FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1011	Certificate of Translation (pg. 1), Translation (pgs. 2-183) & Original (pgs. 184-364) of PCT International Publication No. WO2009/041621 A1 ("WO '621")
Ex. 1012	Sequence Listing for WO2009/041621 A1
Ex. 1013	Chugai Pharmaceutical Co., "Product Overview of Actemra" (May 22, 2008) ("Product Overview of Actemra")
Ex. 1014	P Emery et al., "IL-6 Receptor Inhibition with Tocilizumab Improves Treatment Outcomes in Patients with Rheumatoid Arthritis Refractor to Anti-Tumour Necrosis Factor Biologicals: Results from a 24-Week Multicenter Randomized Placebo-Controlled Trial," *Annals of the Rheumatic Diseases* 67:1516-23 (2008) ("Emery")
Ex. 1015	Josef S. Smolen et al., "Effect of Interleukin-6 Receptor Inhibition with Tocilizumab in Patients with Rheumatoid Arthritis (OPTION Study): A Double-Blind, Placebo-Controlled, Randomised Trial," *Lancet* 371:987-97 (2008) ("Smolen")
Ex. 1016	Melvin Berger, "Subcutaneous Administration of IgG," *Immunology and Allergy Clinics of North America* 28:779-802 (2008) ("Berger")
Ex. 1017	Hans D. Ochs et al., "Safety and Efficacy of Self-Administered Subcutaneous Immunoglobulin in Patients with Primary Immunodeficiency Diseases," *Journal of Clinical Immunology* 26(3):265-73 (2006) ("Ochs")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1018	Pharmaceuticals and Medicals Devices Agency of Japan, Annual Report FY 2008, https://www.pmda.go.jp/files/000232775.pdf ("PMDA 2008 Report")
Ex. 1019	Archived European Medicines Agency, Assessment Report for Ro-Actemra (July 7, 2009) (pgs. 5-59), with Affidavit of Duncan Hall, Internet Archive (pgs. 1-4) ("EMA Assessment Report")
Ex. 1020	Food and Drug Administration, BLA 125276 Approval Letter for Actemra® (January 8, 2010), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/125276s000ltr.pdf ("BLA Approval Letter")
Ex. 1021	Francisco A. Bonilla, "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes," *Immunology and Allergy Clinics of North America* 28:803-19 (2008) ("Bonilla")
Ex. 1022	Diane D. Wang et al., "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," *Journal of Clinical Pharmacology* 49:1012-24 (Sept. 2009) ("Wang")
Ex. 1023	Humira® (adalimumab) Package Insert (Dec. 2002) ("2002 Humira FDA Label")
Ex. 1024	"CIMZIA (certolizumab pegol)," *Physicians' Desk Reference* (63rd ed. 2009) ("2009 PDR – Cimzia")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1025	R. N. Maini et al., "Double-Blind Randomized Controlled Clinical Trial of the Interleukin-6 Receptor Antagonist, Tocilizumab, in European Patients with Rheumatoid Arthritis Who Had an Incomplete Response to Methotrexate," *Arthritis & Rheumatism* 54(9):2817-29 (2006) ("Maini 2006")
Ex. 1026	Mark C. Genovese, "Interleukin-6 Receptor Inhibition with Tocilizumab Reduces Disease Activity in Rheumatoid Arthritis with Inadequate Response to Disease-Modifying Antirheumatic Drugs," *Arthritis & Rheumatism* 58(10):2968-80 (2008) ("Genovese")
Ex. 1027	"Treat," *The American Heritage Medical Dictionary* 838-39 (2007) ("AHM Dictionary")
Ex. 1028	ClinicalTrials.gov, NCT00965653, "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis," available at https://clinicaltrials.gov/ct2/show/NCT00965653 ("NCT00965653")
Ex. 1029	U.S. National Library of Medicine, National Institutes of Health, Press Release: National Institutes of Health Launches "ClinicalTrials.gov" (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html ("Feb. 29, 2000 NIH Press Release")
Ex. 1030	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *Glossary of Common Site Terms*, https://clinicaltrials.gov/ct2/about-studies/glossary (Dec. 14, 2020) ("ClinicalTrials.gov Glossary")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1031	Application for Patent Term Extension Under 35 U.S.C. § 156 to the PTO for U.S. Patent. No. 5,795,965
Ex. 1032	September 17, 2013 PTO Notice of Final Determination and Requirement for Election for U.S. Patent No. 5,795,965
Ex. 1033	Norihiro Nishimoto et al., "Toxicity, Pharmacokinetics, and Dose-Finding Study of Repetitive Treatment with the Humanized Anti-Interleukin 6 Receptor Antibody MRA in Rheumatoid Arthritis. Phase I/II Clinical Study," *The Journal of Rheumatology* 30:1426-35 (2003) ("Nishimoto 2003")
Ex. 1034	Shuji Ohta et al., "1115 Optimal Dose Prediction by Pharmacokinetic and Biomarker Response of Subcutaneous Tocilizumab Treatment – A Phase I/II Study Evaluating the Safety, Pharmacokinetics and Clinical Response in Patients with Rheumatoid Arthritis," *Arthritis & Rheumatism* 62(10 Supplement):S467-68 (2010) ("Ohta 2010")
Ex. 1035	Excerpt of Physicians' Desk Reference, 59th Edition (2005) for Humira® (adalimumab) ("2005 PDR – Humira")
Ex. 1036	"TNF Blocker Wins Approvals," *Internal Medicine News*, Vol. 42, No. 11 (2009) ("TNF Blocker Wins Approval")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1037	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *History of Changes for Study: NCT00965653*, https://clinicaltrials.gov/ct2/history/NCT00965653 (Dec. 14, 2020) ("NCT00965653 History of Changes")
Ex. 1038	U.S. National Library of Medicine ClinicalTrials.gov, NCT00965653, "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis" (August 21, 2009), available at https://clinicaltrials.gov/ct2/history/NCT00965653?V_1 ("NCT00965653 Aug. 21, 2009 Record")
Ex. 1039	U.S. National Library of Medicine ClinicalTrials.gov, NCT00965653, "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis" (September 15, 2009), available at https://clinicaltrials.gov/ct2/history/NCT00965653?V_3 ("NCT00965653 Sept. 15, 2009 Record")
Ex. 1040	U.S. National Library of Medicine ClinicalTrials.gov, NCT00965653, "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis" (October 15, 2009), available at https://clinicaltrials.gov/ct2/history/NCT00965653?V_4 ("NCT00965653 Oct. 15, 2009 Record")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1041	Ravinder N. Maini et al., "Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis," *Arthritis & Rheumatism* 41(9):1552-63 (1998) ("Maini 1998")
Ex. 1042	Edward Keystone et al., "Certolizumab Pegol Plus Methotrexate Is Significantly More Effective than Placebo Plus Methotrexate in Active Rheumatoid Arthritis," *Arthritis & Rheumatism* 58(11):3319-29 (2008) ("Keystone 2008")
Ex. 1043	E. C. Keystone et al., "Golimumab, a Human Antibody to Tumour Necrosis Factor a Given by Monthly Subcutaneous Injections, in Active Rheumatoid Arthritis Despite Methotrexate Therapy: the GO-FORWARD Study," *Annals of Rheumatic Diseases* 68:789-96 (2009) ("Keystone 2009")
Ex. 1044	Georgy et al., A Clinical Study to Assess the Pharmacokinetics and Pharmacodynamics of Tocilizumab After a Single Dose of Administration by Subcutaneous and Intravenous Routes to Healthy Subjects," Clinical Pharmacology & Therapeutics, Vol. 87 Supp. 1 (February 2010) ("Georgy")
Ex. 1045	Roche, "Investor Event at EULAR 2009," June 12, 2009 ("Roche 2009 Report")
Ex. 1046	"Overview of Development Pipeline," Chugai Pharmaceutical Co., Ltd., Tatsuro Kosaka, February 4/5, 2009 ("Chugai 2009 Report")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1047	Archived ClinicalTrials.gov Pages, *About ClinicalTrials.gov* (Oct. 13, 2018) (pg. 4), *About the ClinicalTrials.gov Results Database* (Aug. 26, 2009) (pg. 5-6), *Fact Sheet* (Sept. 2, 2009) (pgs. 7-12), with Affidavit of Elizabeth Rosenthal, Internet Archive (pgs. 1-3) ("About ClnicalTrials.gov")
Ex. 1048	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *Clinicaltrials.gov Home page*, https://clinicaltrials.gov/ (June 21, 2021) ("ClinicalTrials.gov Home Page")
Ex. 1049	Archived ClinicalTrials.gov Pages, *ClinicalTrials.gov Protocol Data Element Definitions* (Apr. 11, 2009) (pgs. 4-12), *FAQ: ClinicalTrials.gov – Submission and Review of Information* (May 11, 2009) (pgs. 13-15), with Affidavit of Duncan Hall, Internet Archive (pgs. 1-2) ("ClinicalTrials.gov Pages")
Ex. 1050	ClinicalTrials.gov, *Registering Clinical Trials with ClinicalTrials.gov*, http://prsinfo.clinicaltrials.gov/registering.pdf (Apr. 10, 2009) (pgs. 4-5), with Affidavit of Duncan Hall, Internet Archive (pgs. 1-2)
Ex. 1051	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *How to Edit Your Study Record*, https://clinicaltrials.gov/ct2/manage-recs/how-edit (Dec. 14, 2020)

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1052	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *Key Record Dates – NCT00965653*, https://clinicaltrials.govct2/keydates/NCT00965653 (Dec. 14, 2020)
Ex. 1053	U.S. National Library of Medicine, U.S. National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 21, 2009 (v1) – November 1, 2016 (v69)*, https://clinicaltrials.gov/ct2/history/NCT00965653?A=1&B=69&C=merged#StudyPageTop (Dec. 14, 2020) ("NCT00965653 Comparison of Versions")
Ex. 1054	Lawrence W. Dick et al., "Determination of the origin of the N-terminal pyro-glutamate variation in monoclonal antibodies using model peptides," *Biotechnology & Bioengineering* 97(3):544-53 (November 10, 2006) ("Dick")
Ex. 1055	Dick Chelius et al., "Formation of Pyroglutamic Acid from N-terminal glutamic acid In immunoglobulin gamma antibodies," *Analytical Chemistry* 78:2370-76 (April 1, 2006) ("Chelius")
Ex. 1056	Y. Diana Liu et al., "N-terminal glutamate to pyroglutamate conversion in vivo for human IgG2 antibodies," *J. of Biol. Chem.* 286(13):11211-17 (April 1, 2011) ("Liu")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1057	William E. Werner et al., "The removal of pyroglutamic acid from monoclonal antibodies without denaturation of the protein chains," *Analytical Biochem.* 342:120-25 (2005) ("Werner")
Ex. 1058	Alain Beck et al., "Characterization by liquid chromatography combined with mass spectrometry of monoclonal anti-IGF-1 receptor antibodies produced in CHO and NS0 cells," *J. of Chromatography B* 819:203-18 (2005) ("Beck")
Ex. 1059	G. Jones et al., "Comparison of Tocilizumab Monotherapy Versus Methotrexate Monotherapy in Patients with Moderate to Severe Rheumatoid Arthritis: The AMBITION Study," *Annals of the Rheumatic Diseases* 69:88-96 (2010) ("Jones")
Ex. 1060	Certificate of Translation (pg. 1), Translation (pgs. 2–27), & Original (pg. 28-52) of PCT International Publication No. WO2005/090405 A1 ("WO2005090405")
Ex. 1061	U.S. Patent No. 5,795,965 ("'965 patent")
Ex. 1062	Michael E. Weinblatt et al., "Adalimumab, a Fully Human Anti-Tumor Necrosis Factor α Monoclonal Antibody, for the Treatment of Rheumatoid Arthritis in Patients Taking Concomitant Methotrexate," *Arthritis & Rheumatism* 48(1):35-45 (Jan. 2003) ("Weinblatt")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1063	Eric L. Matteson, "Concise Review for Clinicians, Current Treatment Strategies for Rheumatoid Arthritis," *Mayo Clinic Proceedings* 75:69-74 (2000) ("Matteson")
Ex. 1064	Certificate of Translation (pg. 1), Translation (pgs. 2–6), & Original (pgs. 7–10) of Norihiro Nishimoto, *Anti-IL-6 Receptor Antibodies, Usefulness and Issues in Rheumatoid Arthritis*, ChiryoGaku 36(12):1264-67 (2002) ("Nishimoto 2002")
Ex. 1065	Norihiro Nishimoto et al., "A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Humanized Anti-interleukin-6 (IL-6) Receptor Monoclonal Antibody (MRA) in Rheumatoid Arthritis (RA)," *Arthritis & Rheumatism*, Vol. 46, No. 9 (Supplement):S559 (2002) ("Nishimoto Abstract")
Ex. 1066	Charles A. Janeway et al., "Antigen Recognition by B-cell and T-cell Receptors," *Immunobiology: The Immune System in Health and Disease* 93-104 (2001, 5th ed.) ("Janeway")
Ex. 1067	Pei-Show Juo, *Concise Dictionary of Biomedicine and Molecular Biology* (2002, 2nd ed.) ("Concise Dictionary of Biomedicine")
Ex. 1068	Nicolas Fischer and Olivier Léger, "Bispecific Antibodies: Molecules That Enable Novel Therapeutic," *Pathobiology* 74:3-14 (2007) ("Fischer 2007")
Ex. 1069	ACTEMRA® (tocilizumab) Prescribing Information (Jan. 2010) ("2010 FDA Actemra® Label")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1070	Alan Kivitz and Oscar G. Segurado, "HUMIRA® Pen: a novel autoinjection device for subcutaneous injection of the fully human monoclonal antibody adalimumab," *Expert Rev. Med. Devices* 4(2):109-16 (2007) ("Kivitz")
Ex. 1071	NCATS description of tocilizumab, available online at: https://gsrs.ncats.nih.gov/ginas/app/substance/fff5a4c0-d59d-4327-b2e7-7e36e4e676e1
Ex. 1072	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 21, 2009 (v1) – August 26, 2009 (v2)*, https://clinicaltrials.gov/ct2/history/NCT00965653?A=1&B=2&C=merged#StudyPageTop (July 13, 2021) ("NCT Record Comparison of Versions 1 and 2")
Ex. 1073	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 26, 2009 (v2) – September 15, 2009 (v3)*, https://clinicaltrials.gov/ct2/history/NCT00965653?A=2&B=3&C=merged#StudyPageTop (July 13, 2021) ("NCT Record Comparison of Versions 2 and 3")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1074	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, September 15, 2009 (v3) – October 15, 2009 (v4)*, https://clinicaltrials.gov/ct2/history/NCT00965653?A=3&B=4&C=merged#StudyPageTop (July 13, 2021) ("NCT Record Comparison of Versions 3 and 4")
Ex. 1075	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *History, Policies, and Laws*, https://clinicaltrials.gov/ct2/about-site/history#InternationalCommittee (July 13, 2021)
Ex. 1076	Evaluation & Licensing Division, Pharmaceutical & Food Safety Bureau; Ministry of Health, Labour and Welfare, Report on the Deliberation Results for Tocilizumab (March 6, 2008), available at https://www.pmda.go.jp/files/000153709.pdf ("March 6, 2008 Report")
Ex. 1077	U.S. National Library of Medicine, National Institutes of Health, *ClinicalTrials.gov, ClinicalTrials.gov Background*, https://www.clinicaltrials.gov/ct2/about-site/background (July 13, 2021)
Ex. 1078	Form 8-K, Abbott Laboratories (April 9, 2003) ("Abbott 8K")
Ex. 1079	FDA Approves New Therapy for Rheumatoid Arthritis, Dec. 31, 2002, www.fda.gov/bbs/topics/ANSWERS/2002/ANS01186.html, with Affidavit of Duncan Hall (Internet Archive) ("FDA Talk Paper")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1080	"Treat," *Webster's Third New International Dictionary of the English Language Unabridged* 2434-35 (2002) ("Webster's")
Ex. 1081	Products Approved for Marketing during 1998, Editorial, *Journal of Clinical Pharmacology* 39:439-441 (1999) ("1999 J. Clinical Pharm")
Ex. 1082	Excerpt of Physicians' Desk Reference, 54th Edition (2000) for Enbrel® (etanercept) ("2000 PDR Excerpt – Enbrel")
Ex. 1083	Mazumdar et al., "Golimumab," *mAbs* 1(5):422-31 (September/October 2009) ("Golimumab")
Ex. 1084	Simponi (golimumab) Package Insert (Apr. 2009) ("2009 Simponi FDA Label")
Ex. 1085	World Intellectual Property Office, WO2009041621, available at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009041621&tab=PCTDOCUMENTS
Ex. 1086	ACTEMRA® (tocilizumab) Prescribing Information (2013) ("2013 FDA Actemra® Label")
Ex. 1087	Lobo et al., Antibody Pharmacokinetics and Pharmacodynamics, *J. of Pharmaceutical Sciences*, Vol. 93, No. 11 (Nov. 2004) ("Lobo")
Ex. 1088	David Macht, The History of Intravenous and Subcutaneous Administration of Drugs, *J. of Am. Med. Assn'n*, Vol. LXVI, No. 12 (March 18, 1916) ("Macht)

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1089	Nishimoto et al., "Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab," *Ann. Rheum. Dis.*, 66; 1162-1167 (2007) ("Nishimoto 2007")
Ex. 1090	Keystone et al., "What to do with TNF failures," *Expert Opinion on Drug Safety*, 4:2, 149-115 (2005) ("Keystone 2005)
Ex. 1091	Oldfield et al., "Tocilizumab: A Review of its Use in the Management of Rheumatoid Arthritis," *Adis Drug Evaluation, Drugs 2009*, 69 (5) ("Oldfield")
Ex. 1092	Braun et al., "Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis," *Clinical and Experimental Rheumatology* 2009:27 (Supp. 55) ("Braun")
Ex. 1093	Kremer at al., "Tocilizumab Inhibits Joint Structural Damage in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate: The LITHE Study," *Arthritis & Rheumatism*, Vol. 58, No. 12 (December 2008) ("Kremer")
Ex. 1094	Guidelines for the Management of Rheumatoid Arthritis, 2002 Update, American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, *Arthritis & Rheumatism*, Vol. 46, No. 2 (February 2002) ("ACR Guidelines")

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 4, 5, and 12 of U.S. Patent No. 8,580,264 ("the '264 patent," Ex. 1001). 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 administration of a 162 mg fixed dose of tocilizumab every week or every two weeks. By November 2009, more than a year before the earliest priority date for the '264 patent, a clinical study protocol was published on ClinicalTrials.gov, a website maintained by the U.S. National Library of Medicine to provide public access to information on clinical trials. This protocol (NCT00965653) disclosed a method of treating RA by subcutaneous administration of a 162 mg fixed dose of tocilizumab every week or every two

[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.

Inc. v. Eon Labs., Inc., 616 F.3d 1267, 1274-76 (Fed. Cir. 2010). And even if the functional result recited in the "wherein" clause were not inherent, Claim 12 is nevertheless obvious because other prior art disclosed that tocilizumab inhibited structural joint damage.

Claims 4, 5, and 12 are also obvious because a person of skill in the art ("POSA") would have been motivated to administer tocilizumab subcutaneously to treat RA patients in view of successful results with intravenous (IV) tocilizumab. Tocilizumab had been approved in the United States, Japan, and Europe for the treatment of RA by IV administration, based on successful Phase III clinical trials that demonstrated that 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. It was also known by November 2010 that immunoglobulins—like tocilizumab—are preferably administered subcutaneously, as it allows 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 IV medications. A POSA would have understood that a subcutaneous fixed dose of 162 mg of tocilizumab administered every week or every other week is equivalent to the known effective IV 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).[3] This is Petitioners' first petition challenging claims 4, 5, and 12 of the '264 patent, and the Petition raises arguments that have not previously been presented to the Office.

[3] On August 18, 2021, Petitioners filed a petition seeking *inter partes* review of claims 1-3 and 6-11 of the '264 patent. IPR 2021-01288. As explained in Petitioners' Notice of Ranking, the filing of two petitions—each of which is directed to ***different*** claims—is necessitated in this case by Patent Owners' actions, and application of the *General Plastic* factors strongly favors institution. *See General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha*, IPR 2016-01357, Paper 19 at 17, 21 (PTAB Sept. 6, 2017) (precedential). Nor is there any "parallel district court proceeding" under which to deny institution pursuant to the *Fintiv*/*NHK* line of cases. *See Apple Inc. v. Fintiv Inc.*, IPR 2020-00019, Paper 11, at 5-16 (PTAB, March 20, 2020) (precedential). Under these circumstances, each of the *Fintiv* factors would necessarily favor institution.

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.

On August 18, 2021, Petitioners filed a petition seeking *inter partes* review of claims 1-3 and 6-11 of the '264 patent. *See* IPR 2021-01288. A Certificate of Correction for the '264 patent issued on August 17, 2021, just one day before Petitioners filed their petition in IPR 2021-01288. The Certificate of Correction amended the claims to add claims 4, 5, and 12 to the '264 patent, which are the

claims that are at issue in this Petition. Petitioners intend to seek consolidation of the two proceedings at the appropriate time.

On August 18, 2021, Petitioners also filed a petition seeking *inter partes* review of U.S. Patent No. 10,874,677, which claims priority to the '264 patent. *See* IPR No. 2021-01336.

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

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

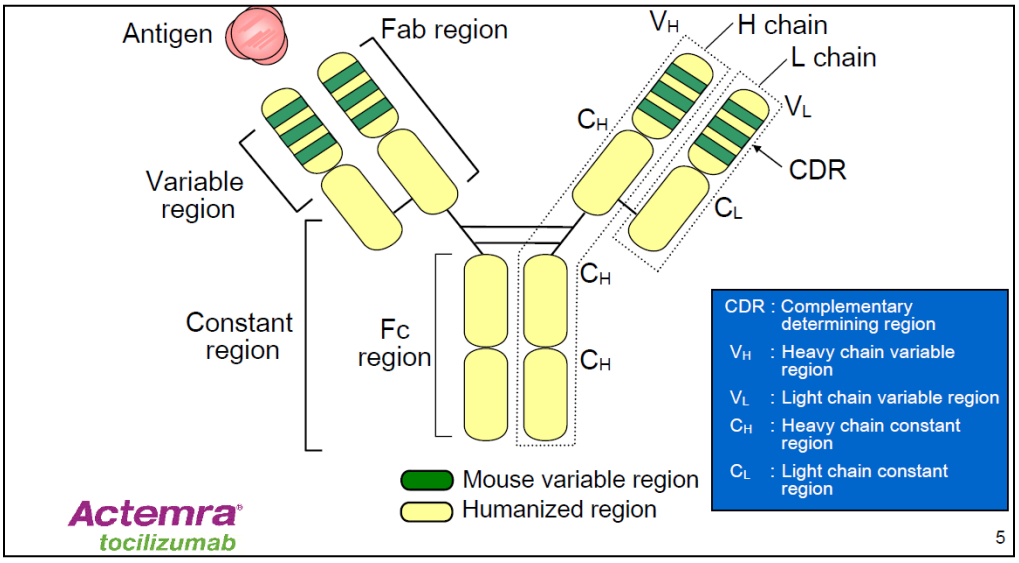
V. TECHNICAL BACKGROUND

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

Rheumatoid arthritis 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 ¶37. 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.* ¶38; Ex. 1059 (Jones) at 1; Ex. 1062 (Weinblatt) at 4. In such patients, other DMARDs were often added to the MTX regimen in order to

improve disease control. Ex. 1062 (Weinblatt) at 4; Ex. 1063 (Matteson) at 4. New drugs were accordingly sought that could be used to treat RA patients who had inadequately responded to MTX. Ex. 1002 ¶38.

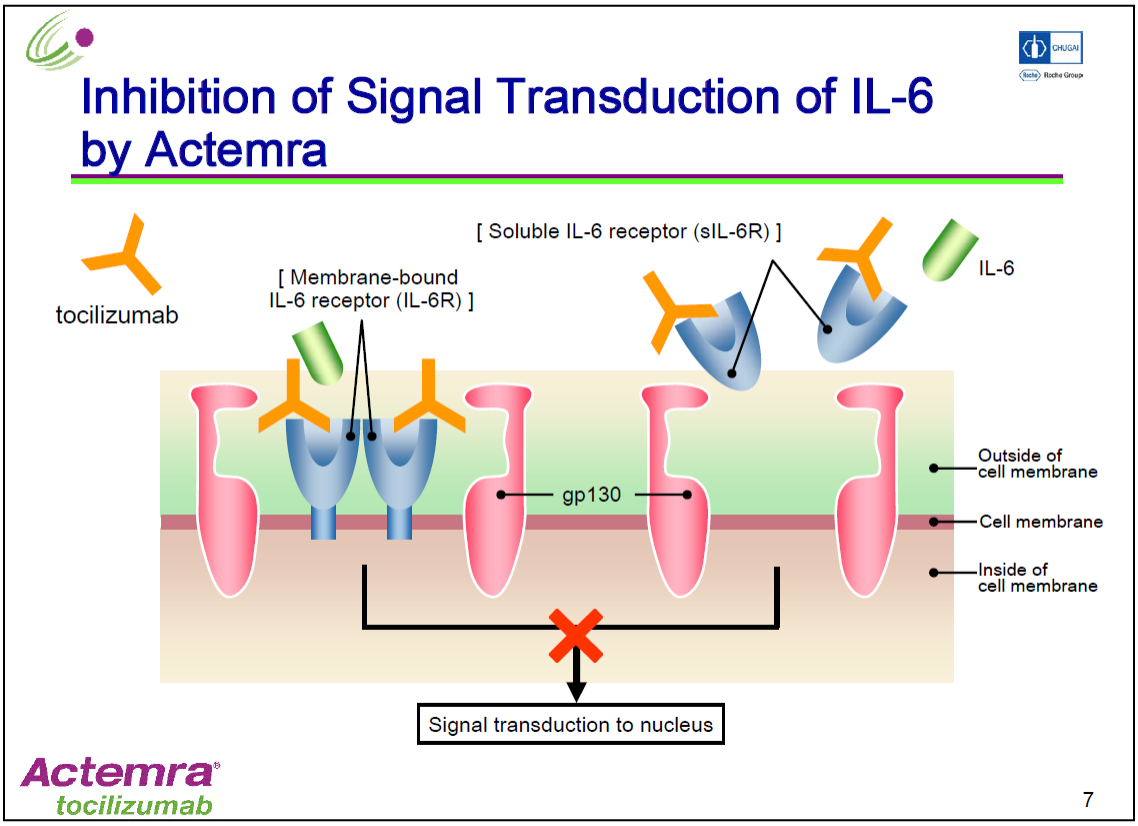
Tocilizumab, also known as MRA, is a humanized anti-IL-6 receptor monoclonal antibody of the immunoglobulin IgG1 subclass. Ex. 1025 (Maini 2006) at 3; Ex. 1003 ¶20; Ex. 1002 ¶39. Like all antibodies, it has two heavy chains and two light chains forming two antigen-binding sites. Ex. 1003 ¶20; Ex. 1002 ¶39. 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 6.

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 ¶40. Although originally intended as a treatment for

multiple myeloma, by 1995 Chugai had begun studying tocilizumab for the treatment of RA 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. *Id.* at 7. As shown 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 ¶40.

By 2009, several clinical trials had been completed that confirmed that tocilizumab was a safe and effective treatment for RA. Ex. 1002 ¶¶41-45. Maini 2006 demonstrated that tocilizumab was safe and effective for treating RA when administered intravenously at a dose of either 4 mg/kg or 8 mg/kg every four weeks in patients who had discontinued methotrexate. Ex. 1025 (Maini 2006) at 2-3, 9-10. The results of the SAMURAI clinical study, published in 2007, showed that 8 mg/kg intravenous "tocilizumab monotherapy in patients with active RA significantly inhibited the progression of structural joint damage compared with conventional DMARDs therapy." Ex. 1089 (Nishimoto 2007) at 5. Results from the LITHE study published in 2008 demonstrated that both 4 mg/kg and 8 mg/kg tocilizumab administered intravenously every four weeks "significantly inhibited the progression of structural joint damage." Ex. 1093 (Kremer) at 6. 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. Ex. 1002 ¶42; Ex. 1014 (Emery) at 5-6.

Intravenous tocilizumab was approved for the treatment of rheumatoid arthritis in Japan in 2008, and in Europe in January 2009. Ex. 1076 (March 6, 2008 Report) at 4; Ex. 1018 (PMDA 2008 Report) at 124; Ex. 1019 (EMA Assessment Report) at 11. On January 8, 2010, the U.S. Food and Drug

Administration approved intravenous tocilizumab for the treatment of RA. Ex. 1020 (BLA Approval Letter) at 1; Ex. 1069 (2010 FDA Actemra Label) at 2, 25; *see also* Ex. 1001 at 2:19-23 ("TCZ 8 mg/kg IV has been approved in over 70 countries for use in RA, including Japan and Europe. In the United States, TCZ IV (4 mg/kg and 8 mg/kg) has been approved in RA patients who have had an inadequate response to anti-TNF agents.").

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 ¶47; 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 physicians 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 ¶48; 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 ¶¶48, 61.

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 ¶48. 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 ¶48. 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.
- 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 Humira FDA label) at 7, 14, 16; Ex. 1078 (Abbott 8K) at 5; Ex. 1079 (FDA Talk Paper) at 5.
- 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.
- 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; Ex. 1084 (2009 Simponi FDA Label) at 1,4.

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 4, 5, and 12 of the '264 patent. Claims 4 and 5 depend from claim 1, and claim 12 is an independent claim. The claims are recited below, along with independent claim 1.

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 antibody is administered as a fixed [dose][4] of 162 mg per dose every week or every [two][5] weeks, and wherein the anti-IL-6R antibody comprises the

[4] The Certificate of Correction that issued on August 17, 2021 omits the word "dose" from claim 1. The original claim 1 included the word "dose." Ex. 1001 at col. 63, claim 1. Furthermore, claims 2 and 9 depend from claim 1 and still refer to "the fixed dose," which suggests that the term, "fixed," as it appears in claim 1, is intended to mean "fixed dose."

[5] The Certificate of Correction that issued on August 17, 2021 omits the word "two" from claim 1. The original claim 1 included the word "two." Ex. 1001 at col. 63, claim 1. Furthermore, claim 9 depends from claim 1, and further requires that the fixed dose is administered "every two weeks," which confirms that claim 1 must encompass administering the fixed dose every two weeks.

light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively.

4. The method of claim 1 wherein the RA patient is a TNF-inhibitor-inadequate responder.

5. The method of claim 1 wherein the RA patient is a methotrexate (MTX) naïve or has discontinued MTX.

12. A method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient comprising subcutaneously administering a fixed dose of 162 mg of tocilizumab to the patient every two weeks, wherein structural joint damage at week 24 or week 48 is found to be inhibited.

B. Prosecution History

On April 3, 2013, the Examiner rejected the then-pending claims as anticipated by Ohta 2010, an abstract published online in September 2010[6] and in print in *Arthritis & Rheumatism* in October 2010 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

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

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 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.* The Examiner concluded that Ohta 2010 anticipated the pending claims 1, 2, and 12. *Id.*

The applicant did not dispute the Examiner's reasoning or conclusions, and instead submitted a declaration 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 the three additional claims (claims 4, 5, and 12), which are at issue in this Petition.

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 ¶35. A POSA would have easily understood the prior art references referred to herein and would have had the capacity to draw inferences from them.

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

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 4 and 5)

Dependent claims 4 and 5 recite a "method of treating 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 ¶104; *Bristol-Myers Squibb Co. v. Ben Venue*

[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.

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. Indeed, the preamble at issue in *Bristol-Myers Squibb* was not limiting even though it provided antecedent basis for the "patient." *Id.* 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 ¶105; *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 ¶106. 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 at 14:46-50 (emphasis added); *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").

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 ¶107. 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 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. In short, "treatment" occurs regardless of whether it is effective.

B. "fixed dose" (claims 4 and 5)

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 at 14:64-67.

C. "TNF-inhibitor-inadequate responder" (claim 4)

A "TNF-inhibitor-inadequate responder" is defined in the specification 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." *Id.* at 14:51-54. A "TNF inhibitor" is defined as "an agent that inhibits, to some extent, a biological function of TNF-alpha, generally through binding to TNF-alpha and neutralizing its activity." *Id.* at 14:39-41. The specification states that "[e]xamples of TNF inhibitors specifically contemplated herein are etanercept (ENBREL®), infliximab (REMICADE®), and adalimumab (HUMIRA®), certolizumab pegol (CIMZIA®), and golimumab (SIMPONI®)." *Id.* at 14:41-45.

D. "a method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient" (claim 12)

The term "inhibiting progression of structural joint damage in a RA patient" is defined in the '264 patent specification to refer to "preventing or slowing structural joint damage caused by RA, for example, based on eroded joint count and/or joint damage score." *Id.* at 15:14-17. The specification states that

"[m]ethods for measuring progression of structural joint damage are known to the skilled person, and include, without limitation Genant modified Total Sharp Score (TSS), erosion score (ES), and/or joint space narrowing (JSN) score." *Id.* at 15:17-21. "[A] method for inhibiting progression of structural joint damage in a rheumatoid arthritis patient" therefore means "a method for preventing or slowing structural joint damage caused by RA," as measured by, *e.g.*, TSS, ES, or JSN. Ex. 1002 ¶110.

IX. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claims 4, 5, and 12 of the '264 patent under §§ 102 and 103 for the reasons explained in this Petition, which are summarized as follows:

Ground No	Claims and Basis
1	Claim 4 is obvious over NCT00965653 and Emery
2	Claim 4 is obvious over Ohta 2010 and Emery
3	Claim 5 is obvious over NCT00965653 and Maini 2006
4	Claim 5 is obvious over Ohta 2010 and Maini 2006
5	Claim 12 is anticipated by Ohta 2010
6	Claim 12 is obvious over Ohta 2010 and Nishimoto 2007
7	Claim 12 is obvious over NCT00965653 and Nishimoto 2007
8	Claim 4 is obvious over Emery, Bonilla, and Wang

9	Claim 5 is obvious over Maini 2006, Bonilla, and Wang
10	Claim 12 is obvious over Maini 2006, Nishimoto 2007, Bonilla, and Wang

A. Ground 1: Claim 4 Is Obvious Over NCT00965653 and Emery

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, more than one year before the earliest claimed priority date of the '264 patent. Ex. 1004 ¶¶11-32; Ex. 1002 ¶¶83-88. NCT00965653 is prior art 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

[9] During prosecution, the applicant submitted an excerpt of NCT00965653 from ClinicalTrials.gov. Ex. 1005 ('264 Patent File History) at 676-78, 909. The excerpt 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 NCT00965653 was publicly available before the filing date of the '264 patent.

discussed by either the Examiner or the applicant, and there is no evidence that the Examiner considered the arguments set forth herein.

1. NCT00965653 Was Publicly Available Before November 2009

NCT00965653 discloses the subcutaneous 162 mg tocilizumab dosage for treatment of RA recited in claim 1. *Infra* § IX.A.2. NCT00965653 is a prior art printed publication, which was available on ClinicalTrials.gov before November 2009. Ex. 1004 ¶¶11-32; Ex. 1002 ¶¶83-88. The study record 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 NCT00965653 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.

ClinicalTrials.gov provides key publication dates for each study. 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. These insignificant differences aside, the current version of 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").

[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").

2. All Elements of Claim 1 (From Which Claims 4 and 5 Depend) Are Disclosed In 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 tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate." Ex. 1028 at 2. 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 ¶112.

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 ¶113. 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." *King Pharms., Inc.*, 616 F.3d at 1275-76. The Federal Circuit explained that the patent at issue disclosed 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 the claims at issue in *King Pharms.*, the '264 patent claims are directed to the same method disclosed in 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 ¶113.

b. "subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient, wherein the antibody is administered as a fixed [dose] of 162 mg per dose every week or every [two] weeks"

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. 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 ¶¶114-115.

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

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 a 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/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 (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 ¶¶66-73.

- As explained by Dr. Levine, tocilizumab inherently has the claimed amino acid sequences for the heavy and light chains. Ex. 1003 ¶¶42-56.

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. *See generally* Ex. 1003; Ex. 1002 ¶¶116-121. Thus, NCT00965653 discloses all elements of claim 1.

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

3. Claim 4 Is Obvious Over NCT00965653 and Emery

Claim 4 is directed to the method of claim 1, "wherein the RA patient is a TNF-inhibitor-inadequate responder." As discussed above, NCT00965653 discloses a method of treating RA comprising subcutaneously administering a fixed dose of 162 mg tocilizumab every week or every other week to an RA patient that meets each and every limitation of claim 1. The only difference between NCT00965653 and claim 4 is that NCT00965653 does not specifically disclose that the RA patient to whom the regimen is administered is a TNF-inhibitor-inadequate responder.

Emery was published in 2008 and is prior art under pre-AIA § 102(b). Ex. 1014. Emery discloses results of the "phase III RADIATE study [that] examined the efficacy and safety of tocilizumab … in patients with rheumatoid arthritis (RA) refractory to tumour necrosis factor (TNF) antagonist therapy." *Id.* at 3. "499 patients with inadequate response to one or more TNF antagonists were randomly assigned to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo (control) intravenously every 4 weeks with stable methotrexate for 24 weeks," and "[n]inety-five per cent of previous TNF antagonist failures were due to inadequate

efficacy."[12] *Id.* Treated patients had previously received either adalimumab, etanercept, or infliximab, all of which are TNF antagonists or "TNF-inhibitors," as that term is defined in the '264 patent. *Id.* at 6. Emery discloses that tocilizumab was safe and effective in treating patients who did not adequately respond to previous therapy with a TNF-inhibitor, concluding 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, regardless of the number of previous failed agents." *Id.* at 9.

A POSA would have been motivated to combine NCT00965653 and Emery, and apply the subcutaneous tocilizumab regimen disclosed in NCT00965653 to treat "TNF-inhibitor-inadequate responders." Before Emery was published, it was well known that many RA patients did not respond to TNF-inhibitors, which had in part prompted the development of additional therapeutic agents for treatment of RA, including tocilizumab. Ex. 1002 ¶131; Ex. 1090 (Keystone) at 3. Based on

[12] This subset of patients are "TNF-inhibitor-inadequate responders," as that term is defined in the '264 patent, i.e., they experienced an inadequate response to previous or current treatment with one or more TNF inhibitors because of toxicity or inadequate efficacy." Ex. 1002 ¶132.

the successful results published in Emery with intravenous tocilizumab, a POSA would have been motivated to treat "TNF-inhibitor-inadequate responders" with tocilizumab. Ex. 1002 ¶¶131-135. And a POSA would have been motivated to administer tocilizumab subcutaneously, as disclosed in NCT00965653, because it offers significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered therapy. *Id.* ¶136. Indeed, the prior art taught that tocilizumab was preferably administered subcutaneously. Ex. 1011 (WO '621) at 4 (tocilizumab's "preferred form of administration in chronic autoimmune diseases is thought to be subcutaneous formulation"). The resulting method would have met each and every limitation of claim 4. Ex. 1002 ¶144.

A POSA would have reasonably expected administration of the 162 mg fixed dose of tocilizumab every week or every two weeks disclosed by NCT00965653 to be successful in treating RA patients that had previously failed prior treatment with TNF-inhibitors. Ex. 1002 ¶139. The prior art makes clear that an intravenously-administered antibody is at least as safe and effective if instead administered at an equivalent amount subcutaneously. *Id.*; Ex. 1021 (Bonilla) at 15 (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"). Therefore, a POSA would have reasonably expected that a

subcutaneous dose equivalent to the 4 mg/kg and 8 mg/kg every four week IV doses Emery had demonstrated were safe and effective would be similarly safe and effective. Ex. 1002 ¶139.

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 the intravenous dose. Ex. 1002 ¶140; 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 ¶140. 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 ¶140; 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 ¶140; 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 ¶140.

A POSA would have known that, for a typical 70 kg patient, the 4 mg/kg and 8 mg/kg every four week regimens amounts to a total of 140 mg every other week or every week, respectively, and therefore would have understood that the equivalent subcutaneous dose would be somewhere between this amount and up to about 39% higher, or approximately 195 mg. Ex. 1002 ¶¶141-142; Ex. 1016 (Berger) at 6-7. Because 162 mg falls squarely within this range, a POSA would have reasonably expected 162 mg tocilizumab administered subcutaneously every other week or every week to be safe and effective for treating RA. Ex. 1002 ¶¶141-142.

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 ¶143. The prior art taught that large differences in AUC for tocilizumab "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 a 162 mg fixed dose of

tocilizumab, administered subcutaneously every week or every other week would be safe and effective notwithstanding weight-based differences in tocilizumab clearance rate. Ex. 1002 ¶143.

Claim 4 is therefore obvious over NCT00965653 and Emery.

B. Ground 2: Claim 4 Is Obvious Over Ohta 2010 and Emery

Ohta 2010 is an abstract published online in September 2010 and in print in *Arthritis and Rheumatism* in October 2010, and is prior art under pre-AIA § 102(a). Ex. 1034; *see supra* n.6. Like NCT00965653, Ohta 2010 discloses administering a 162 mg subcutaneous fixed dose of tocilizumab every week or every other week to treat RA patients, as recited in claim 1. *Infra* IX.B.1. 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 a declaration alleging prior invention; however, as explained *infra* § X.B, the Examiner erred in finding that the declaration established prior inventorship.

1. All Elements of Claim 1 (From Which Claims 4 and 5 Depend) Are Disclosed In Ohta 2010

a. "[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 limiting, it is disclosed in Ohta 2010, which describes a Phase I/II study to "evaluate the safety,

pharmacokinetics, and efficacy of tocilizumab subcutaneous injection" in patients with rheumatoid arthritis. Ex. 1034 (Ohta 2010) at 2-3; Ex. 1002 ¶124. 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 ¶125.

b. "subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody, wherein the antibody is administered as a fixed dose of 162 mg per dose every week or every two weeks"

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. 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 ¶¶126-127.

c. "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 forth above with respect to NCT00965653 (*supra* §

IX.A.2.c), 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. S*ee also* Ex. 1002 ¶128; *see generally* Ex. 1003.

2. Claim 4 Is Obvious Over Ohta 2010 and Emery

As discussed above, Ohta 2010 discloses a method of treating RA comprising subcutaneously administering a fixed dose of 162 mg tocilizumab every week or every other week to an RA patient, that meets each and every limitation of claim 1. The only difference between Ohta 2010 and claim 4 is that Ohta 2010 does not specifically disclose that the RA patient to whom the regimen is administered is a TNF-inhibitor-inadequate responder.

Emery discloses that administration of tocilizumab to patients who did not respond to previous therapy with a "TNF-inhibitor" is safe and effective for treating RA. *Supra* § IX.A.3. A POSA would have been motivated to combine Ohta 2010 and Emery, and subcutaneously administer a 162 mg fixed dose of tocilizumab every week or every two weeks, as disclosed by Ohta 2010, to treat "TNF-inhibitor-inadequate responders," whom Emery taught could be treated with tocilizumab. Ohta 2010 itself discloses that a 162 mg subcutaneous dose of tocilizumab was safe and effective in treating RA. Ex. 1002 ¶145. And Emery discloses that patients that did not respond to TNF-inhibitors could be effectively treated with tocilizumab. *Id.* ¶146. Moreover, as further motivation, a POSA

would have known that subcutaneous administration offers significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered therapy. *Id.* ¶148.

A POSA would also have reasonably expected the resulting method to be successful in treating RA. As discussed with respect to Ground 1, a POSA would have expected that subcutaneously administering a 162 mg fixed dose of tocilizumab every week or every other week would be as safe and effective as the intravenous regimens disclosed by Emery. *Supra* § IX.A.3. Furthermore, Ohta 2010 confirmed that 162 mg subcutaneous tocilizumab was "well tolerated" and "associated with a good clinical response" in RA patients, and in fact disclosed ACR responses that were higher than those reported in Emery for its intravenous regimens. Ex. 1002 ¶¶147, 149. Emery also discloses that tocilizumab, unlike TNF-inhibitors, directly inhibits IL-6 signaling to effectively treat RA. Ex. 1014 (Emery) at 8. A POSA would have known that the same mechanism would apply for subcutaneously administered tocilizumab, and therefore would have expected that tocilizumab would effectively treat RA patients who had inadequately responded to TNF-inhibitors, whether administered subcutaneously or intravenously. Ex. 1002 ¶149. A POSA would therefore have reasonably expected that the subcutaneous 162 mg fixed dose of tocilizumab administered every week

or every two weeks would be safe and effective to treat RA patients who had previously failed treatment with TNF-inhibitors. *Id.* ¶150. Claim 4 is therefore obvious over Ohta 2010 and Emery.

C. Ground 3: Claim 5 Is Obvious Over NCT00965653 and Maini 2006

Claim 5 is directed to the method of claim 1, "wherein the RA patient is a methotrexate (MTX) naïve or has discontinued MTX." As set forth above, NCT00965653 discloses all elements of claim 1. *Supra* § IX.A.2. The only difference between NCT00965653 and claim 5 is that NCT00965653 does not specifically disclose that the RA patient to whom the regimen is administered is methotrexate naïve or has discontinued methotrexate.

Maini 2006 was published in 2006, and is prior art under pre-AIA § 102(b). Ex. 1025. Maini 2006 discloses results from a clinical trial in which "[t]ocilizumab was used either as monotherapy (***by discontinuation of MTX***) or concomitantly with MTX therapy." *Id.* at 3 (emphasis added). Maini 2006 reported that intravenous administration of 4 mg/kg or 8 mg/kg tocilizumab every four weeks was safe and effective for treating RA patients that had discontinued methotrexate. Ex. 1002 ¶154; Ex. 1025 at 6, 12-13.

A POSA would have been motivated to combine NCT00965653 and Maini 2006, and thereby use the subcutaneous tocilizumab regimen disclosed in NCT00965653 to treat patients whom had discontinued MTX treatment because

Maini 2006 discloses that patients who had discontinued MTX were effectively treated with intravenous tocilizumab as a monotherapy, and a POSA would have understood that subcutaneous administration would be preferable to intravenous administration. Ex. 1002 ¶155. Although NCT00965653 discloses administering methotrexate concomitantly with tocilizumab, a POSA would have understood from Maini 2006 that tocilizumab could be administered as a monotherapy instead. *Id.*

A POSA would have reasonably expected the resulting method to be successful in treating RA in patients whom had had discontinued methotrexate treatment. As discussed above, a POSA would have understood that an intravenously-administered antibody would be at least as safe and effective if instead administered at an equivalent amount subcutaneously. *Supra* § IX.A.3. Therefore, a POSA would have reasonably expected that safety and efficacy would be maintained when using a subcutaneous dose equivalent to a known IV dose. Ex. 1002 ¶156. And, as explained above, 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 a 4 mg/kg and 8 mg/kg every four week IV regimen, which Maini 2006 disclosed was safe and efficacious when administered to patients whom had discontinued methotrexate. *Supra* § IX.C. Claim 5 is therefore obvious over NCT00965653 and Maini 2006.

D. Ground 4: Claim 5 Is Obvious Over Ohta 2010 and Maini 2006

As set forth above, Ohta 2010 discloses all elements of claim 1. *Supra* § IX.B.1. The only difference between Ohta 2010 and claim 5 is that Ohta 2010 does not specifically disclose that the RA patient to whom the regimen is administered is methotrexate naïve or has discontinued methotrexate.

A POSA would have been motivated to combine Ohta 2010 and Maini 2006, and use the subcutaneous tocilizumab regimen disclosed in Ohta 2010 (i.e., a fixed dose of 162 mg tocilizumab administered weekly or every other week) to treat patients who had discontinued MTX treatment because Maini 2006 discloses that patients whom had discontinued MTX were effectively treated with intravenous tocilizumab, and a POSA would have understood that subcutaneous administration would be preferable to intravenous administration. Ex. 1002 ¶161.

A POSA would have reasonably expected the resulting method to be successful in treating RA. Ohta 2010 teaches that a fixed dose of 162 mg subcutaneous tocilizumab administered weekly or every two weeks was "well tolerated" and "associated with a good clinical response." Ex. 1034 (Ohta 2010) at 2-3. Maini 2006 discloses that intravenous tocilizumab at 4 mg/kg or 8 mg/kg every four weeks was safe and effective in treating RA patients who had discontinued MTX. Ex. 1025 (Maini 2006) at 1, 5. A POSA would have reasonably expected that the 162 mg subcutaneous dose would also be effective in

treating RA patients who had discontinued MTX because it would have been known to be equivalent to the known IV doses. Ex. 1002 ¶162. Claim 5 is therefore obvious over Ohta 2010 and Maini 2006.

E. Ground 5: Claim 12 Is Anticipated By Ohta 2010

1. "a method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient"

Ohta 2010 describes a clinical study to "evaluate the safety, pharmacokinetics and efficacy of tocilizumab subcutaneous injection" administered as a fixed dose of 162 mg weekly and every other week in RA patients. Ex. 1034 (Ohta 2010) at 3. Ohta 2010 concludes that "[t]ocilizumab subcutaneous injection is well tolerated up to 162 mg QW and is associated with good clinical response [at] both 162 mg Q2W and QW." *Id.* A POSA would have understood that RA causes structural joint damage, and that an "ultimate goal" of treating RA patients is to prevent or slow structural joint damage caused by RA. Ex. 1094 (ACR Guidelines) at 1; Ex. 1002 ¶166. As discussed in section IX.E.3, *infra*, the 162 mg fixed dose every two week regimen disclosed in Ohta 2010 "inhibit[s] progression of structural joint damage in a rheumatoid arthritis patient." Therefore, this limitation is disclosed by Ohta 2010. Ex. 1002 ¶¶165-166.

2. "subcutaneously administering a fixed dose of 162 mg of tocilizumab to the patient every two weeks"

Ohta 2010 discloses subcutaneously administering a fixed dose of 162 mg of tocilizumab to a patient every two weeks. *Supra* § IX.B.1; Ex. 1002 ¶167.

3. "wherein structural joint damage at week 24 or week 48 is found to be inhibited"

This functional limitation is an inherent result of the 162 mg every two week tocilizumab regimen disclosed in Ohta 2010. Ex. 1002 ¶¶168-173. "To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *King Pharm.*, 616 F.3d at 1276. The '264 patent merely provides a prophetic example (*see* Example 3) with no actual results in which structural damage at week 24 or 48 was found to be inhibited. Ex. 1002 ¶169. The patent nevertheless states that "treatment with SC anti-IL-6R antibody TCZ) ***can inhibit progression*** of structural joint damage at week 24 and week 48." Ex. 1001 at 38:22-24 (emphasis added). The '264 patent provides no disclosure concerning how to inhibit structural joint damage at week 24 or week 48 beyond administering the claimed regimen of subcutaneously administering a fixed dose of 162 mg of tocilizumab every two weeks, the same regimen disclosed in Ohta 2010. Ex. 1002 ¶171. Therefore, like the bioavailability limitation deemed inherent by the Federal Circuit in *King Pharm.*, the functional result limitation of claim 12 merely reflects the "natural result" of administering the claimed regimen, and is inherently disclosed by Ohta 2010's disclosure of the same regimen. Accordingly, Ohta 2010

discloses and enables each and every limitation of claim 12, and therefore anticipates that claim. Ex. 1002 ¶¶164-174.

F. Ground 6: Claim 12 Is Obvious Over Ohta 2010 and Nishimoto 2007

Claim 12 is also obvious over Ohta 2010 and Nishimoto 2007. The only difference between claim 12 and Ohta 2010 is that Ohta 2010 does not expressly indicate that structural joint damage at week 24 or week 48 is found to be inhibited. This limitation is inherent in the disclosure of Ohta 2010 because it is the natural result of administering the claimed regimen. *Supra* § IX.E.3. Even if the functional limitation were not an inherent result of the claimed regimen, claim 12 would nevertheless have been obvious. *See* Ex. 1002 ¶175.

Nishimoto 2007 published in 2007, and is prior art under pre-AIA § 102(b). Ex. 1089. Nishimoto 2007 discloses that tocilizumab inhibits progression of structural joint damage in patients with RA, an "important therapeutic endpoint[]." *Id.* at 1. Patients were treated with 8 mg/kg tocilizumab intravenously every 4 weeks for 52 weeks. *Id.* The treatment "was generally well tolerated and provided radiographic benefit in patients with RA." *Id.* Nishimoto 2007 discloses that radiographic scores, including the Total Sharp Score (TSS), erosion score, and Joint space narrowing score, were found to increase to a lesser extent at week 28 and week 52 relative to those patients that did not receive tocilizumab,

demonstrating that treating RA patients with tocilizumab successfully inhibits structural joint damage by week 48. *Id.* at 3; Ex. 1002 ¶176.

A POSA would have been motivated to combine Ohta 2010 and Nishimoto 2007 and subcutaneously administer a fixed dose of 162 mg of tocilizumab to RA patients every two weeks, and to find structural joint damage to be inhibited between weeks 28 and 52, including at week 48.[13] As discussed above, a POSA would have considered subcutaneous administration of tocilizumab to be preferable to intravenous administration, and Nishimoto 2007 identifies inhibition of structural joint damage as an important goal of RA treatment. Ex. 1002 ¶177.

A POSA would also have reasonably expected the resulting method to be successful. Ohta 2010 teaches that 162 mg subcutaneous tocilizumab administered every two weeks was "well tolerated" and "associated with good clinical response," and Nishimoto 2007 discloses that tocilizumab successfully inhibited structural joint damage by week 48. Ex. 1002 ¶178. Furthermore, a POSA would have been aware that the prior art also disclosed that an intravenous dose of 4 mg/kg administered every four weeks—which, as discussed above, a POSA would

[13] Week 48 falls within the prior art range of weeks 28 to 52, and there is no evidence that the particularly claimed week is critical. *See E.I. DuPont de NeNemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018).

have recognized as equivalent to a 162 mg every two week regimen—inhibited progression of structural joint damage to a similar extent as Nishimoto's 8 mg/kg regimen. *Id.*; Ex. 1093 (Kremer) at 6. A POSA therefore would have reasonably expected that a 162 mg fixed dose of tocilizumab administered subcutaneously every two weeks to an RA patient would allow inhibition of structural joint damage to be found at week 48. Ex. 1002 ¶¶178-180.

Accordingly, claim 12 is obvious over Ohta 2010 and Nishimoto 2007.

G. Ground 7: Claim 12 Is Obvious Over NCT00965653 and Nishimoto 2007

As set forth above, NCT00965653 discloses administration of a 162 mg subcutaneous fixed dose of tocilizumab every two weeks to treat RA patients. *Supra* § IX.A.2. The only difference between claim 12 and NCT00965653 is that NCT00965653 does not expressly indicate that structural joint damage at week 24 or week 48 is found to be inhibited.

A POSA would have been motivated to combine NCT00965653 and Nishimoto 2007, and thereby administer a 162 mg fixed dose of tocilizumab every two weeks and find structural joint damage to be inhibited at week 24 or 48. Ex. 1002 ¶¶182-185. A POSA would have known that subcutaneous administration of tocilizumab (as disclosed in NCT00965653) offers significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered therapy. *Supra* § IX.A.3.

And, Nishimoto 2007 discloses the importance of finding structural joint damage to be inhibited between weeks 28 and 52 when treating RA patients, which includes week 48. Ex. 1089 (Nishimoto 2007) at 1; *see E.I. DuPont*, 904 F.3d at 1006.

A POSA would also have reasonably expected the resulting method to be successful. Ex. 1002 ¶¶186-188. As explained above, a POSA would have understood that the subcutaneous fixed dose of 162 mg every other week regimen disclosed by NCT00965653 was equivalent to the known effective 4 mg/kg every four week IV dose, and therefore would have expected it too would safely and effective treat RA. *Supra* § IX.A.3. Also, as discussed above, Nishimoto 2007 disclosed that progression of structural joint damage was found to be inhibited by week 48, and a POSA would have known that a 4 mg/kg every four week regimen inhibited progression of structural joint damage to a similar extent as the 8 mg/kg regimen disclosed by Nishimoto, and so would have expected the same for a 162 mg fixed dose every two week regimen. Ex. 1002 ¶¶186-188. Claim 12 is therefore obvious over NCT00965653 and Nishimoto 2007.

H. Grounds 8, 9, and 10: Claims 4, 5, and 12 Are Obvious Over Emery, Maini 2006, and Nishimoto 2007, Respectively, in View of Bonilla and Wang

Emery discloses that intravenous tocilizumab administered at doses of 4 and 8 mg/kg every four weeks was safe and effective for treating RA in patients who

had previously failed treatment with TNF-inhibitors. Ex. 1014 at 3. Maini 2006 discloses that RA patients whom had discontinued methotrexate were effectively treated with intravenous 4 or 8 mg/kg every four weeks of tocilizumab. Ex. 1025 at 2. The only difference between claims 4 and 5 of the '264 patent and Emery and Maini 2006, respectively, is that the claims recite a subcutaneous fixed dose of 162 mg for tocilizumab administered every week or every other week, whereas the prior art disclose an intravenous dose of tocilizumab of 4 mg/kg to 8 mg/kg administered every four weeks. As explained below, a POSA would have been motivated to combine Emery or Maini 2006 with Bonilla and Wang to arrive at the methods of claims 4 and 5 with a reasonable expectation of success.

Claim 12 is directed to the same 162 mg every other week subcutaneous fixed dose regimen, and further requires that structural joint damage is found to be inhibited at weeks 24 or 48, a result that is disclosed by Nishimoto 2007. Ex. 1089 (Nishimoto 2007) at 3. A POSA would have been further motivated to combine Maini 2006 and Nishimoto 2007 with Bonilla and Wang to arrive at this method with a reasonable expectation of success for the reasons set forth below.

Bonilla was published in a printed publication as of 2008, and is prior art under pre-AIA § 102(b). Ex. 1021. Bonilla discloses that it is preferable to administer an equivalent amount of an immunoglobulin as a subcutaneous dose every week or every two weeks rather than an IV dose every four weeks because it

reduces serum concentration fluctuation around the same mean. Ex. 1021 (Bonilla) at 15. Bonilla 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.

Wang was published in September 2009, and is prior art under pre-AIA § 102(b). Ex. 1022. 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 "[w]hen a drug has a wide therapeutic window, an AUC difference more than ±20% may still be tolerated without additional safety issues." *Id.* at 17.

A POSA would have been motivated to combine the teachings of Emery or Maini 2006 with Bonilla and Wang to administer tocilizumab subcutaneously as a 162 mg fixed dose every other week to treat an RA patient who is a TNF-inhibitor-inadequate responder and had discontinued methotrexate, respectively. Ex. 1002 ¶¶ 190-202. Emery and Maini 2006 disclose that intravenous tocilizumab at 4 mg/kg and 8 mg/kg every four weeks was safe and effective for treating RA in these patient populations, respectively. Ex. 1014 (Emery) at 3; Ex. 1025 (Maini 2006) at 2-3. A POSA would have been motivated to substitute an equivalent every other week subcutaneous dose for these IV doses because Bonilla taught that antibodies were preferably administered subcutaneously every two weeks rather than intravenously every four weeks. Ex. 1002 ¶194. This was consistent with other prior art disclosures 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 ¶195; Ex. 1016 (Berger) at 12-13; Ex. 1070 (Kivitz) at 2; Ex. 1017 (Ochs) at 7. Indeed, Chugai had itself announced that subcutaneous was the "preferred" form of tocilizumab. Ex. 1011 (WO '621) at 4.

To determine an equivalent subcutaneous dosing regimen based on the Maini 2006 and Emery tocilizumab regimens, a POSA would have looked to Bonilla and Wang. Ex. 1002 ¶¶193. 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 to 8 mg/kg, despite the AUC for the 8 mg/kg dose being more than double the AUC of the 4 mg/kg dose. Ex. 1025 (Maini 2006) at 2; Ex. 1033 (Nishimoto 2003) at 7. It was also known 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 ¶197. 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 ¶197.

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.* ¶198. As discussed in section IX.A.3, *supra*, a POSA would have understood from Bonilla that the equivalent amount of an antibody administered subcutaneously would be somewhere between 100% and 139% of the intravenous dose. Ex. 1002

¶198. 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 ¶199. Thus, 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 every other week. *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"). By applying the teachings of Bonilla and Wang to Emery or Maini 2006, a POSA would have arrived at a method of treating RA comprising administering tocilizumab subcutaneously at a fixed dose of 162 mg every week or every other week. Ex. 1002 ¶¶197-201.

A POSA would have reasonably expected a 162 mg fixed subcutaneous dose of tocilizumab every other week to be successful for treating TNF-inhibitor-

[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.

inadequate responders and patients who had discontinued methotrexate at least because Emery and Maini 2006 taught that 4 mg/kg of tocilizumab administered by IV every four weeks was a safe and effective dose for such patients, and Bonilla taught that an equivalent subcutaneous dose would provide equivalent results. Ex. 1002 ¶201. 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, and 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).

A POSA would also 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 ¶200. 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 ¶200.

Moreover, several IgG antibodies and other biologics 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 ¶202.

1. Ground 8: Claim 4 Is Obvious Over Emery in View of Bonilla and Wang

Claim 4 is directed to "the method of claim 1 wherein the RA patient is a TNF-inhibitor-inadequate responder." For the reasons set forth above, a POSA would have been motivated to combine Emery with Bonilla and Wang, and thereby administer tocilizumab subcutaneously at a fixed dose of 162 mg every other week to an RA patient who was a TNF-inhibitor-inadequate responder, with a reasonable expectation of success. This method would have met each and every limitation of claim 4.[15] *Supra* § IX.H. Hence, claim 4 is obvious over Emery in view of Bonilla and Wang. Ex. 1002 ¶¶189-205.

[15] 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. *Supra* § IX.A.2.

2. Ground 9: Claim 5 Is Obvious Over Maini 2006, Bonilla and Wang

Claim 5 is directed to "the method of claim 1 wherein the RA patient is a methotrexate (MTX) naïve or has discontinued MTX." For the reasons set forth above, a POSA would have been motivated to combine Maini 2006 with Bonilla and Wang, and thereby administer tocilizumab subcutaneously at a fixed dose of 162 mg every other week to an RA patient who had discontinued methotrexate, with a reasonable expectation of success. *Supra* § IX.H. This method would have met each and every limitation of claim 5. Hence, claim 5 is obvious over Maini 2006 in view of Bonilla and Wang. Ex. 1002 ¶¶189-202, 206-208.

3. Ground 10: Claim 12 Is Obvious Over Maini 2006, Nishimoto 2007, Bonilla and Wang

Claim 12 is directed to a "method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient comprising subcutaneously administering a fixed dose of 162 mg of tocilizumab to the patient every two weeks, wherein structural joint damage at week 24 or week 48 is found to be inhibited." As discussed above, a POSA would have been motivated to combine Maini 2006 with Bonilla and Wang, and subcutaneously administer a fixed dose of 162 mg every other week to treat an RA patient. *Supra* § IX.H.

Nishimoto 2007 discloses that inhibiting structural joint damage is an "important therapeutic endpoint" in treating RA patients, and that administration of

tocilizumab results in such inhibition beginning as early as week 28 and through at least week 52, which means that such inhibition would be found at week 48. Ex. 1002 ¶¶210-211. A POSA would therefore have been motivated to combine Nishimoto 2007 and Maini 2006 with Bonilla and Wang to administer a fixed dose of 162 mg every other week to treat an RA patient (for the reasons set forth above) and to also find structural joint inhibition at week 48. *Id.* Week 48 falls within the prior art range of weeks 28 to 52, and there is no evidence that the particular week within this range at which structural joint inhibition is found is critical. *See E.I. DuPont*, 904 F.3d at 1006.

A POSA would also have expected this regimen to be successful. As discussed with respect to Ground 9, above, a subcutaneous fixed dose of 162 mg tocilizumab administered every other week would have been expected to be safe and effective. *Supra* § IX.H. A POSA would also have reasonably expected structural joint damage to be found at week 48. Nishimoto 2007 discloses that tocilizumab successfully inhibited structural joint damage by week 48, and a POSA would have known that an intravenous dose of 4 mg/kg administered every four weeks—which, as discussed above, a POSA would have recognized as equivalent to a 162 mg every two week regimen—inhibited progression of structural joint damage to a similar extent as Nishimoto's 8 mg/kg regimen. Ex. 1002 ¶¶212-213; Ex. 1093 (Kremer) at 6. A POSA therefore would have

A. Grounds 1, 3, and 7

With regards to Grounds 1, 3, and 7, Petitioners rely on NCT00965653, which discloses treating patients with subcutaneous fixed dose of 162 mg to treat RA. Although NCT00965653 was disclosed on an IDS during prosecution, it was never substantively evaluated by the Examiner. *Supra* § IX.A. Mere inclusion of a reference on an IDS does not mean that it was involved or evaluated during prosecution. *See Digital Check Corp. v. E-ImageData Corp.*, IPR 2017-00178, Paper 6, at 12-13 (PTAB April 25, 2017). Even more critically, the excerpt provided by Applicant omitted the "First Posted" date of August 25, 2009 (*see supra* n.9), 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.1. Factors (a) and (b) therefore favor institution.

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.*, IPR 2017-00178, Paper 6, at 12-13.

Factors (e) and (f) also strongly support institution. The Examiner's failure to appreciate that a reference was publicly available that discloses the claimed 162 mg subcutaneous tocilizumab dose reflects a plain error in evaluating the prior art (factor (e)) and the arguments set forth in Petitioners' Grounds 1, 3, and 7 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 934522, at *5-6 (PTAB Feb. 15, 2018).

B. Grounds 2, 4, 5, and 6

Grounds 2, 4, 5, and 6 assert that claims 4, 5, and 12 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 the rejections by submitting an inventor declaration alleging prior invention. As explained below, the declaration does not establish a prior invention date.

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 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, 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.").

The Examiner erred in finding that the declaration established prior inventorship, and therefore discretionary denial of institution is inappropriate for Grounds 2, 4, 5, and 6 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. Grounds 8, 9, and 10

Grounds 8, 9, and 10 assert that claims 4, 5, and 12 of the '264 patent are obvious in view of Bonilla and Wang. Neither reference was before the Examiner during prosecution of the '264 patent, much less cited as a basis for a rejection. 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.[17] Moreover, the

[17] As discussed in § X.B, *supra*, the Examiner erred in finding that the inventors had antedated Ohta 2010.

Examiner did not have the benefit of Bonilla or Wang (or any similar prior art) which disclose advantages of subcutaneous administration and would have provided motivation to use a fixed subcutaneous dose in view of the effective intravenous dosages. *Supra* § IX.H. 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 Bonilla and Wang, relied upon by Petitioners for Grounds 3, 6, and 10, were not before the Examiner.

***

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 request that trial be instituted and the challenged claims cancelled.

Dated: September 24, 2021

Respectfully submitted,

By: /*Elizabeth J. Holland*/

Elizabeth J. Holland (Reg. No. 47,657)
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018

T: (212) 459 7236
Fax: (212) 658 9563
eholland@goodwinlaw.com

Counsel for Petitioners

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 13,680 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: September 24, 2021

By: */Elizabeth J. Holland/*

Elizabeth J. Holland (Reg. No. 47,657)
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
T: (212) 459 7236
Fax: (212) 658 9563
eholland@goodwinlaw.com

Counsel for Petitioners

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, September 24, 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: September 24, 2021

By: */Elizabeth J. Holland/*

Elizabeth J. Holland (Reg. No. 47,657)
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
T: (212) 459 7236
Fax: (212) 658 9563
eholland@goodwinlaw.com

Counsel for Petitioners