Id.* at 64–65.

As noted above, the Board's discretionary denial analysis, set forth in *NHK Spring/Fintiv* pertains to matters before us that involve a parallel proceeding—typically an ongoing lawsuit in court. Here, Patent Owner has identified, at best, a hypothetical future district court litigation. Because Patent Owner has not identified an existing parallel proceeding, we decline Patent Owner's invitation for us to consider discretionary denial of institution under *Fintiv*.

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.

PETITIONER:

Elizabeth J. Holland
Kevin J. DeJong
Daryl L. Wiesen
Daniel P. Margolis
Emily L. Rapalino
GOODWIN PROCTER LLP
eholland@goodwinprocter.com
kdejong@goodwinlaw.com
dwiesen@goodwinlaw.com
dmargolis@goodwinlaw.com
erapalino@goodwinlaw.com

PATENT OWNER:

Thomas S. Fletcher
David I. Berl
Paul B. Gaffney
Ana C. Reyes
Charles L. McCloud
Angela X. Gao
WILLIAMS & CONNOLLY LLP
tfletcher@wc.com
dberl@wc.com
pgaffney@wc.com
areyes@wc.com
lmccloud@wc.com
agao@wc.com