UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and FRESENIUS KABI SWISSBIOSIM GmbH
Petitioners
v.

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

IPR2021-01288

Patent No. 8,580,264

Title: SUBCUTANEOUSLY ADMINISTERED ANTI-IL-6 RECEPTOR ANTIBODY

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,580,264

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I. INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH, pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, *et seq.*,[2] petition for *Inter Partes* Review ("IPR") of claims 1-3 and 6-11 of U.S. Patent No. 8,580,264 ("the '264 patent," Ex. 1001).[3] Petitioners' request is supported by the Expert Declarations of Thomas M. Zizic, M.D. (Ex. 1002), Howard L. Levine, Ph.D. (Ex. 1003), and Robert A. Paarlberg (Ex. 1004), and the other exhibits submitted herewith.

The claims of the '264 patent are generally directed to methods of treating rheumatoid arthritis (RA) by subcutaneous (SC) administration of a 162 mg fixed dose of tocilizumab every week or every two weeks. More than one year prior to the earliest alleged priority date, a clinical study protocol, entitled "A Study of

[2] Unless otherwise stated, all statutory and regulatory citations herein are to 35 U.S.C. or 37 C.F.R. The page numbers for exhibits cited herein are the stamped page numbers for each exhibit, not the original page numbers.

[3] On August 17, 2021, the PTO issued a Certificate of Correction for the '264 patent, adding three additional claims (claims 4-5 and 12). The claims at issue in this Petition are claims 1-3 and 6-11, which correspond to the claims of the originally issued patent.

Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis," was published on ClinicalTrials.gov, a website maintained by the U.S. National Library of Medicine to provide the public access to information on clinical trials. This protocol disclosed a method of treating RA that anticipates claims 1-3 and 6-11 of the '264 patent.

Subcutaneous administration of 162 mg of tocilizumab in accordance with the claimed methods would also have been obvious in view of the prior art. Before the November 8, 2010 filing date of the '264 patent, overproduction of the cytokine IL-6 was known to be responsible for the pathogenesis of RA. It was also well known that tocilizumab inhibits the binding of IL-6 to its receptors, and thus reduces its pro-inflammatory activity. The results of several Phase III clinical trials had published by 2009 that demonstrated that intravenous (IV) administration of tocilizumab was safe and effective for treating RA within a wide therapeutic dose range of 4 to 8 mg/kg every four weeks. Tocilizumab also had been approved in several countries for the treatment of RA by IV administration, including the United States and Japan, and within Europe.

Subcutaneous administration of drugs dates back to at least the 1850s. By November 2010, it was also known that immunoglobulins—like tocilizumab—are preferably administered by subcutaneous injection of an equivalent amount every week or every other week instead of every four weeks by IV. A person of skill in

the art would have understood that subcutaneous injection allowed patients to self-administer the drug in the setting they chose, rather than mandating a clinic or hospital setting, leading to reduced costs for patients and providers (e.g., travel- and office visit-related costs) compared with the costs of intravenous medications. Fixed dosing can also avoid or reduce errors that may occur in calculating and preparing individualized weight-based doses for patients. Indeed, Patent Owner Chugai itself had publicly stated in the prior art that subcutaneous injection is the "preferred" route of administration for tocilizumab. Ex. 1011 (WO '621) at 4. A person of skill in the art would have understood that a subcutaneous fixed dose of 162 mg for tocilizumab administered every week or every other week is equivalent to the known effective intravenous doses of 4 mg/kg or 8 mg/kg, and would have therefore been motivated to administer tocilizumab in accordance with the claimed methods with a reasonable expectation of success.

The Board should institute review because there is at least a reasonable likelihood that Petitioners will prevail with respect to at least one challenged claim. § 314(a). Moreover, there are no persuasive grounds for denying institution under § 314(a) or § 325(d). This is Petitioners' first petition challenging any claim of the '264 patent, and the Petition raises arguments that have not previously been presented to the Office.

II. GROUNDS FOR STANDING

Pursuant to § 42.104(a), Petitioners certify that the '264 patent is available for IPR and that Petitioners are not barred or estopped from requesting IPR on the grounds raised in this petition. Moreover, neither Petitioners nor their privies or the real parties in interest have filed or been served with any complaint alleging infringement or invalidity of the '264 patent, and therefore are not subject to any bar under § 315(a) or (b).

III. MANDATORY NOTICES

A. Real Parties-In-Interest (§ 42.8(b)(1))

The real parties-in-interest are Fresenius Kabi USA, LLC; Fresenius Kabi SwissBioSim GmbH; Fresenius Kabi AG; Fresenius Kabi Pharmaceuticals Holding LLC; Fresenius Kabi Deutschland GmbH; and Fresenius SE & Co. KGaA.

B. Related Matters (§ 42.8(b)(2))

The '264 patent is not currently the subject of any litigation or post-grant proceedings. Petitioners are concurrently filing a petition seeking *inter partes* review of U.S. Patent No. 10,874,677, which claims priority to the '264 patent.

C. Identification of Counsel (§ 42.8(b)(3))

Elizabeth J. Holland (lead counsel) Reg. No. 47,657	Daryl Wiesen (backup counsel) to seek *pro hac vice* admission

Daniel P. Margolis (backup counsel) to seek *pro hac vice* admission Goodwin Procter LLP 620 Eighth Avenue, New York, NY 10018, T: (212) 459 7236 Fax: (212) 658 9563	Emily Rapalino (backup counsel) to seek *pro hac vice* admission Kevin J. DeJong (backup counsel) Reg. No. 64,762 Goodwin Procter LLP 100 Northern Ave. Boston, MA 02210 T: (617) 570 1156 Fax: (617) 649 1430

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioners consent to electronic mail service at the following addresses: eholland@goodwinlaw.com; dwiesen@goodwinlaw.com; erapalino@goodwinlaw.com; dmargolis@goodwinlaw.com; and kdejong@goodwinlaw.com.

D. Service Information (§ 42.8(b)(4))

This Petition is being served by Federal Express Next Business Day Delivery to the correspondence address of record for the '264 patent: Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

E. Power of Attorney (§ 42.10(b))

The Petitioners' Power of Attorney forms will be filed concurrently herewith in accordance with 37 C.F.R. § 42.10(b).

IV. FEE PAYMENT (§ 42.15(a))

The required fee set forth in § 42.15(a) is paid pursuant to § 42.103, and the Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

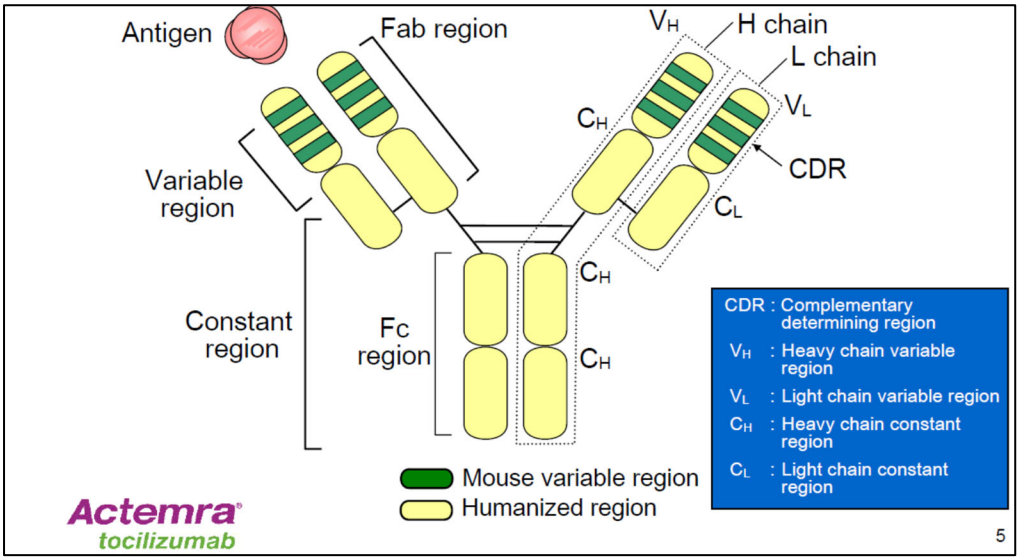
V. TECHNICAL BACKGROUND

A. Tocilizumab Was Well Known as an Effective Treatment of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic disease characterized by pain, swelling and progressive destruction of the smalls joints of the hands and feet. Ex. 1002 ¶36. By the mid-1990s, methotrexate ("MTX") had become the most commonly used disease-modifying antirheumatic drug ("DMARD") for treating RA, yet many patients did not adequately respond to MTX alone. *Id.*; Ex. 1059 (Jones) at 1; Ex. 1062 (Weinblatt) at 4. In such patients, other DMARDs were often added to the methotrexate regimen in order to improve disease control. Ex. 1062 (Weinblatt) at 4; Ex. 1063 (Matteson[4]) at 4. New drugs were accordingly sought that could be used to treat RA patients who had inadequately responded to MTX. Ex. 1002 ¶36.

[4] Eric L. Matteson, "Concise Review for Clinicians, Current Treatment Strategies for Rheumatoid Arthritis," *Mayo Clinic Proceedings* 75:69–74 (2000) ("Matteson").

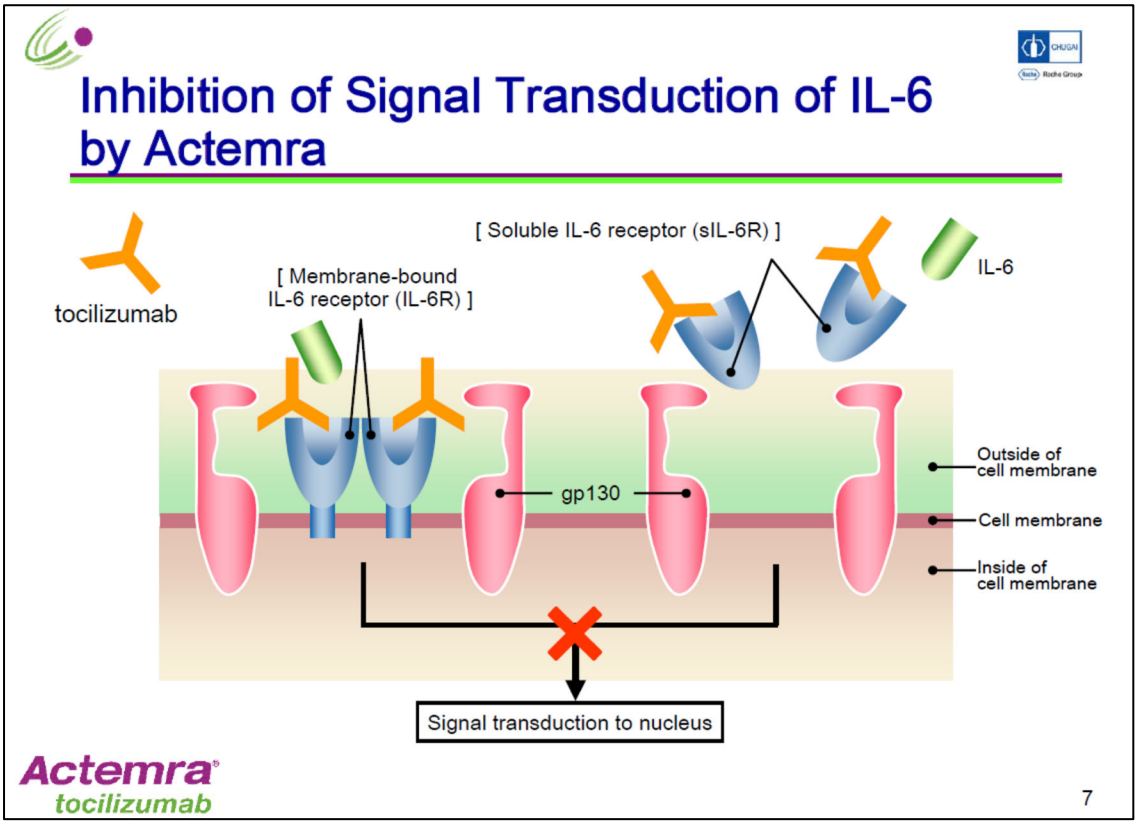
Tocilizumab, also known as MRA, is a humanized anti-IL-6 receptor monoclonal antibody of the immunoglobulin IgG1 subclass. Ex. 1025 (Maini 2006) at 3; Ex. 1003 ¶19; Ex. 1002 ¶ 37. Like all antibodies, it has two heavy chains and two light chains forming two antigen-binding sites. Ex. 1003 ¶19; Ex. 1002 ¶37. As shown below, the light chains and heavy chains both include a constant region (shown as C_H and C_L), and variable regions (shown as V_H and V_L).



Ex. 1013 (Product Overview of Actemra) at 5.

Overproduction of IL-6, a cytokine, and its interaction with its receptor, IL-6R, which is expressed on effector cells, causes and prolongs inflammation associated with RA. Ex. 1002 ¶38. Although originally intended as a treatment for multiple myeloma, by 1995 Chugai had begun studying tocilizumab for the treatment of rheumatoid arthritis based on its ability to block the action of IL-6, which was known to be involved in the pathogenesis of RA. *Id.*; Ex. 1064

(Nishimoto 2002) at 3-4. Tocilizumab inhibits the binding of IL-6 to both soluble and membrane-bound receptors. Ex. 1013 (Product Overview of Actemra) at 8. Upon binding IL-6, these receptors activate signals to the nucleus that result in an inflammatory response. *See id.* at 7. As shown in the figure below, tocilizumab-bound IL-6 receptors are unable to transduce IL-6's signal to the nucleus, thus reducing the cytokine's pro-inflammatory activity.



Id. at 8; Ex. 1002 ¶38.

Early studies established that tocilizumab was safe and effective for treating RA patients who had inadequately responded to traditional DMARDs, including methotrexate. Ex. 1002 ¶39; Ex. 1064 (Nishimoto 2002) at 4. Subsequent studies

established that tocilizumab was safe and effective for treating RA when administered intravenously at a dose of 4 mg/kg or 8 mg/kg every four weeks, either with or without methotrexate. Ex. 1065 (Nishimoto Abstract) at 2; Ex. 1025 (Maini 2006) at 3, 8-9; Ex. 1002 ¶38.

Additional clinical trials further confirmed that tocilizumab was a safe and effective treatment for rheumatoid arthritis. Ex. 1002 ¶39. By 2009, tocilizumab was well known as an effective treatment for RA, often administered in combination with other DMARDs, like methotrexate. *Id.* ¶¶40-42. The results of the Phase III RADIATE clinical study, published in 2008, showed that both 8 mg/kg and 4 mg/kg tocilizumab every four weeks, in combination with methotrexate, was superior to placebo in treating RA in patients who had inadequately responded to TNF antagonists. *Id.* ¶40; Ex. 1014 (Emery) at 5-6. The investigators concluded that "[i]n patients with moderate to severe active RA responding inadequately or who are intolerant to TNF antagonists, changing to tocilizumab plus methotrexate is effective, and the safety profile is manageable." Ex. 1014 (Emery) at 9.

In March 2008, results of the Phase III OPTION clinical study were published indicating that administration of tocilizumab at 4 mg/kg or 8 mg/kg every four weeks, in combination with MTX, "significantly and rapidly improves the signs and symptoms of rheumatoid arthritis" in patients who had inadequately

responded to MTX alone. Ex. 1015 (Smolen) at 9. The TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy) clinical study "examined the efficacy and safety of tocilizumab in combination with a range of DMARDs in patients with moderate-to-severe RA in whom the response to these agents was inadequate." Ex. 1026 (Genovese) at 3. The investigators concluded that in "patients with moderate-to-severe RA, treatment with tocilizumab in combination with traditional DMARDs significantly and rapidly reduced disease activity over 24 weeks as compared with treatment with DMARDs plus placebo." *Id.* at 12. Methotrexate was one of several DMARDs in that study that were shown to be effective in combination with tocilizumab. *Id.* at 5. And, in March 2009, results of the Phase III AMBITION trial published, indicating that tocilizumab administered intravenously at a dose of 4 mg/kg or 8 mg/kg every four weeks was superior to methotrexate for treating RA patients who had not previously failed MTX treatment. Ex. 1059 (Jones) at 3, 8.

Tocilizumab was approved for the treatment of rheumatoid arthritis by the Pharmaceuticals and Medicals Devices Agency of Japan (PMDA) in 2008, supplied in 80 mg, 200 mg, and 400 mg vials and in which the "usual dosage" was 8 mg/kg given as an intravenous infusion every 4 weeks. Ex. 1076 (March 6, 2008 Report) at 4; Ex. 1018 (PMDA 2008 Report) at 124. In January 2009, the European Medicine Agency (EMA), also approved intravenous tocilizumab,

supplied in 80 mg, 200 mg, and 400 mg vials, which had "been selected to provide flexible combinations over the likely body weight range of patients." Ex. 1019 (EMA Assessment Report) at 11; *id.* at 27 (based on pivotal trials using 8 mg/kg every four weeks). And on January 8, 2010, the U.S. Food and Drug Administration (FDA) approved intravenous tocilizumab for the treatment of rheumatoid arthritis. Ex. 1020 (BLA Approval Letter) at 1; Ex. 1069 (2010 FDA Actemra Label) at 2, 22.

B. Subcutaneous Administration of Antibodies Was Known to Be a Preferable Alternative to Intravenous Administration

Subcutaneous administration of therapeutics dates back to at least the 1850s. Ex. 1088 (Macht) at 4. Although tocilizumab was originally administered intravenously, it was well known in the prior art that subcutaneous administration provides significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered therapy. Ex. 1002 ¶44; Ex. 1016 (Berger) at 12-13; Ex. 1017 (Ochs) at 2. IV therapy also was "not ideal for all patients and may be difficult for those with poor venous access or those experiencing recurrent systemic reactions." Ex. 1017 (Ochs) at 1. According to the physician investigators involved in clinical studies of Humira®, subcutaneous administration offered "several advantages that promote adherence to therapy":

> These agents are portable, allowing patients to self-administer the drug in the setting they choose, rather than mandating a clinic or hospital setting. Similarly, these agents can be administered at the patient's convenience rather than requiring an appointment for treatment. Finally, self-administered medications may reduce costs for patients and providers (e.g., travel-related costs and office visit-related costs) compared with the costs of intravenous medications.

Ex. 1070 (Kivitz) at 2.

It was also known in the prior art that administering an equivalent amount of an immunoglobulin, like tocilizumab, as a subcutaneous dose every week or every other week, rather than an IV dose every four weeks, was preferable because it reduces serum concentration fluctuation around the same mean. Ex. 1002 ¶45; Ex. 1021 (Bonilla) at 15. Less fluctuation around the mean (i.e., lower peaks and higher troughs) would be expected to potentially decrease adverse events while retaining efficacy. Ex. 1002 ¶45, 58.

Moreover, a fixed subcutaneous dose (i.e., not based on the weight of the patient) was considered preferable for monoclonal antibodies in the absence of a specific reason to favor body-weight based dosing, as the former provides "better compliance, less risk of medical errors, and cost-effectiveness." Ex. 1022 (Wang) at 7, 18; Ex. 1002 ¶45. A POSA would also have known that fixed dosing can also avoid or reduce errors that may occur in calculating and preparing individualized weight-based doses for patients. Ex. 1002 ¶45. Indeed, by 2009, there were at

least four other biologics approved by FDA for subcutaneous administration with a fixed dose:

- Enbrel® (etanercept), approved by FDA in 1998 for treatment of RA with a subcutaneous fixed dose of 25 mg twice weekly. Ex. 1081 (1999 J. Clinical Pharm) at 3; Ex. 1082 (2000 PDR Excerpt – Enbrel) at 4-5. Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of human tumor necrosis factor linked to the Fc (fragment, crystallizable) portion of human IgG1. Ex. 1082 (2000 PDR Excerpt – Enbrel) at 3.
- Humira® (adalimumab), approved by the FDA in 2002 for the treatment of RA at a subcutaneous fixed dose of 40 mg every other week. Ex. 1023 (2002 FDA label for Humira®) at 14, 16; Ex. 1078 (Abbott 8K) at 5; Ex. 1079 (FDA Talk Paper) at 5. Adalimumab is a recombinant human IgG1 monoclonal antibody. Ex. 1023 (2002 FDA Label for Humira®) at 1.
- Cimzia® (certolizumab pegol), approved by the FDA in 2008 for treatment of Crohn's disease at a subcutaneous fixed dose of 400 mg weekly. Ex. 1024 (2009 PDR – Cimzia) at 4-5. Certolizumab pegol is a recombinant, humanized antibody fragment conjugated to polyethylene glycol. *Id.* at 6.
- Simponi® (golimumab), approved by the FDA in April 2009 for the treatment of RA, among other indications, at a subcutaneous fixed dose of 50 mg monthly. Ex. 1036 (TNF Blocker Wins Approval) at 1; Ex. 1083

(Golimumab) at 1. Golimumab is a human anti-TNFα IgG1 monoclonal antibody. Ex. 1083 (Golimumab) at 1; Ex. 1084 (2009 Simponi FDA Label) at 1.

For tocilizumab specifically, the subcutaneous route was identified as the "preferred form of administration" well before the earliest claimed priority date of the '264 patent. Ex. 1011 (WO '621) at 4. And not only was there no recognized need to employ weight-based dosing, the available pharmacokinetic data suggested just the opposite—that tocilizumab could be administered as a fixed dose. Ex. 1002 ¶¶132-35.

VI. The '264 PATENT

The '264 patent, entitled "Subcutaneously Administered Anti-IL-6 Receptor Antibody," issued on November 12, 2013, and claims priority to a provisional application filed on November 8, 2010.

A. Challenged Claims

Petitioners challenge claims 1-3 and 6-11 of the '264 patent. Independent claims 1 and 10 each recite a "method of treating rheumatoid arthritis" by administering a fixed dose of 162 mg of tocilizumab every week or every two weeks:

Claim 1	Claim 10
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][5] 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.	10. A method of treating rheumatoid arthritis in a patient comprising subcutaneously 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.

Claims 2 and 9, both of which depend from claim 1, specify the schedule for administering a fixed dose "every week" (claim 2) and "every two weeks" (claim 9). Claim 3, which depends from claim 1, further recites "wherein the RA patient is a DMARD-inadequate responder."

[5] The Certificate of Correction that issued on August 17, 2021 omits the word "dose" from claim 1. The original claim 1, however, included the word "dose." Ex. 1001 at col. 63, claim 1.

Claims 6-8 (which depend from claim 1) and claim 11 (which depends from claim 10) further recite administering an additional drug. Specifically, claim 6 further recites "administering to the RA patient one or more additional drug [sic] which treats the RA." Claim 7, which depends from claim 6, further specifies that 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." Claim 8, which depends from claim 7, further recites "wherein the additional drug is selected from the group consisting of non-biological DMARDS, NSAIDs, and corticosteroids." Likewise, claim 11, which depends from claim 10, further recites "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."

B. Prosecution History

The '264 patent issued from U.S. Patent Application No. 13/290,366, filed on November 7, 2011, and claims priority to U.S. Provisional Application No. 61/542,615, filed on October 3, 2011 and U.S. Provisional Application No. 61/411,015, filed on November 8, 2010.

On April 3, 2013, the Examiner rejected the then-pending claims as anticipated by Ohta 2010, an abstract published in *Arthritis & Rheumatism* in October 2010[6] with results of Chugai's clinical study for subcutaneous administration of tocilizumab. The Examiner stated that Ohta 2010 "discloses a method of treating rheumatoid arthritis (RA) patients, by subcutaneously administering a recombinant humanized, IgG1 monoclonal antibody to IL-6 receptor, tocilizumab (TCZ), wherein the antibody comprises the light and heavy chain sequences set forth in SEQ ID NO:1, and 2, respectively, and these amino acid sequence characteristics would be inherent in the antibody of the prior art." Ex. 1005 ('264 Patent File History) at 1004. The Examiner also acknowledged that Ohta 2010 disclosed administering one group of patients with "162 mg of TCZ Q2W" (every two weeks) and another group of patients with "162 mg TCZ QW" (every week), and that both dosage schedules of TCZ (tocilizumab) were "well tolerated" and provided a "good clinical response." *Id.* Accordingly, the Examiner concluded that Ohta 2010 anticipated the then-pending claims 1, 2, and 12. *Id.*

[6] During prosecution of U.S. Patent No. 10,874,677, the inventors submitted a declaration that stated that Ohta 2010 "was first published September 28, 2010 on the ACR website." Ex. 1007 ('677 Patent File History) at 325.

In the same Office Action, the Examiner rejected claims directed to administering tocilizumab with methotrexate. The Examiner concluded that "it would have been *prima facie* obvious to one having ordinary skill in the art to modify the method of [Ohta 2010] such that it includes administering methotrexate in combination with TCZ, to obtain the known functions and advantages of both, TCZ and methotrexate, and to increase the clinical efficacy of the TCZ, because the combination would be synergistic." *Id.* at 1006. As explained by the Examiner:

> One of skill in the art would have both the motivation and ability to administer the combination of methotrexate and TCZ, because combination therapies comprising antibodies and other agents are well-known in the art for treatment of rheumatoid arthritis. To subcutaneously administer TCZ with other compounds, such as methotrexate, routinely used in the treatment of rheumatoid arthritis in patients, at the time that the instant invention was made, would have been *prima facie* obvious to an artisan in light of the references.

Id.

The applicant did not dispute the Examiner's reasoning or conclusions, and instead submitted a Declaration Under 37 C.F.R. § 131 to antedate Ohta 2010. *Id.* at 1021, 1025-44. According to the applicant, the supporting declaration established "that the inventors had conceived of and reduced to practice the inventions of claims 1, 2, and 12 prior to September

2010." *Id.* at 1022. The declaration included a copy of a "Synopsis" of a Clinical Study report, summarizing the results of a study entitled, "MRA227." Consistent with the Examiner's conclusion that amino acid sequence characteristics would be inherent in the tocilizumab disclosed in Ohta 2010, the inventors stated that "MRA227 was a phase I/II clinical study of the anti-IL-6 receptor antibody 'tocilizumab' also called 'MRA' which we understand comprises the light chain and heavy chain amino acid sequences as in Figs. 7A–B of the above application." *Id.* at 1025, 1027. In response, the Examiner allowed the claims, concluding that the declaration established that the inventors had conceived of and reduced to practice the claims prior to September 2010.[7] *Id.* at 1058.

The '264 patent issued on November 12, 2013 with nine claims. On August 17, 2021, the PTO issued a Certificate of Correction for the '264 patent, adding three additional claims (claims 4-5 and 12), which are not at issue in this Petition.

[7] As explained in § IX.C, *infra*, the Examiner erred in finding that the declaration established prior inventorship.

VII. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art ("POSA") to whom the '264 patent is directed 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. Ex. 1002 ¶33. A POSA would have easily understood the prior art references referred to herein and would have had the capacity to draw inferences from them.

VIII. CLAIM CONSTRUCTION

In an IPR, the terms of challenged claims are construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," just as they are in district court. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). For the purpose of this proceeding, any term not expressly discussed should be given its ordinary and customary meaning to a

POSA as of the filing date of the '264 patent, which Petitioners assume for purposes of this IPR only to be November 8, 2010.[8]

A. "[a] method of treating rheumatoid arthritis in a patient" (claims 1 and 10)

Independent claims 1 and 10 both recite a "method of treating rheumatoid arthritis in a patient." The preamble is not limiting. The remainder of the claims set forth all the necessary steps of the claimed methods, and the preamble merely states an intended purpose. *See* Ex. 1002 ¶96; *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). In *Bristol-Myers Squibb*, the Federal Circuit held that the preamble reciting "a method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" was a statement of purpose and the intended result, and therefore was not limiting because it "does not result in a manipulative difference in the steps of the claim." *Id.* at 1374-76; *see also In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018) (holding that the preamble

[8] Petitioners adopt these claim construction positions for purposes of this IPR only and reserve the right to change or modify their positions in future litigation, for example in response to expert opinions, statements by the patent owners, or court rulings. Petitioners do not waive any argument concerning indefiniteness or invalidity under 35 U.S.C. § 112.

was not limiting where it "does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims"). Indeed, the preamble at issue in *Bristol-Myers Squibb* was not limiting even though it provided antecedent basis for the "patient." *Bristol-Myers Squibb*, 246 F.3d at 1374-76. Likewise, the preamble here is not limiting because it merely recites a statement of intended purpose and does not change the express dosing amount or result in any difference in the steps of the claims.

Even if the preamble was limiting, the intrinsic record makes clear that the term should not be construed to require that the treatment be ***effective*** for a ***particular*** patient. As Dr. Zizic explains, 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. Ex. 1002 ¶97; *see also* Ex. 1080 (Webster's) at 3-4 (defining "treat" as to "give a medical treatment to"; "to seek cure or relief of (as a disease)"); Ex. 1027 (AHM Dictionary) at 3 (defining "treat" as "to give medical aid to someone").

This plain meaning of the term is consistent with its usage in the specification of the '264 patent, which refers to administering a drug regardless of whether it was effective in a particular patient. Ex. 1002 ¶98. For example, the

specification 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***." Ex. 1001 ('264 patent) at 14:46-50 (emphasis added); *see also id.* at 14:51-57 (similarly defining "TNF inhibitor inadequate responder" as one who "has experienced an inadequate response to previous or current treatment with one or more TNF inhibitors because of toxicity or inadequate efficacy"), 14:58-63 (similarly defining "methotrexate inadequate responder" as one who "has experienced an inadequate response to previous or current treatment with methotrexate because of toxicity or inadequate efficacy"). In short, "treatment" occurs regardless of whether it is effective.

The examples in the specification also make clear that a "treatment" may or may not result in effective therapy for a particular patient. Ex. 1002 ¶99. Example 2 describes results of a Phase 3 clinical trial in which some patients had "failed previous anti-TNF-α treatment," confirming that "treatment" does not require efficacy. Ex. 1001 ('264 patent) at 32:10-27. Example 6 describes a clinical trial in which 85% of the "treated" patients met the efficacy endpoint, implying that at least some patients may be "treated" without an efficacious response. *Id.* at 47:35-52.

Finally, even if the claims are construed to require efficacy, the claims are nonetheless invalid (*see infra* §§ IX.B–E, below).

B. "fixed dose" (claims 1 and 10)

The term "fixed dose" is defined in the specification as "a dosage of a drug, such as an anti-IL-6R antibody which is administered without regard to the patient's weight or body surface area (BSE), i.e., it is not administered as either a mg/kg or mg/m^2 dose." Ex. 1001 ('264 patent) at 14:64-67.

C. "DMARD inadequate responder" (claim 3)

A "DMARD inadequate responder" (claim 3) is defined in the specification 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." Ex. 1001 ('264 patent) at 14:46-50. A "DMARD" is a "disease-modifying antirheumatic drug." Methotrexate is an example of a DMARD. *Id.* at 14:22-32.

D. "treats the rheumatoid arthritis [RA]" (claims 6 and 11)

As explained above, the term "treating" does not require efficacy in a particular patient, but instead has the plain meaning, consistent with the specification, as "attempting to cause a therapeutic improvement in rheumatoid arthritis in a patient," and does not require that the administration result in an effective treatment for a particular patient. For the same reasons, the term "treats the rheumatoid arthritis," as used in claims 6 and 11, should be construed as

"attempt to cause a therapeutic improvement in rheumatoid arthritis in a patient," and does not require that the administration result in an effective treatment for a particular patient. Ex. 1002 ¶102.

IX. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claims 1-3 and 6-11 of the '264 patent under §§ 102 and 103 for the reasons explained in this petition, which may be summarized as follows:

Ground No	Claims and Basis
1	Claims 1-3 and 6-11 are anticipated by NCT00965653
2	Claims 1-3 and 6-11 are obvious over NCT00965653
3	Claims 1, 2, 9, and 10 are anticipated by Ohta 2010
4	Claims 1-3 and 6-11 are obvious Ohta 2010 and Maini 2006
5	Claims 1-3 and 6-11 are obvious over Maini 2006, Bonilla, and Wang

A. Ground 1: Claims 1-3 and 6-11 Are Anticipated By NCT00965653

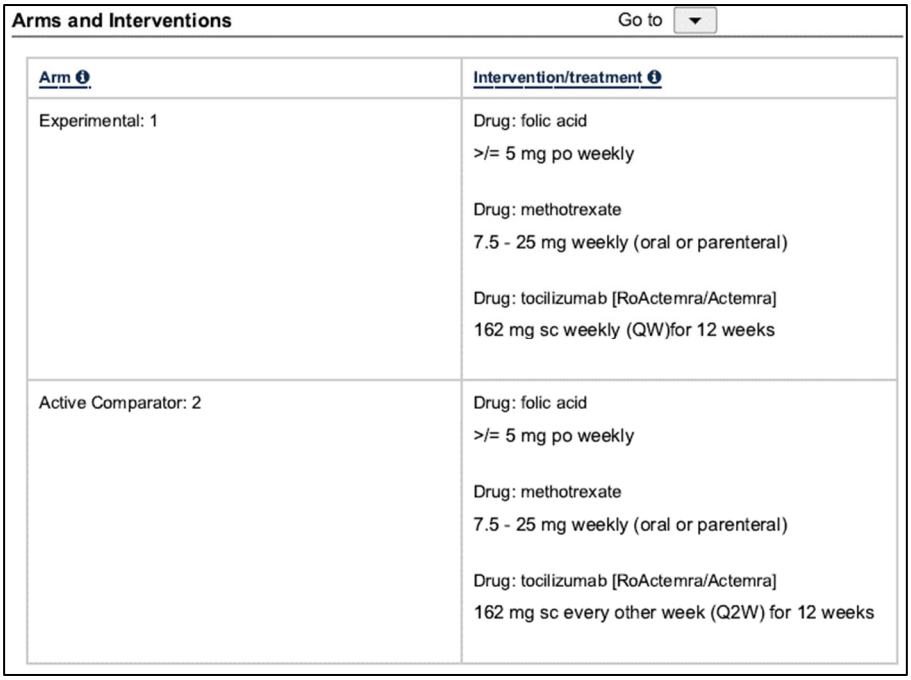
NCT00965653 (Ex. 1028) is a clinical trial protocol, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients With Rheumatoid Arthritis," which was publicly available on ClinicalTrials.gov before November, 2009, or more than one year before the earliest claimed priority date of the '264 patent. Ex. 1004 ¶¶11-32; Ex. 1002 ¶¶66-69. NCT00965653 is prior art to the '264 patent under pre-AIA § 102(b). Although NCT00965653 was identified as

one of 150 references during prosecution of the '264 patent,[9] it was never substantively discussed by either the Examiner or the applicant, and there is no evidence that the Examiner considered the arguments set forth herein.

1. Disclosure of NCT00965653

NCT00965653 describes an "open-label randomized 2 arm study" of "subcutaneously administered tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate." Ex. 1028 at 2. According to the public posting, "[p]atients will be randomized to receive tocilizumab 162 mg sc either weekly or every other week, in combination with methotrexate, for 12 weeks." *Id.* The two treatment arms are reproduced below:

[9] During prosecution, the applicant submitted an excerpt of the NCT00965653 posting from ClinicalTrials.gov. *See* Ex. 1005 ('264 Patent File History) at 676-78, 909. The excerpt submitted by applicant identified a "First Received" date of August 18, 2009, but did not identify the "First Posted" date of August 25, 2009. *Compare id.* at 676 *with* Ex. 1028 at 1 (identifying a "First Posted" date of August 25, 2009). Accordingly, the Examiner was not presented with any evidence that the clinical trial posting was publicly available before the filing date of the '264 patent.



Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: 1	Drug: folic acid >/= 5 mg po weekly Drug: methotrexate 7.5 - 25 mg weekly (oral or parenteral) Drug: tocilizumab [RoActemra/Actemra] 162 mg sc weekly (QW)for 12 weeks
Active Comparator: 2	Drug: folic acid >/= 5 mg po weekly Drug: methotrexate 7.5 - 25 mg weekly (oral or parenteral) Drug: tocilizumab [RoActemra/Actemra] 162 mg sc every other week (Q2W) for 12 weeks

Id. at 3. Only patients who had an "inadequate response to at least 12 weeks of methotrexate, the last 8 prior to baseline on stable dose" were eligible for treatment. *Id.* at 4.

2. NCT00965653 Was Publicly Available Prior to November 2009

NCT00965653 is a prior art printed publication, which was available on ClinicalTrials.gov prior to November 2009. Ex. 1004 ¶¶11-32; Ex. 1002 ¶¶66-69. The study record for NCT00965653 was "First Posted" on August 25, 2009 and updated several times in September and October 2009. Ex. 1004 ¶¶24-32. As Mr. Robert Paarlberg explains, ClinicalTrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials, and

NCT009656653 was publicly accessible more than one year before the earliest claimed priority date. Ex. 1004 ¶¶19, 24-32.

Some background on ClinicalTrials.gov is warranted. In 1997, the FDA Modernization Act required that the National Institutes of Health ("NIH") establish a database of information on clinical trials conducted in the United States for drugs for serious or life threatening diseases and conditions. *Id.* ¶12. The National Library of Medicine, under the NIH, launched ClinicalTrials.gov in February 2000, providing the public with access to information on clinical studies. *Id.* ¶13. The database is intended to provide "patients, families and members of the public ***easy access to information***." Ex. 1029 (Feb. 29, 2000 NIH Press Release) at 1 (emphasis added). The FDA Amendments Act of 2007 later expanded the database by requiring additional submission information, mandating searchable categories in the database, and imposing a fine for failure to submit information within 21 days of first patient enrollment. Ex. 1004 ¶¶15-16.

The ClinicalTrials.gov database provides key publication dates for each study submitted. According to the NIH, the "First Posted" date is "[t]he date on which the study record was first available on ClinicalTrials.gov." Ex. 1030 (ClinicalTrials.gov Glossary) at 7. The date accounts for the delay of a few days between study protocol submission, quality control review by ClinicalTrials.gov staff, and posting of the information to the public database. Ex. 1004 ¶28. NIH

also tracks, and makes available to the public, all subsequent versions of the study in a History of Changes. *Id.* ¶23.

The study record for NCT00965653 was "First Posted" on August 25, 2009. Ex. 1028 at 1. As Mr. Paarlberg explains, that alone is sufficient to indicate that the posting was available to the public by August 2009. Ex. 1004 ¶28. The History of Changes indicates subsequent updates on August 26, 2009, September 15, 2009, October 15, 2009, and additional updates all the way up to 2016. *Id.* ¶¶29-30, 33. While there have been changes made to the study status (e.g., "recruiting" vs. "completed"), the study locations, and the duration of one of the treatment arms (from 11 weeks to 12 weeks), according to ClinicalTrials.gov, the protocol disclosed in the latest version is otherwise identical to the "First Posted" version. *Id.* ¶¶34-35. Therefore, these insignificant differences aside, the current version NCT00965653 reflects the clinical trial protocol as it was publicly available by October 2009. *Id.* ¶35.

The totality of the evidence, including the indicia on the face of these 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.[10] *See, e.g.*, *Grunenthal GmbH v. Antecip Bioventures II, LLC.*, PGR 2019-00003, 2020 WL 2203740, at *7-8 (PTAB May 5, 2020) (finding a protocol available on ClinicalTrials.gov to have been publicly available as of its "first posting" date and therefore a "prior art printed publication").

3. Claims 1 and 10 Are Anticipated by NCT00965653

a. "[a] method of treating rheumatoid arthritis in a patient"

As set forth above, the preamble is not limiting. *Supra* § VIII.A. Even if the preamble was limiting, it is disclosed in NCT00965653, which describes an "open-label randomized 2 arm study" to "investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of subcutaneously administered

[10] Chugai, one of the patent owners, also sponsored the NCT00965653 clinical study, and therefore likely has documents reinforcing that the study was publicly available on ClinicalTrials.gov before November 2009. To the extent Chugai disputes whether the ClinicalTrials.gov posting is prior art, Petitioners intend to seek "routine discovery" and/or "additional discovery" from Chugai that is inconsistent with that position. *See* PTAB Trial Practice Guide (Nov. 2019) at 23-24 (providing for "routine discovery" on "relevant information that is inconsistent with a position advanced during the proceeding" and "additional discovery … in the interests of justice").

tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate." Ex. 1028 at 2. Further, the protocol states that "assessments will be made at regular intervals during ***treatment*** and on the 3 weeks of follow-up." *Id.* (emphasis added). Accordingly, NCT00965653 discloses an attempt to cause a therapeutic improvement in RA in a patient. Ex. 1002 ¶104.

Moreover, even if the preamble were construed to require efficacy in a particular patient, the preamble as so construed would be inherent in the treatment disclosed in NCT00965653. Ex. 1002 ¶¶105. In the context of an analogous method of treatment claim, the Federal Circuit held that, "[t]o anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *See King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010). The Federal Circuit explained that the patent at issue provided nothing more than the prior art with respect to how to carry out the claimed method, and "to the extent such a method increases the bioavailability of metaxalone, the identical prior art method does as well." *Id*. As in *King*, the '264 patent claims are directed to the same method disclosed by the prior art, and to the extent such a method provides effective treatment, then the prior art method does as well. And, as explained by Dr. Zizic, the method would inherently result in an effective treatment for some patients because clinical trials established that a subcutaneous fixed 162 mg dose of tocilizumab, weekly or every other week, was

effective and the FDA approved Actemra® based on those clinical trials. Ex. 1002 ¶105.

b. "subcutaneously administering [an anti-IL-6 receptor (IL-6R) antibody] [tocilizumab] to the patient"

Claim 1	Claim 10
"subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient"	"subcutaneously administering tocilizumab to the patient"

NCT00965653 describes a study of "subcutaneously administered tocilizumab in patients." Ex. 1028 at 2. Tocilizumab is an anti-IL-6 receptor antibody. Ex. 1001 ('264 patent) at 5:9-10 ("The invention also concerns subcutaneously administering an anti-IL-6R antibody (e.g. tocilizumab)."). Accordingly, this limitation is also met. Ex. 1002 ¶106.

c. "administered as a fixed dose of 162 mg per dose every week or every two weeks"

Claim 1	Claim 10
"wherein the anti-IL-6R antibody is administered as a fixed dose of 162 mg per dose every week or every two weeks"	"wherein the tocilizumab is administered as a fixed dose of 162 mg per dose every week or every two weeks"

NCT00965653 states that "[p]atients will be randomized to receive tocilizumab 162 mg sc either weekly or every other week, in combination with

methotrexate, for 12 weeks" Ex. 1028 at 2. Patients were administered a fixed dose of 162 mg regardless of body weight or body surface area, i.e., it is not administered as either a mg/kg or mg/m^2 dose. *Id.* Accordingly, this limitation is also disclosed in NCT00965653. Ex. 1002 ¶107.

d. "wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively" (claim 1)

NCT00965653 discloses administration of tocilizumab, which comprises the light chain and heavy chain amino acid sequences of SEQ ID. Nos. 1 and 2, respectively. The following evidence—including Chugai's and the '264 patent inventors' own admissions—makes clear that tocilizumab has the claimed amino acid sequences:

- The patent specification confirms that tocilizumab comprises the claimed sequences: "FIGS. 7A and 7B depict the amino acid sequences of the **light chain** (FIG. 7A: **SEQID NO: 1**) and **heavy chain** (FIG. 7B: **SEQID NO:2**) **of Tocilizumab**." Ex. 1001 ('264 patent) at 6:60-62 (emphasis added).

- The Examiner understood that tocilizumab inherently has the claimed sequences. During prosecution, the Examiner rejected claims directed to SEQ ID Nos. 1 and 2 as anticipated by Ohta 2010 which discloses tocilizumab, asserting that the "amino acid sequence characteristics would be

inherent in the antibody of the prior art." Ex. 1005 ('264 Patent File History) at 1004.

- During prosecution, the listed inventors confirmed that tocilizumab has the claimed sequences. In an inventor declaration submitted to the Examiner in an effort to antedate Ohta 2010, the listed inventors admitted that tocilizumab has the claimed sequence: "MRA227 was a phase I/Il clinical study of the anti-IL-6 receptor antibody '***tocilizumab***' also called 'MRA' ***which we understand comprises the light chain and heavy chain amino acid sequences as in Figs. 7A-B*** of the above application." Ex 1005 at 1025-1027 (emphasis added).[11]

- Chugai, one of the owners of the '264 patent, confirmed in a Request for Patent Extension that tocilizumab has the claimed amino acid sequences. *See* Ex. 1031 (Application for Patent Term Extension) at 2; Ex. 1003 ¶¶63-68.

- As explained by Dr. Levine, tocilizumab inherently has the claimed amino acid sequences for the heavy and light chains. Ex. 1003 ¶¶37-51.

[11] Likewise, the inventors made the same admission during prosecution of U.S. Patent No. 10,874,777, which shares the same specification as the '264 patent. Ex. 1007 ('677 Patent File History) at 181, 257.

Accordingly, for all of the many reasons set forth above, the tocilizumab disclosed in NCT00965653 is an "anti-IL-6R antibody compris[ing] the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively," as set forth in claim 1 of the '264 patent. Ex. 1002 ¶¶108-113.

4. Claims 2 and 9 Are Anticipated By NCT00965653

Dependent claim 2 further recites "wherein the fixed dose is administered every week," and dependent claim 9 further recites "wherein the fixed dose is administered every two weeks." As explained above, NCT00965653 discloses administration at a fixed dose every week or every two weeks. *See supra* § IX.A.3.c. Accordingly, claims 2 and 9 are also anticipated by NCT00965653. Ex. 1002 ¶114.

5. Claim 3 Is Anticipated By NCT00965653

Dependent claim 3 further recites "wherein the RA patient is a DMARD-inadequate responder." NCT00965653 discloses that the inclusion criteria for the study was "inadequate response to at least 12 weeks of methotrexate." Ex. 1028 at 4. Methotrexate is a DMARD. Ex. 1001 ('264 patent) at 14:22-33 ("Exemplary DMARDS herein are non-biological DMARDs including, in particular . . . methotrexate . . . with methotrexate being the DMARD according to one embodiment of the invention."). Accordingly, claim 3 is also anticipated by NCT00965653. Ex. 1002 ¶115.

6. Claims 6-8 and 11 Are Anticipated By NCT00965653

Dependent claims 6-8 and 11 further recite administration with an additional drug. Claim 6 further recites "administering to the RA patient one or more additional drug which treats the RA." Claim 7, which depends from claim 6, further recites "wherein 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." Claim 8, which depends from claim 7, further recites "wherein the additional drug is selected from the group consisting of non-biological DMARDS, NSAIDs, and corticosteroids." Likewise, claim 11, which depends from claim 10, further recites "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."

NCT00965653 discloses administration of tocilizumab with methotrexate, a DMARD. Ex. 1028 at 3. The experimental arm and the active comparator both involved treatment with tocilizumab and methotrexate. *Id.* Thus, NCT00965653 discloses the subject matter of claims 4-6 and 9, and therefore these claims are also anticipated. Ex. 1002 ¶116-117.

B. Ground 2: Claims 1-3 and 6-11 Are Obvious Over NCT00965653

As set forth above for Ground 1, claims 1-3 and 6-11 of the '264 patent are anticipated by NCT00965653. NCT00965653 discloses administration of a 162 mg subcutaneous fixed dose either weekly or every other week to treat RA. These regimens meet each and every limitation of claims 1-3 and 6-11 of the '264 patent, as discussed above. The only difference between the challenged claims and the prior art disclosure—assuming the claims are construed to require efficacy—is that NCT00965653 does not expressly indicate that the methods are efficacious. As discussed above, the challenged claims should not be construed to require efficacy in a particular patient, and therefore there is no difference between the prior art disclosure and the challenged claims. Furthermore, even if the claims were construed to require efficacy in a particular patient, any efficacy would be inherent in practice of the claimed method.

Nevertheless, Ground 2 is included to the extent the Board finds otherwise on these issues. The claims are also unpatentable as obvious over NCT00965653 even to the extent the claims are construed to require efficacy in particular patient. The claims would have been obvious because a POSA would have been motivated to administer these regimens and would have had a reasonable expectation of success in achieving some efficacy. *See* Ex. 1002 ¶¶125-135.

A POSA would have been motivated to carry out the claimed methods, for at least the following reasons. *Id.* ¶¶126-130. First, NCT00965653 itself discloses subcutaneous administration of a fixed dose of 162 mg of tocilizumab every week and every other week for treatment of rheumatoid arthritis. *Id.* ¶126. NCT00965653 also discloses subcutaneous administration of tocilizumab in combination with methotrexate for patients that were inadequate-DMARD responders. *Id.* Second, while it was well known that intravenous (IV) administration of 4 mg/kg and 8 mg/kg tocilizumab every four weeks was safe and effective for treating RA (Ex. 1014 (Emery) at 7; Ex. 1015 (Smolen) at 1, 7-8; Ex. 1026 (Genovese) at 2-3), the prior art taught that tocilizumab was preferably administered subcutaneously. Ex. 1002 ¶127; Ex. 1011 (WO '621) at 4 (tocilizumab's "preferred form of administration is thought to be subcutaneous formulation in chronic autoimmune diseases"). This was consistent with the general knowledge that subcutaneous administration of antibodies is preferable as compared to intravenous administration because it allows for more constant serum levels and improved convenience for patients. Ex. 1002 ¶¶127-131.

Although IV administration was common, subcutaneous treatment provides significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered subcutaneous therapy. *Id.* ¶128. As explained by physician

investigators involved in the clinical trials for Humira®, subcutaneous administration offers significant advantages over intravenous treatment:

> These agents are portable, allowing patients to self-administer the drug in the setting they choose, rather than mandating a clinic or hospital setting. Similarly, these agents can be administered at the patient's convenience rather than requiring an appointment for treatment. Finally, self-administered medications may reduce costs for patients and providers (e.g., travel-related costs and office visit-related costs) compared with the costs of intravenous medications.

Ex. 1070 (Kivitz) at 2.

A POSA would have had a reasonable expectation that a fixed dose of 162 mg subcutaneously given weekly or every other week would be effective in treating RA. Ex. 1002 ¶131. The prior art makes clear that an intravenously-administered antibody would be at least as safe and effective if instead administered at an equivalent amount subcutaneously. *Id.* For example, Bonilla discloses that antibodies may be administered subcutaneously every week or every other week instead of intravenously every four weeks in an amount that "over time is generally equivalent." Ex. 1021 (Bonilla) at 15. Subcutaneous administration provides the same mean serum levels along with fluctuations that are "much smaller" and therefore trough levels are higher and peak levels are lower than with

intravenous administration. *Id.* And, for tocilizumab, it was known that the efficacy of tocilizumab depends upon maintaining adequate serum trough levels throughout treatment. Ex. 1033 (Nishimoto 2003) at 9. Therefore, a POSA would have reasonably expected that safety and efficacy would be maintained when using a subcutaneous dose equivalent to the known IV dose. Ex. 1002 ¶131.

A POSA would have understood that the subcutaneous fixed dose of 162 mg every week or every other week disclosed in NCT00965653 was equivalent to the known efficacious 4 mg/kg and 8 mg/kg every four week IV doses. Ex. 1002 ¶132. Because the bioavailability of a drug may differ when administered subcutaneously as compared to intravenously, a POSA would have understood that an equivalent subcutaneous dose may not necessarily be identical to these intravenous dosages. Ex. 1002 ¶132; Ex. 1016 (Berger) at 6. The prior art had reported a subcutaneous bioavailability of 72% for tocilizumab, which means administering 139% (1/0.72 = 1.39) of the intravenous dosage subcutaneously would provide the same amount of tocilizumab over time. Ex. 1019 (EMA Assessment Report) at 18; Ex. 1002 ¶132. However, the prior art had also disclosed that, because subcutaneous administration typically maintains higher trough levels than the same amount of drug administered intravenously, such an overage may not be necessary when subcutaneously administering an immunoglobulin in order to maintain equivalent efficacy. Ex. 1002 ¶132; Ex. 1016

(Berger) at 6-7. For example, while the immunoglobulin reported in Berger required a 37% increase in dosage to account for the reduced bioavailability associated with subcutaneous administration, and such high doses were indeed found to be safe and effective, doses as low as 100% of the intravenous amount over time were also effective, and in fact "showed no difference in … efficacy" as compared to the higher dosage amount. Ex. 1002 ¶132; Ex. 1016 (Berger) at 6-7. A POSA would thus have reasonably expected that a subcutaneous dose of between 100% and 139% of the known intravenous tocilizumab dose would be equivalent to the intravenous dose. Ex. 1002 ¶132.

In assessing the equivalent subcutaneous dose for the known IV dose of 4 mg/kg every four weeks (a known safe and efficacious IV dose for treating RA), a POSA would have known that a dosage of 4 mg/kg every four weeks amounts to a total of 140 mg every other week for a typical 70 kg patient. Ex. 1002 ¶133. A POSA would have understood that the equivalent subcutaneous dose would be somewhere between this amount and up to about 39% higher than the IV dose, or approximately 195 mg. *Id.*; *see* Ex. 1016 (Berger) at 6. Because 162 mg every other week falls squarely within this range, a POSA would have reasonably expected 162 mg tocilizumab administered subcutaneously every other week to be safe and efficacious for treating RA. Ex. 1002 ¶133.

In assessing the equivalent subcutaneous dose for the known IV dose of 8 mg/kg every four weeks (also known to be a safe and efficacious IV dose for treating RA), a POSA would have known that 8 mg/kg every four weeks amounts to 140 mg every week for a typical 70 kg patient. A POSA would have understood that an equivalent subcutaneous dose would be somewhere between this amount and up to about 39% higher than the IV dose, or approximately 195 mg. Ex. 1002 ¶134; *see* Ex. 1016 (Berger) at 6. Because 162 mg every week falls squarely within this range, a POSA would have reasonably expected 162 mg tocilizumab administered subcutaneously every week to be safe and efficacious for treating RA. Ex. 1002 ¶134.

A POSA would have further expected that the same dose could be successfully administered to RA patients regardless of weight (i.e., as a fixed dose). Ex. 1002 ¶135. The prior art taught that large differences in AUC "did not affect efficacy or safety in a clinically relevant manner." Ex. 1019 (EMA Assessment Report) at 24. For drugs with such a large therapeutic window, fixed dosing was in fact considered preferable. Ex. 1022 (Wang) at 7, 17. Accordingly, a POSA would have reasonably expected that this tocilizumab fixed dose would retain its safety and efficacy despite weight-based differences in tocilizumab clearance rate. Ex. 1002 ¶135.

C. Ground 3: Claims 1, 2, 9, and 10 Are Anticipated By Ohta 2010

Ohta 2010 is an abstract published in the journal *Arthritis and Rheumatism* in October 2010. Ex. 1034. Ohta 2010 is prior art to the '264 patent under pre-AIA § 102(a). During prosecution of the '264 patent, the Examiner rejected all of the claims as either anticipated by or obvious over Ohta 2010. As explained above, the applicant overcame these rejections by submitting an inventor declaration alleging prior invention. *See supra* § VI.B. However, the Examiner erred in finding that the declaration established prior inventorship.

The declaration was submitted by two of the four named inventors—Xiaoping Zhang and Kimio Terao—and alleges that "[p]rior to September 2010, we had conceived of and reduced to practice the invention of said claims." Ex. 1005 ('264 File History) at 1025. To establish prior invention, a conclusory assertion by an alleged inventor must be corroborated by independent evidence. *See Kolcraft Enterprises, Inc. v. Graco Children's Prods., Inc.*, 927 F.3d 1320, 1324 (Fed. Cir. 2019) ("Inventor testimony of conception must be corroborated by other, independent information."). Yet no such independent evidence supporting these individuals' alleged prior invention was provided to the Examiner. While a "Synopsis" of a clinical study report allegedly describing administration of tocilizumab in accordance with the claimed methods was attached to the declaration, no dates are identified in the Synopsis, and so it does not corroborate

that the methods were conceived or reduced to practice prior to the publication of Ohta 2010. Ex. 1005 ('264 Patent File History) at 1031-1044. Furthermore, nothing in the Synopsis suggests that any of the named inventors were even involved in the clinical study. *Id.* The Synopsis identifies several individuals involved with the clinical study—including the lead author of Ohta 2010—but the purported inventors' names are noticeably absent. *Id.* The declaration thus does not corroborate the inventors' statement that they conceived of and reduced to practice the claimed invention prior to the publication of Ohta 2010, and therefore Ohta 2010 remains prior art under pre-AIA § 102(a). *See Kolcraft*, 927 F.3d at 1325 (affirming PTAB's finding that patentee failed to corroborate inventor testimony where "exhibits are undated and lack any showing of authorship"); *In re NTP, Inc.*, 654 F.3d 1279, 1291 (Fed. Cir. 2011) ("It has long been the case that an inventor's allegations of earlier invention alone are insufficient—an alleged date of invention must be corroborated.").

Ohta 2010 discloses the results of a clinical study wherein patients received 162 mg tocilizumab subcutaneously either weekly or every other week for the treatment of RA. Ex. 1034 (Ohta 2010) at 2. Ohta 2010 reports that both regimens were "well tolerated" and "associated with good clinical response." *Id.* at 3.

1. Claims 1, 2, 9, and 10 Are Anticipated By Ohta 2010

a. The Preamble

Claims 1 and 10
"a method of treating rheumatoid arthritis in a patient"

As set forth above, the preamble should not be construed as limiting. *See supra* § VIII.A. However, even if the preamble was a necessary limitation of the claims, it is disclosed in Ohta 2010, which describes a Phase I/II study to evaluate the safety, pharmacokinetics and clinical response in patients with rheumatoid arthritis. Ex. 1034 (Ohta 2010) at 2-3; Ex. 1002 ¶119. Moreover, even if the preamble was construed to require that the treatment be effective, that limitation is also described in Ohta 2010, which reports that "[t]ocilizumab subcutaneous injection is well tolerated up to 162 mg QW and is associated with good clinical response both 162 mg Q2W and QW." Ex. 1034 (Ohta 2010) at 3; Ex. 1002 ¶120.

b. "subcutaneously administering [an anti-IL-6 receptor (IL- 6R) antibody] (claim 1) / [tocilizumab] (claim 10)

Claim 1	Claim 10
"subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient"	"subcutaneously administering tocilizumab to the patient"

Ohta 2010 describes a Phase I/II study of tocilizumab subcutaneously injected in patients. Ex. 1034 (Ohta 2010) at 2-3. Tocilizumab is an anti-IL-6

receptor antibody. Ex. 1001 at 5:9-10 ("The invention also concerns subcutaneously administering an anti-IL-6R antibody (e.g. tocilizumab)."). Therefore, this limitation is disclosed in Ohta 2010. Ex. 1002 ¶121.

c. "administered as a fixed dose of 162 mg per dose every week or every two weeks"

Claim 1	Claim 10
"wherein the anti-IL-6R antibody is administered as a fixed dose of 162 mg per dose every week or every two weeks"	"wherein the tocilizumab is administered as a fixed dose of 162 mg per dose every week or every two weeks"

Ohta 2010 discloses that patients were treated with 162 mg weekly or every other week. Ex. 1034 (Ohta 2010) at 2. Patients were administered a fixed dose of 162 mg regardless of body weight or body surface area, i.e., it was not administered as either a mg/kg or mg/m^2 dose. *Id.* Therefore, this limitation is also disclosed in Ohta 2010. Ex. 1002 ¶122.

d. "wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively"

Ohta 2010 discloses administration of tocilizumab. Ex. 1034 (Ohta 2010) at 2. For the same reasons set both above with respect to NCT00965653 (*see supra* § IX.A.3.d), the tocilizumab disclosed in Ohta 2010 necessarily has the light chain

and heavy chain amino acid sequences of SEQ ID Nos. 1 and 2, respectively. *See also* Ex. 1002 ¶123.

2. Claims 2 and 9

Dependent claim 2 further recites "wherein the fixed dose is administered every week," and dependent claim 9 further recites "wherein the fixed dose is administered every two weeks." As explained above, Ohta 2010 discloses administration at a fixed dose every week or every two weeks. *See supra* § IX.C. Therefore, claims 2 and 9 are also anticipated by Ohta 2010. Ex. 1002 ¶124.

D. Ground 4: Claims 1-3 and 6-11 are Obvious over Ohta 2010 in view of Maini 2006

As discussed above, Ohta 2010 discloses each and every limitation of claims 1, 2, 9, and 10. These claims are also obvious over Ohta 2010 in view of Maini 2006. Although Ohta 2010 does not disclose co-administration with methotrexate or administration to a DMARD-inadequate responder, as set forth in claims 3, 6-8, and 11, these additional limitations would also have been obvious over Ohta 2010 in view of Maini 2006. It was well known that the combination of tocilizumab and methotrexate was an effective treatment, particularly for patients that were DMARD-inadequate responders. Ex. 1002 ¶¶137-142.

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,"

Arthritis & Rheumatism, Vol. 54, No. 9, Sept. 2006 ("Maini 2006") was published in 2006. Ex. 1025. Accordingly, Maini 2006 is prior art to the '264 patent under pre-AIA § 102(b). Maini 2006 discloses results of the CHARISMA (Chugai Humanize Anti-Human Recombinant Interleukin-6 Monoclonal Antibody) study, a double-blind randomized clinical trial of tocilizumab in combination with methotrexate in treatment of RA in patients who had an incomplete response to methotrexate alone. *Id.* at 3. Maini 2006 discloses that "[c]ombination therapy with tocilizumab plus MTX demonstrated superior efficacy compared with tocilizumab monotherapy." *Id.* at 12.[12]

[12] Additional clinical trials further confirmed that tocilizumab in combination with methotrexate was well tolerated and effective in treating RA patients. *See* Ex. 1014 (Emery) at 9 ("In patients with moderate to severe active RA responding inadequately or who are intolerant to TNF antagonists [a DMARD], changing to tocilizumab plus methotrexate is effective, and the safety profile is manageable."); Ex. 1026 (Genovese) at 12 ("[P]atients with moderate-to-severe RA, treatment with tocilizumab in combination with traditional DMARDs [including methotrexate] significantly and rapidly reduced disease activity over 24 weeks as compared with treatment with DMARDs plus placebo.").

A POSA would have been motivated to combine Ohta 2010 with Maini 2006 to arrive at the claimed methods at least because Ohta 2010 discloses that 162 mg tocilizumab administered subcutaneously every week or every other week is safe and effective for treating RA, and Maini 2006 discloses that tocilizumab can be safely and effectively administered in combination with methotrexate. Ex. 1002 ¶143. Moreover, combination therapies of methotrexate and other anti-cytokine antibodies were also well known in the art for treatment of RA. *Id.* ¶¶144-46. A POSA would have been motivated to modify the method of Ohta 2010 to include administration with methotrexate to obtain the known functions and advantages of both because the combination would have been expected to be more effective than methotrexate alone. Ex. 1002 ¶¶ 143-147.

A POSA would have reasonably expected the resulting method to be successful at least because Ohta 2010 disclosed that the claimed tocilizumab subcutaneous regimens were safe and efficacious and a POSA would have had no reason to believe either safety or efficacy would be adversely impacted by adding methotrexate to the regimen. Ex. 1002 ¶147.

E. Ground 5: Claims 1-3 and 6-11 Would Have Been Obvious over Maini 2006, Bonilla and Wang

Claims 1-3 and 6-11 would also have been obvious from a combination of Maini 2006, Bonilla and Wang. Ex. 1002 ¶¶148-169.

1. Scope and Content of the Prior Art and Differences Between the Prior Art and the Challenged Claims

Maini 2006 discloses that tocilizumab administered by IV at a dose of 4 mg/kg and 8 mg/kg every four weeks was safe and effective for treating RA. Ex. 1025 (Maini 2006) at 2-3, 12. Maini 2006 also discloses that administering methotrexate along with tocilizumab improves safety and efficacy, and that tocilizumab may be administered—either with or without methotrexate—to patients who had a prior inadequate response to methotrexate. Ex. 1025 (Maini 2006) at 12-13.

The 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. As explained below, a POSA would have been motivated to combine Maini 2006 with Bonilla and Wang to arrive at the claimed methods with a reasonable expectation of success.

Bonilla, "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes," *Immunology & Allergy Clinics of North America*, Vol 28 ("Bonilla") was published in a printed publication as of 2008. Ex. 1021. Accordingly, Bonilla is prior art to the '264 patent under pre-AIA § 102(b). Bonilla discloses that it is preferable to administer an equivalent amount of an immunoglobulin as a subcutaneous dose every week rather than an IV dose every

four weeks because it reduces serum concentration fluctuation around the same mean. Ex. 1021 (Bonilla) at 15. Bonilla also discloses that subcutaneous administration "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," and that "[a]lthough SCIG [subcutaneous administration of IgG] is usually given weekly (sometimes more often), . . . a 2-week interval is also practical." *Id.* at 18.

Bonilla also discloses that 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. Bonilla thus discloses that an equivalent amount of an antibody administered by subcutaneous injection is between 100% of the IV dose and the amount necessary to provide 100% of the IV dose when accounting for the reduction in bioavailability.

Wang et al., "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," *Pharmacokinetics & Pharmacodynamics*, Vol. 49 ("Wang") was published in September 2009. Ex. 1022. Accordingly, Wang is prior art to the '264 patent under pre-AIA § 102(b). Wang was not cited

during examination of the '264 patent. Wang is directed to evaluating the relative advantages and disadvantages of weight-based and fixed dosing of monoclonal antibodies. Wang concludes that, all else being equal, monoclonal antibodies are preferably administered as a fixed dose rather than a weight-based dose due to its convenience, better compliance, less risk for medical errors, and cost-effectiveness. Ex. 1022 (Wang) at 7, 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."). Wang also discloses that "[f]or drugs with a wide therapeutic window, a fixed dosing approach is generally chosen for adult patients, regardless of the influence of body size on PK and PD properties due to its convenience, better compliance, less risk of medical errors, and cost-effectiveness." *Id.* at 7. Wang clarifies that "when a drug has a wide therapeutic window, an AUC difference more than ±20% may still be tolerated without additional safety issues." *Id.* at 17.

2. Motivation To Combine

A POSA would have been motivated to combine the teachings of Maini 2006, Bonilla, and Wang to arrive at the claimed invention for at least the following reasons. Ex. 1002 ¶¶148-162.

Maini 2006 discloses that 4 mg/kg of tocilizumab administered by IV every four weeks was safe and effective for treating RA. Ex. 1025 (Maini 2006) at 2.

By June 2009, Chugai and Roche had also publicly disclosed their development of a subcutaneous tocilizumab. Ex. 1046 (Chugai 2009 Report) at 4; Ex. 1045 (Roche 2009 Report) at 12. A POSA would have been motivated to use a subcutaneous formulation of tocilizumab because Chugai had itself announced that subcutaneous was the "preferred" form of a drug that had been found to be safe and effective. Ex. 1011 (WO '621) at 4.

A POSA would also have known that subcutaneous administration offers significant advantages over IV administration, including improved convenience, flexibility, reduced cost for patients, and reduced risk of medical errors in preparing the dosage. Ex. 1002 ¶154; Ex. 1016 (Berger) at 12-13; Ex. 1070 (Kivitz) at 2; Ex. 1017 (Ochs) at 7. Bonilla discloses that immunoglobulins[13] 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. Ex. 1021 (Bonilla) at 8, 15-18. Hence, a POSA would have been motivated to administer tocilizumab subcutaneously, the "preferred form" of

[13] Although Bonilla discusses polyclonal human immunoglobulin IgG therapy, a POSA would understand that the same reasoning applies to IgG monoclonal antibodies like tocilizumab. Ex. 1002 ¶154, n.45.

tocilizumab, every other week in an amount equivalent to the 4 mg/kg every four week dose disclosed by Maini 2006. Ex. 1002 ¶¶ 154, 157.

To determine an equivalent subcutaneous dosing regimen based on the known effective IV regimens, a POSA would have looked to Bonilla and Wang. *Id.* ¶¶156-58. A POSA would have understood from Wang that a fixed dose would be preferable to a weight-based dose in the absence of a reason to the contrary. Ex. 1022 (Wang) at 18. For a drug with a "wide therapeutic window," a POSA would have understood that a fixed dose was even more preferable. *Id.* at 7. Tocilizumab was known in the prior art to be safe and effective over a wide range of doses, from 4 mg/kg to 8 mg/kg, despite the AUC for 8 mg/kg dose being more than double the AUC for the 4 mg/kg dose. Ex. 1025 (Maini 2006) at 2; Ex. 1033 (Nishimoto 2003) at 7. It had also been reported that an "almost two-fold" increase in tocilizumab's AUC "did not affect efficacy or safety parameters in a clinically relevant manner." Ex. 1019 (EMA Assessment Report) at 23-24; Ex. 1002 ¶156. Particularly in view of this wide therapeutic window, a POSA would have been motivated from Wang to administer tocilizumab subcutaneously as a fixed dose, rather than as a weight-based dose. Ex. 1002 ¶156.

A POSA would have looked to Bonilla to determine an equivalent subcutaneous fixed dose of the 4 mg/kg every four week intravenous regimen. *Id.* ¶157. As taught by Bonilla, the equivalent amount of an antibody administered

subcutaneously 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. Ex. 1021 (Bonilla) at 16-17. The reported bioavailability of subcutaneously administered tocilizumab was 72%, which means that as much as 139% of the IV dose may be required if administered subcutaneously. *See* Ex. 1019 (EMA Assessment Report) at 18; Ex. 1002 ¶ 157 (an excess of 39% is required to account for a 72% bioavailability). However, because subcutaneous administration provides higher trough concentrations than intravenous administration, the prior art taught that there may, in fact, be no need to increase the dose at all to maintain efficacy when converting to subcutaneous administration, notwithstanding the reduced bioavailability. Ex. 1016 (Berger) at 6; Ex. 1021 (Bonilla) at 17. Thus, a POSA would have understood that the optimal subcutaneous dose that would maintain safety and efficacy would be somewhere between 100% and 139% of the intravenous dose. Ex. 1002 ¶157

Starting from the 4 mg/kg every four week IV dose, a POSA would have determined that approximately 140 mg tocilizumab would be administered every

other week for a typical 70 kg patient.[14] Ex. 1002 ¶158. Accounting for the potential 39% increase, a POSA would have understood that an equivalent subcutaneous every other week regimen would require administering a fixed dose of between 140 mg and 195 mg. *Id.* A POSA 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.*; *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (finding claims requiring specific dosages obvious where "the experimentation needed to arrive at the claimed dosages was nothing more than routine"); *see also EI DuPont de NeNemours & Co. v. Synvina CV*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results, or other pertinent evidence of nonobviousness.").

3. Reasonable Expectation of Success

A POSA would have reasonably expected a 162 mg fixed subcutaneous dose of tocilizumab every other week to be successful at least because Maini 2006

[14] 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.

taught that 4 mg/kg of tocilizumab administered by IV every four weeks was a safe and effective dose, and Bonilla taught that an equivalent subcutaneous dose would provide equivalent results. Ex. 1002 ¶159. As just discussed, a POSA would have understood that 162 mg tocilizumab administered subcutaneously every other week was equivalent to 4 mg/kg administered by IV every four weeks for a typical 70 kg patient.

Furthermore, a POSA would have understood that the efficacy of tocilizumab depended upon maintaining trough concentrations above a minimum threshold. Ex. 1033 (Nishimoto 2003) at 9. And a POSA would have understood from Bonilla that the trough concentrations would be even higher for a subcutaneous dose administered every other week than an equivalent intravenous dose administered every four weeks. Ex. 1021 (Bonilla) at 17; Ex. 1002 ¶160. Even though the 162 mg dose is slightly less than the 195 mg amount that would provide an identical amount of tocilizumab over time when differences in bioavailability are accounted for, it is well within the range of doses for which a POSA would have reasonably expected the trough concentration to exceed those provided by the IV administration. Ex. 1002 ¶160.

A POSA would have also reasonably expected this dose to be successful over a wide range of patient weights (i.e., as a fixed rather than weight-based dose). *Id.* ¶161. Although it was known that tocilizumab's clearance was

dependent upon body weight, and hence a fixed dose would result in heavier patients having a lower AUC than lighter patients, AUC was also known to vary significantly when tocilizumab was administered as a weight-based dose, with the prior art reporting as much as a two-fold increase in AUC as between light and heavy patients. Ex. 1019 (EMA Assessment Report) at 23-24. This doubling of AUC was notably found to "not affect efficacy or safety in a clinically relevant manner." *Id*. 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. Ex. 1002 ¶161.

Moreover, several IgG antibodies and other proteins were approved in the prior art that were used in a subcutaneous fixed dose—e.g., etanercept (approved by FDA in 1998), adalimumab (approved by FDA in 2004), certolizumab (approved by FDA in April 2008), and golimumab (approved by FDA in April 2009). *See supra* § V.B. These approvals would have further reinforced to a POSA that a subcutaneous fixed dose of tocilizumab would have reasonably been expected to be successful. Ex. 1002 ¶162.

4. Application to the Claims

a. Claims 1 and 10

As discussed above, a POSA would have been motivated to combine Maini, Bonilla, and Wang to arrive at a method of treating RA comprising administering

tocilizumab subcutaneously at a fixed dose of 162 mg every other week. As discussed above, tocilizumab is an anti-IL-6 receptor antibody comprising the light and heavy chain amino acid sequences of SEQ ID NOS. 1 and 2, respectively. *See supra* § IX.A.3.d. Accordingly, the combined method would have met each and every limitation of claims 1 and 10, and therefore these claims would have been obvious. Ex. 1002 ¶163.

b. Claim 2

Claim 2 depends from claim 1 and further requires that "the fixed dose is administered every week." In addition to disclosing a 4 mg/kg every four week dose, Maini 2006 also discloses that that tocilizumab is safe and effective when administered by IV every four weeks at a dose of 8 mg/kg. Ex. 1025 (Maini 2006) at 2–3, 12. Bonilla discloses that, although IV administration is usually every 3-4 weeks, subcutaneous treatment is usually every week. Ex. 1021 (Bonilla) at 15-16, 18. For substantially the same reasons set forth above, a POSA would have therefore found it similarly obvious to use an 8 mg/kg every four week IV dose as a starting point for identifying an appropriate weekly subcutaneous regimen for administering tocilizumab to treat RA. Ex. 1002 ¶164.

Starting from the 8 mg/kg every four week IV dose, a POSA would have determined that approximately 140 mg tocilizumab would be administered every week to a typical 70 kg patient. *Id.* ¶165. Accounting for the potential 39%

increase to account for bioavailability, a POSA would have understood that an equivalent subcutaneous every week regimen would require administering a fixed dose between 140 mg and 195 mg. *Id.* A POSA 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.* Claim 2 would therefore have been obvious for substantially the same reasons as set forth with respect to claims 1 and 8.

c. Claim 3

Dependent claim 3 depends from claim 1, and further requires that "the RA patient is a DMARD-inadequate responder." Maini 2006 discloses that tocilizumab is administered to patients who has an inadequate response to methotrexate. Ex. 1025 (Maini 2006) at 2. It would therefore have been obvious to administer the method discussed with respect to claims 1 and 8, above, to a patient who was a DMARD-inadequate responder. Ex. 1002 ¶166. Claim 3 would therefore also have been obvious.

d. Claim 6-8 and 11

Dependent claims 6-8 and 11 recite administration with an additional drug. Claim 6 further recites "comprises administering to the RA patient one or more additional drug which treats the RA." Claim 7, which depends from claim 6, further recites "wherein 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." Claim 8, which depends from claim 7, further recites "wherein the additional drug is selected from the group consisting of non-biological DMARDS, NSAIDs, and corticosteroids." Likewise, claim 11, which depends from claim 10, further recites "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."

Maini 2006 discloses that administering methotrexate in combination with tocilizumab "demonstrated superior efficacy compared with tocilizumab monotherapy." Ex. 1025 (Maini 2006) at 12. It therefore would have been obvious to administer methotrexate along with the regimen discussed with respect to claims 1 and 8, above. Ex. 1002 ¶168. Claims 6-8 and 11 therefore also would have been obvious.

e. Claim 9

Claim 9 depends from claim 1 and further requires that "the fixed dose is administered every two weeks." The method discussed with respect to claims 1 and 10, above, would have involved administering the fixed dose every two weeks.

Ex. 1002 ¶169. Claim 9 would therefore also have been obvious for substantially the same reasons as set forth with respect to those claims.

F. Secondary Considerations

Petitioners are not aware of any relevant secondary considerations that have a nexus to, or are commensurate in scope, with any of the challenged claims. Petitioners reserve the right to respond to any allegations of secondary considerations.

X. Section 325(d) Should Not Prevent Institution

Section 325(d) provides discretion to deny institution where (1) the same or substantially the same art or arguments were previously presented to the patent office; and (2) the petitioner has failed to demonstrate that the Examiner erred in a manner material to the claims. *Sony Interactive Entertainment LLC v. Bot M8, LLC*, 2020 WL 5924211, at *2 (PTAB Oct. 6, 2020). The so-called *Becton Dickinson* factors are applied to aid in answering these questions. These factors include: "(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or

Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Becton, Dickinson & Co. v. B. Braun Melsungen, AG*, IPR 2017-01586, Paper 8, at 17-18 (PTAB Dec. 15, 2017).

A. Grounds 1 and 2

With regards to Grounds 1 and 2, Petitioners rely upon NCT00965653, which discloses treating patients with subcutaneous fixed dose of 162 mg to treat rheumatoid arthritis. Although NCT00965653 was disclosed on an IDS during prosecution, it was never substantively evaluated by the Examiner. *See supra* § IX.A. Mere inclusion of a reference on an IDS does not mean that it was involved or evaluated during prosecution. *See Fox Factory, Inc. v. SRAM, LLC*, IPR 2016-01876, 2017 WL 1240081, at *3 (PTAB April 3, 2017). Even more critically, the excerpt provided by Applicant omitted the "First Posted" date of August 25, 2009 (*see supra* § IX.A), and the Examiner was not otherwise presented with evidence that NCT00965653 was available in the prior art. Petitioners here, to the contrary, have provided facts and expert testimony demonstrating NCT00965653 was publicly available before the earliest claimed

priority date of the ’264 patent. *See supra* § IX.A. Factors (a) and (b) therefore favor institution.

Petitioners rely upon NCT00965653 as anticipatory of all claims of the ’264 patent. At no point during prosecution did the Examiner contend that a single § 102(b) reference disclosed each and every limitation of any of the claims.

The remaining factors demonstrate that the Examiner erred in a material way by failing to reject the claims over NCT00965653, and strongly counsel against denying institution. As noted, NCT00965653 was never substantively evaluated during prosecution. Hence, factor (c) weighs in favor of institution. *See Digital Check Corp. v. E-ImageData Corp.*, IPR 2017-00178, Paper 6, at 12-13 (PTAB April 25, 2017).

Factors (e) and (f) also strongly support institution. As discussed above, NCT00965653 discloses and enables each and every limitation of all of the claims of the ’264 patent. The Examiner’s failure to appreciate that a single § 102(b) reference was publicly available and anticipates the claims reflect a plain error in evaluating the prior art (factor (e)) and the arguments set forth in Petitioners’ Grounds 1 and 2 reflect additional evidence and facts presented in the Petition that warrant reconsideration of the prior art (factor (f)). *See Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR 2017-01884, 2018 WL 924243, at *4-5 (PTAB Feb. 15, 2018) (Paper 14) (finding that “because the Examiner did not have the benefit of

Petitioner's additional experimental evidence relating to competition, we are not persuaded that the same or substantially the same prior art or arguments were previously presented to the Office").

B. Grounds 3 and 4

Ground 3 and 4 assert that claims 1-3 and 6-11 of the '264 patent are anticipated and/or obvious in view of Ohta 2010. During prosecution of the '264 patent, the Examiner rejected all of the claims as either anticipated by or obvious over Ohta 2010. The applicant overcame these rejections by submitting an inventor declaration alleging prior invention. *See supra* § VI.B. In support, the inventors submitted an undated "Synopsis" of a clinical study report that failed to identify the inventors' names, and therefore does not corroborate a prior conception and reduction to practice by the inventors. The Examiner erred in finding that the declaration established prior inventorship, and therefore discretionary denial of institution is inappropriate for Grounds 3 and 4 under Section 325(d). *See Boehringer Ingelheim Pharms., Inc. v. Genentech, Inc.*, IPR 2017-02032, 2018 WL 1605268, at *4 (Mar. 29, 2018) (declining to exercise discretion under § 325(d) to deny institution ground where an inventor declaration submitted during prosecution could not antedate a reference).

C. Ground 5

Ground 5 asserts that claims 1-3 and 6-11 of the '264 patent are obvious in view of Maini 2006, Bonilla, and Wang. None of these references were before the Examiner during prosecution of the '264 patent, much less cited as a basis for a rejection. Maini 2006 discloses successful Phase III clinical trial results for intravenous tocilizumab at 4 mg/kg and 8 mg/kg dosages. Although Emery discloses similar results and was cited in an IDS, it was never substantively evaluated by the Examiner. Mere inclusion of a reference on an IDS does not mean that it was involved or evaluated during prosecution. *Fox Factory, Inc. v. SRAM, LLC*, IPR 2016-01876, Paper 8, at 7-9 (PTAB April 3, 2017). Therefore, factors (a)-(c) favor institution.

Furthermore, at no point during prosecution did the Examiner issue an obviousness rejection based on a reference disclosing that intravenous tocilizumab at 4 mg/kg and 8 mg/kg dosages was effective in treating RA. Instead, the Examiner relied upon Ohta 2010 as a primary reference, which discloses that subcutaneous tocilizumab was effective at a fixed dose of 162 mg.[15] Moreover, the Examiner did not have the benefit of Bonilla or Wang (or any similar prior art)

[15] As discussed in § IX.C, *supra*, the Examiner erred in finding that the inventors had antedated Ohta 2010.

which disclose advantages of subcutaneous administration and would have provided motivation to use a fixed subcutaneous dose in view of the effective intravenous dosages. *See supra* § IX.E.2. Therefore, (c) and (d) also favor institution. *Oticon Medical AB v. Cochlear Ltd.*, IPR 2019-00975, 2019 WL 5237817, at *8 (PTAB Oct. 16, 2019) (declining to deny institution where examiner failed to consider specific teachings in the prior art).

Finally, factors (e) and (f) also favor institution because none of references relied upon by Petitioners for Ground 5 were before the Examiner.

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Accordingly, Section 325(d) should not prevent institution of any of the grounds presented in this petition.

XI. CONCLUSION

For the reasons set forth above, Petitioners respectfully submit that they have established a reasonable likelihood of success with respect to the challenged claims and requests that trial be instituted and the challenged claims cancelled.

Dated: August 18, 2021

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 8,580,264 complies with the type-volume limits of 37 C.F.R. §42.24(a)(1)(i) because it contains 13,814 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: August 18, 2021

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,580,264** and the exhibits cited therein by Federal Express Next Business Day Delivery on this day, August 18, 2021 on the Patent Owner's correspondence address of record for the subject patent as follows: Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080

Dated: August 18, 2021

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