UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

CHUGAI SEIYAKU KABUSHIKI KAISHA and HOFFMANN-LA ROCHE INC.
Patent Owners

IPR2021-01336

Patent No. 10,874,677

Title: SUBCUTANEOUSLY ADMINISTERED ANTI-IL-6 RECEPTOR ANTIBODY

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,874,677

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TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

Page

TABLE OF AUTHORITIES

Page(s)

Cases

LIST OF EXHIBITS

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1001	U.S. Patent No. 8,580,264 ("the '264 patent")
Ex. 1002	Declaration of Thomas M. Zizic, M.D. ("Zizic Decl.")
Ex. 1003	Declaration of Howard L. Levine, Ph.D. ("Levine Decl.")
Ex. 1004	Declaration of Robert Paarlberg ("Paarlberg Decl.")
Ex. 1005	Prosecution File History of U.S. Patent No. 8,580,264 ("'264 Patent File History")[1]
Ex. 1006	U.S. Patent No. 10,874,677 ("the '677 Patent")
Ex. 1007	Prosecution File History of U.S. Patent No. 10,874,677 ("'677 Patent File History)
Ex. 1008	Curriculum Vitae of Thomas M. Zizic, M.D.
Ex. 1009	Curriculum Vitae of Howard L. Levine, Ph.D.
Ex. 1010	Curriculum Vitae of Robert Paarlberg
Ex. 1011	Certificate of Translation (pg. 1), Translation (pgs. 2-183) & Original (pgs. 184-364): PCT International Publication No. WO2009/041621 A1 ("WO '621")

[1] Ex. 1005 is a copy of the certified file history for the '264 patent. This copy, however, does not include correspondence in 2021 relating to a Certificate of Correction (which issued on August 17, 2021).

FRESENIUS EXHIBIT NO.	DESCRIPTION
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")
Ex. 1018	Pharmaceuticals and Medicals Devices Agency of Japan, Annual Report FY 2008, https://www.pmda.go.jp/files/000232775.pdf ("PMDA 2008 Report")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1019	Archived European Medicines Agency, Assessment Report for Ro-Actemra (Jul. 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")
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")

FRESENIUS EXHIBIT NO.	DESCRIPTION
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")
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. Pat. No. 5,795,965

FRESENIUS EXHIBIT NO.	DESCRIPTION
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)
Ex. 1036	"TNF Blocker Wins Approvals," *Internal Medicine News*, Vol. 42, No. 11 (2009) ("TNF Blocker Wins Approval")
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")

FRESENIUS EXHIBIT NO.	DESCRIPTION
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 Sep. 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")
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")

FRESENIUS EXHIBIT NO.	DESCRIPTION
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")
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")

FRESENIUS EXHIBIT NO.	DESCRIPTION
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)
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")
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FRESENIUS EXHIBIT NO.	DESCRIPTION
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Ex. 1057	William E. Werner et al., "The removal of pyroglutamic acid from monoclonal antibodies without denaturation of the protein chains," *Anal. 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): PCT International Publication No. WO2005/090405 A1 ("WO2005090405")
Ex. 1061	U.S. Patent No. 5,795,965 ("the '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):35–34 (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): 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")
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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")
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I. INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH, pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, *et seq.*,[2] petition for *Inter Partes* Review ("IPR") of claims 1-8 of U.S. Patent No. 10,874,677 ("the '677 patent," Ex. 1006). 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 '677 patent are directed to a "subcutaneous administration device" that contains and delivers a 162 mg fixed dose of tocilizumab. More than one year prior to the earliest alleged priority date, a clinical study protocol, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis," was published on ClinicalTrials.gov, a website maintained by the U.S. National Library of Medicine to provide the public access to information on clinical trials. This protocol disclosed subcutaneous administration with a 162 mg fixed dose of tocilizumab, and therefore anticipates claims 1 and 5 of the '677

[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.

patent. These claims are also anticipated by Georgy, which likewise discloses subcutaneous administration of 162 mg of tocilizumab to patients.

Subcutaneous administration of a fixed dose of 162 mg of tocilizumab would also have been obvious in view of the prior art. Before November 8, 2010 (the earliest possible priority date of the '677 patent), overproduction of the cytokine, IL-6, was known to be responsible for the pathogenesis of rheumatoid arthritis (RA). It was also well known that tocilizumab inhibits the binding of IL-6 to its receptors, and thus reduces its pro-inflammatory activity. The results of several Phase III clinical trials had published by 2009 demonstrating that intravenous (IV) administration of tocilizumab was safe and effective for treating RA within a wide therapeutic dose range of 4 to 8 mg/kg every four weeks. Tocilizumab also had been approved in several countries for the treatment of RA by IV administration, including the United States and Japan, and within Europe.

Subcutaneous administration of drugs dates back to at least the 1850s. By November 2010, it was also known that immunoglobulins—like tocilizumab—are preferably administered by subcutaneous injection. A person of skill in the art would have understood that subcutaneous injection allowed patients to self-administer the drug in the setting they chose, rather than mandating a clinic or hospital setting, leading to reduced costs for patients and providers (e.g., travel- and office visit-related costs) compared with the costs of intravenous medications.

Indeed, Patent Owner Chugai itself had publicly stated that subcutaneous injection is the "preferred" route of administration for tocilizumab. Ex. 1011 (WO '621) at 4. A person of skill in the art would have understood that a subcutaneous fixed dose of 162 mg for tocilizumab administered every week or every other week is equivalent to the known effective intravenous doses of 4 mg/kg or 8 mg/kg, and would have therefore been motivated to use a "subcutaneous administration device" (e.g., a pre-filled syringe or an autoinjector) to administer tocilizumab to patients.

The Board should institute review because there is at least a reasonable likelihood that Petitioners will prevail with respect to at least one challenged claim. § 314(a). Moreover, there are no persuasive grounds for denying institution under § 314(a) or § 325(d). This is Petitioners' first petition challenging any claim of the '677 patent, and the petition raises arguments that have not previously been presented to the Office.

II. GROUNDS FOR STANDING

Pursuant to § 42.104(a), Petitioners certify that the '677 patent is available for IPR[3] and that Petitioners are not barred or estopped from requesting IPR on the

[3] The '677 patent issued on December 29, 2020 and claims priority to an application filed before March 16, 2013. Because the '677 claims priority to a pre-AIA

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 '677 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 '677 patent is not currently the subject of any litigation or post-grant proceedings. Petitioners are concurrently filing a petition seeking *inter partes* review of U.S. Patent No. 5,580,264 ("the '264 patent"). *See* IPR 2021-01288. The '677 patent claims priority to the application that issued as the '264 patent.

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application, the nine-month waiting period for filing an IPR does not apply. Note to 35 U.S.C. § 311(c) ("Pursuant to Public Law 112-274, § 1(d), 126 Stat. 2456, Jan. 14, 2013, the filing deadlines of subsection (c) do not apply to patents not subject to the first inventor to file provisions of the AIA.").

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 ’677 patent: Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

E. Power of Attorney (§ 42.10(b))

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

IV. FEE PAYMENT (§ 42.15(a))

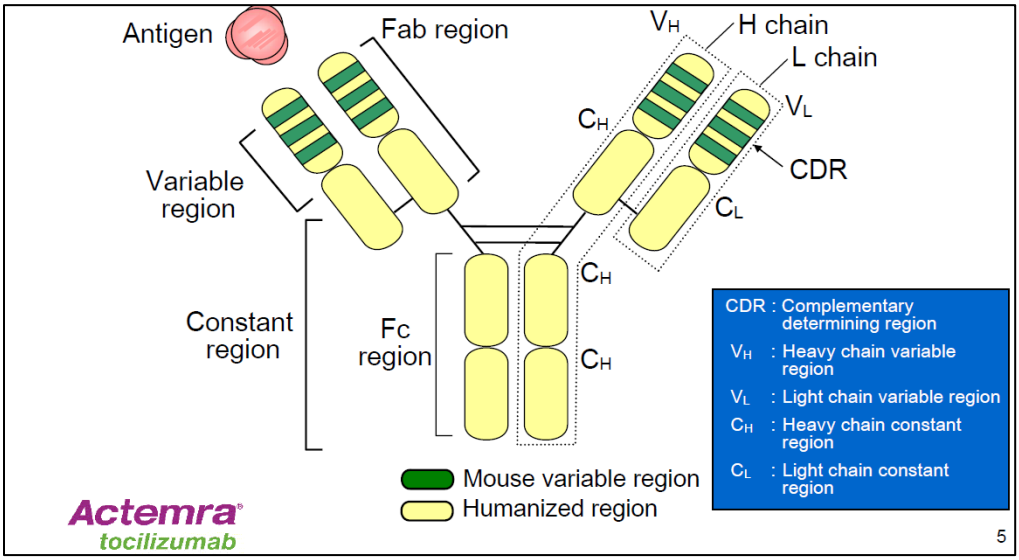
The required fee set forth in § 42.15(a) is paid pursuant to § 42.103, and the Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

V. TECHNICAL BACKGROUND

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

Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic disease characterized by pain, swelling and progressive destruction of the smalls joints of the hands and feet. Ex. 1002 ¶36. By the mid-1990s, methotrexate ("MTX") had become the most commonly used disease-modifying antirheumatic drug ("DMARD") for treating RA, yet many patients did not adequately respond to MTX alone. *Id.* ¶37; Ex. 1059 (Jones) at 1; Ex. 1062 (Weinblatt) at 4. In such patients, other DMARDs were often added to the methotrexate regimen in order to improve disease control. Ex. 1002 ¶37; 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 ¶37.

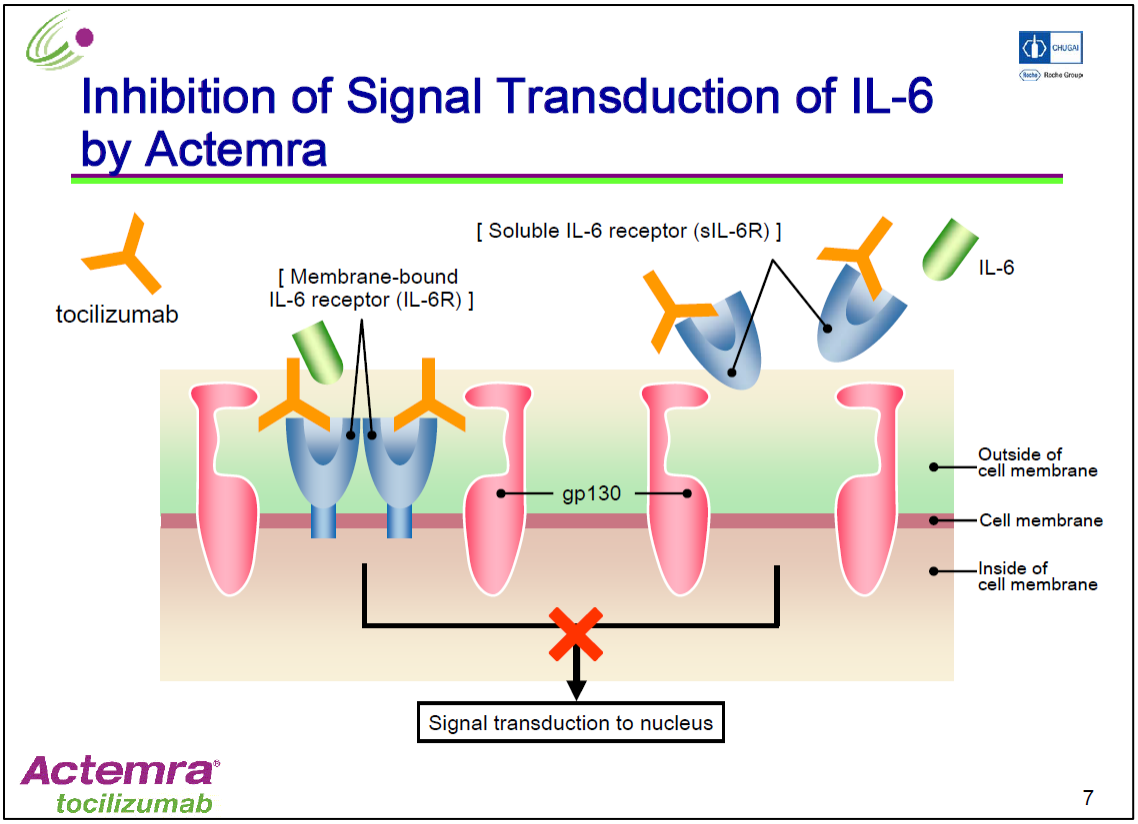
Tocilizumab, also known as MRA, is a humanized anti-IL-6 receptor monoclonal antibody of the immunoglobulin IgG1 subclass. Ex. 1025 (Maini 2006) at 3; Ex. 1003 ¶19; Ex. 1002 ¶38. Like all antibodies, it has two heavy chains and two light chains forming two antigen-binding sites. Ex. 1003 ¶19; Ex. 1002 ¶38. 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. 1003 ¶20; Ex. 1013 (Product Overview of Actemra) at 5.

Overproduction of IL-6, a cytokine, and its interaction with its receptor, IL-6R, which is expressed on effector cells, causes and prolongs inflammation associated with RA. Ex. 1002 ¶39. Although originally intended as a treatment for multiple myeloma, by 1995 Chugai had begun studying tocilizumab for the treatment of rheumatoid arthritis based on its ability to block the action of IL-6, which was known to be involved in the pathogenesis of RA. *Id.*; Ex. 1064

(Nishimoto 2002) at 3-4. Tocilizumab inhibits the binding of IL-6 to both soluble and membrane-bound receptors. Ex. 1002 ¶39; 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. Ex. 1013 (Product Overview of Actemra) at 7. As shown in the figure below, tocilizumab-bound IL-6 receptors are unable to transduce IL-6's signal to the nucleus, thus reducing the cytokine's pro-inflammatory activity.



Id. at 8.

Early studies established that tocilizumab was safe and effective for treating RA patients who had inadequately responded to traditional DMARDs, including

methotrexate. Ex. 1002 ¶40; Ex. 1064 (Nishimoto 2002) at 4. Subsequent studies established that tocilizumab was safe and effective for treating RA when administered intravenously at a dose of 4 mg/kg or 8 mg/kg every four weeks, either with or without methotrexate. Ex. 1002 ¶40; Ex. 1065 (Nishimoto Abstract) at 2; Ex. 1025 (Maini 2006) at 3, 8-9.

Additional clinical trials further confirmed that tocilizumab was a safe and effective treatment for rheumatoid arthritis. Ex. 1002 ¶41. By 2009, tocilizumab was well known as an effective treatment for RA, often administered in combination with other DMARDs, like methotrexate. *Id.* ¶¶40-43. The results of the Phase III RADIATE clinical study, published in 2008, showed that both 8 mg/kg and 4 mg/kg tocilizumab every four weeks, in combination with methotrexate, was superior to placebo in treating RA in patients who had inadequately responded to TNF antagonists. *Id.* ¶41; Ex. 1014 (Emery) at 5-6. The investigators concluded that "[i]n patients with moderate to severe active RA responding inadequately or who are intolerant to TNF antagonists, changing to tocilizumab plus methotrexate is effective, and the safety profile is manageable." Ex. 1014 (Emery) at 9.

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

the signs and symptoms of rheumatoid arthritis" in patients who had inadequately responded to MTX alone. Ex. 1002 ¶42; Ex. 1015 (Smolen) at 9. The TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy) clinical study "examined the efficacy and safety of tocilizumab in combination with a range of DMARDs in patients with moderate-to-severe RA in whom the response to these agents was inadequate." Ex. 1002 ¶42; Ex. 1026 (Genovese) at 3. The investigators concluded that in "patients with moderate-to-severe RA, treatment with tocilizumab in combination with traditional DMARDs significantly and rapidly reduced disease activity over 24 weeks as compared with treatment with DMARDs plus placebo." *Id.* at 12. Methotrexate was one of several DMARDs in that study that were shown to be effective in combination with tocilizumab. *Id.* at 5. And, in March 2009, results of the Phase III AMBITION trial published, indicating that tocilizumab administered intravenously at a dose of 4 mg/kg or 8 mg/kg every four weeks was superior to methotrexate for treating RA patients who had not previously failed MTX treatment. Ex. 1002 ¶43; Ex. 1059 (Jones) at 3, 8.

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

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

B. Subcutaneous Administration Devices for Administration of Antibodies Were Well 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 independent and scheduling flexibility associated with self-administered therapy. Ex. 1002 ¶45; Ex. 1016 (Berger) at 12-13; Ex. 1017 (Ochs) at 2. IV therapy also was "not ideal for all patients and may be difficult for those with poor venous access or those experiencing recurrent systemic reactions." Ex. 1017 (Ochs) at 1. According to the physician investigators involved in clinical

studies of Humira®, subcutaneous administration offered "several advantages that promote adherence to therapy":

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

Ex. 1070 (Kivitz) at 2.

It was also known in the prior art that administering an equivalent amount of an immunoglobulin, like tocilizumab, as a subcutaneous dose every week or every other week, rather than an IV dose every four weeks, was preferable because it reduces serum concentration fluctuation around the same mean. Ex. 1002 ¶46; 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 ¶¶46, 59; Ex. 1016 (Berger) at 8-9.

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 ¶46. 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 ¶46. Indeed, by 2009, there were at least four other biologics approved by FDA for subcutaneous administration with a fixed dose:

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

- Simponi® (golimumab), approved by the FDA in April 2009 for the treatment of RA, among other indications, at a subcutaneous fixed dose of 50 mg monthly. Ex. 1036 (TNF Blocker Wins Approval) at 1; Ex. 1083 (Golimumab) at 1. Golimumab is a human anti-TNFα IgG1 monoclonal antibody. Ex. 1083 (Golimumab) at 1; Ex. 1084 (2009 Simponi FDA Label) at 1.

For tocilizumab specifically, the subcutaneous route was identified as the "preferred form of administration" well before the earliest claimed priority date of the '677 patent. Ex. 1011 (WO '621) at 4. And not only was there no recognized need to employ weight-based dosing, the available pharmacokinetic data suggested just the opposite—that tocilizumab could be administered as a fixed dose. Ex. 1002 ¶122.

By 2009, many biologics were available for the treatment of RA using subcutaneous administration. Enbrel® (etanercept), approved by FDA in 1998, was available in a prefilled syringe and an auto-injection device. Ex. 1082 (2000 PDR Excerpt – Enbrel) at 6; Ex. 1070 (Kivitz) at 3. Kineret® (anakinra) was approved in 2001 as a pre-filled syringe, and by 2009, also in an auto-injection device. Ex 1070 (Kivitz) at 3. Humira® (adalimumab) was approved by FDA in 2002 for delivery in a single, use pre-filled syringe, and in 2006, also made available in an auto-injector pen. Ex. 1023 (2002 FDA label for Humira®) at 2;

Ex. 1070 (Kivitz) at 3. Cimzia®, approved by FDA in 2009, was supplied in a vial, reconstituted, and administered with a syringe. Ex. 1024 (2009 PDR - Cimzia) at 3. Simponi® (golimumab), approved by FDA in 2009, was available as a single dose-prefilled syringe and an auto-injector. Ex. 1084 (Simponi 2009 Label) at 1.

VI. THE '677 PATENT

The '677 patent, entitled "Subcutaneously administered Anti-IL-6 Receptor Antibody," issued on December 29, 2020, from U.S. Patent Application No. 16/254,105, filed on January 22, 2019, claiming priority through a series of applications to U.S. Patent Application No. 13/290,366, which issued as the '264 patent. The '677 patent also claims priority to two provisional applications, the earliest of which was filed on November 8, 2010.

A. Challenged Claims

Petitioners challenge claims 1-8 of the '677 patent. The two independent claims (1 and 5) each recite an "article of manufacture comprising a subcutaneous administration device" that contains and delivers a fixed dose of 162 mg of tocilizumab (claim 1) or "an anti-IL-6R antibody, wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID Nos:1 and 2, respectively" (claim 5).

Claim 1	Claim 8
1. An article of manufacture comprising a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of tocilizumab.	5. An article of manufacture comprising a subcutaneous administration device, which contains and delivers to a patient a 162 mg fixed dose of an anti-IL-6R antibody, wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID Nos:1 and 2, respectively.

Claims 2 and 6, which depend from claims 1 and 5 respectively, specify that the "subcutaneous administration device is selected from the group consisting of a syringe, an injection device, an infusion pump, an injector pen, a needleless device, an autoinjector, and a subcutaneous patch delivery system." Claim 3 and 7, which depend from claims 2 and 6 respectively, further recite "wherein the subcutaneous administration device is a syringe, including a pre-filled syringe." Claims 4 and 8, which depend from claims 2 and 6 respectively, further recite "wherein the subcutaneous administration device is an autoinjector."

B. Prosecution History

On July 16, 2020, the Examiner rejected the then-pending claims[4] as anticipated by Ohta 2010, an abstract published in Arthritis and 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 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. 1007 ('677 Patent File History) at 181. 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 TCW QW" (every week), and that both dosage schedules of

[4] The pending claims included two independent claims, directed to "an article of manufacture comprising a subcutaneous administration device, which delivers to a patient a fixed dose of" tocilizumab and an anti-IL-6R antibody, respectively, "wherein the fixed dose is selected from the group consisting of 162 mg, 324 mg, and 648 mg" of the drug. Ex. 1007 ('677 Patent File History) at 3-4.

TCW (tocilizumab) were "well tolerated" and provided a "good clinical response." *Id.* Accordingly, the Examiner concluded that Ohta 2010 anticipated the then-pending claims 53-62. *Id.*

The applicant did not dispute the Examiner's reasoning or conclusions with respect to Ohta 2010, and instead submitted a Declaration Under 37 C.F.R. § 131 to antedate the reference. *Id.* at 325-26. According to the applicant, the supporting declaration established "that the inventors had conceived of and reduced to practice presently claimed invention … prior to (at least) September 2010." *Id.* at 325. The declaration included a copy of a "Synopsis" of a Clinical Study report, summarizing the results of a study entitled, "MRA227." *Id.* at 257-73. 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 257.

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.[5] *Id.* at 340.

VII. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art ("POSA") to whom the '677 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 ¶34. A POSA would have easily understood the prior art references referred to herein and would have had the capacity to draw inferences from them.

VIII. CLAIM CONSTRUCTION

In an IPR, the terms of challenged claims are construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," just as they are in district court. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d

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

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 '677 patent, which Petitioners assume for purposes of this IPR only to be November 8, 2010.[6]

A. "fixed dose" (claims 1 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. 1006 ('677 patent) at 15:15-18.

B. "subcutaneous administration device" (claims 1 and 5)

The term "subcutaneous administration device" is defined in the specification as "a device, such as syringe, injection device, infusion pump, injector pen, needleless device, patch delivery system, etc, which is adapted or

[6] Petitioners adopt these claim construction positions for purposes of this IPR only and reserves 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.

designed to administer a drug or pharmaceutical formulation by the subcutaneous route." Ex. 1006 ('677 patent) at 20:7-11.

IX. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claims 1-8 of the '677 patent under §§ 102 and 103 for the reasons explained in this petition, which may be summarized as follows:

Ground No	Claims and Basis
1	Claims 1 and 5 are anticipated by NCT00965653
2	Claims 1-8 are obvious over NCT00965653 and Kivitz
3	Claims 1 and 5 are anticipated by Georgy
4	Claims 1- 8 are obvious over Georgy and Kivitz
5	Claims 1-8 are obvious over Maini 2006 and Kivitz in view of Bonilla and Wang

A. Ground 1: Claims 1 and 5 are anticipated by NCT00965653

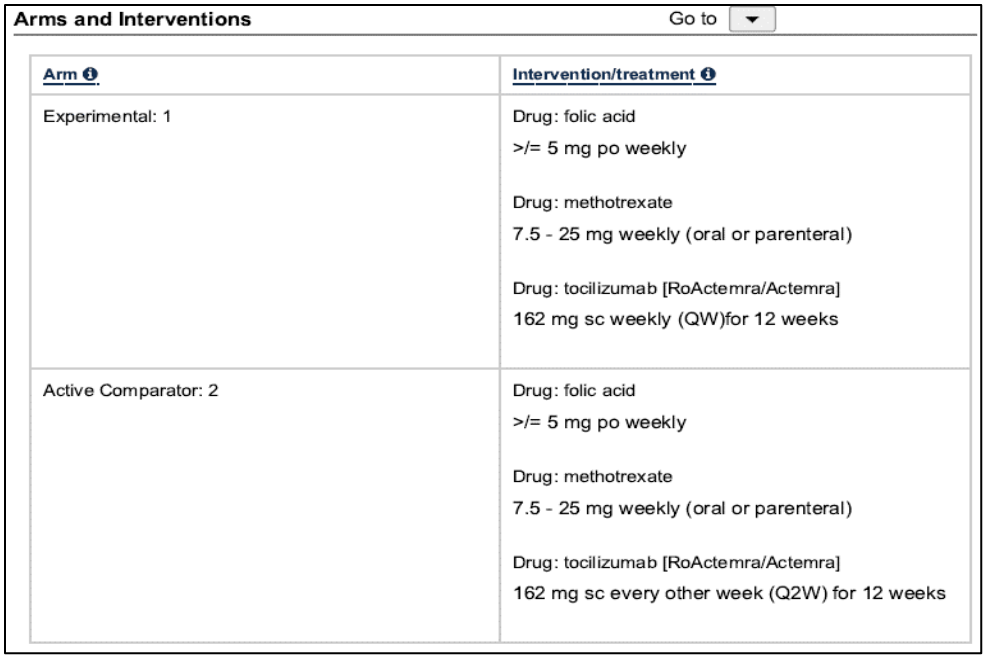
NCT00965653 (Ex. 1028) is a clinical trial protocol, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients With Rheumatoid," which was publicly available on ClinicalTrials.gov prior to November 2009, or more than one year before the earliest claimed priority date of the '677 patent. NCT00965653 is prior art to the '677 patent under pre-AIA § 102(b). Ex. 1004 ¶¶ 24-32; Ex. 1002 ¶¶67-70. Although NCT00965653 was identified as one of over

200 references during prosecution of the '677 patent,[7] it was never substantively discussed by either the Examiner or the applicants.

1. Disclosure of NCT00965653

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

[7] During prosecution, the applicant identified NCT00965653 on an Information Disclosure Statement. But the Applicant's description of NCT00965653 omitted that the protocol was "First Posted" on ClinicalTrials.gov on August 25, 2009. Ex. 1007 ('677 Patent File History) at 149.



Arms and Interventions Go to

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

Id. at 3.

2. NCT00965653 Was Publicly Available Prior to November 2009

NCT00965653 is a prior art printed publication, which was available on ClinicalTrials.gov prior to November 2009. The study record for NCT00965653 was "First Posted" on August 25, 2009 and updated several times in September and October 2009. As Mr. Robert Paarlberg explains, ClinicalTrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials, and NCT009656653 was publicly accessible more than one year before the earliest claimed priority date. Ex. 1004 ¶¶11-32.

Some background on ClinicalTrials.gov is warranted. In 1997, the FDA Modernization Act required that the National Institutes of Health ("NIH") establish a database of information on clinical trials conducted in the United States for drugs

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

The ClinicalTrials.gov database provides key publication dates for each study submitted. According to the NIH, the "First Posted" date is "[t]he date on which the study record was first available on ClinicalTrials.gov." Ex. 1030 (ClinicalTrials.gov Glossary) at 7. The date accounts for the delay of a few days between study protocol submission, quality control review by ClinicalTrials.gov staff, and posting of the information to the public database. Ex. 1004 ¶28. NIH also tracks, and makes available to the public, all subsequent versions of the study in a History of Changes. *Id.* ¶23.

The study record for NCT00965653 was "First Posted" on August 25, 2009. Ex. 1028 (NCT00965653) 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.* ¶¶29-33. While there have been changes made to the study status (e.g., "recruiting" vs. "completed"), the study locations, and the duration of one of the treatment arms (from 11 weeks to 12 weeks), according to ClinicalTrials.gov, the protocol disclosed in the latest version is otherwise identical to the "First Posted" version. *Id.* ¶¶34-35. Therefore, these insignificant differences aside, the current version NCT00965653 reflects the clinical trial protocol as it was publicly available by October 2009. *Id.* ¶35.

The totality of the evidence, including the indicia on the face of these documents and the testimony of Mr. Paarlberg, establishes that NCT00965653 (Ex. 1028) was publicly accessible more than one year before the earliest claimed priority date.[8] *See, e.g.*, *Grunenthal GmbH v. Antecip Bioventures II, LLC.*, PGR

[8] 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

2019-00003, 2020 WL 2203740, at *7-8 (PTAB May 5, 2020) (finding a protocol available on ClinicalTrials.gov to have been publicly available as of its "first posting" date and therefore a "prior art printed publication").

3. Claims 1 and 5 Are Anticipated by NCT00965653

a. "*[a]n article of manufacture comprising a subcutaneous administration device"* (claims 1 and 5)

NCT00965653 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." Ex. 1028 (NCT00965653) at 2. Although NCT00965653 does not expressly disclose the use of a specific "subcutaneous administration device" (e.g., a syringe or an autoinjector), a POSA would have understood that NCT00965653 implicitly discloses a device as the protocol discloses subcutaneous injection of tocilizumab. Ex. 1002 ¶99. In other words, in order to administer tocilizumab subcutaneously, one must necessarily use a "subcutaneous administration device." *Id.*; *see In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) (finding anticipation where "one skilled in the art would have known that Becker was referring to a

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"routine discovery" on "relevant information that is inconsistent with a position advanced during the proceeding" and "additional discovery … in the interests of justice").

DEHP-plasticized bag and a Teflon®)) secondary bag" despite "no express reference to DEHP in the Becker document").

b. *"which contains and delivers to a patient a 162 mg fixed dose of tocilizumab"* (claim 1)

NCT00965653 describes a study of "subcutaneously administered tocilizumab in patients." Ex. 1028 (NCT00965653) at 2. NCT00965653 discloses 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." *Id.* 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.* at 3. Thus, a POSA would have understood that the subcutaneous administration device contains and delivers to a patient a 162 mg fixed dose of tocilizumab. Ex. 1002 ¶100. NCT00965653 therefore discloses this limitation.

c. *"which contains and deliver to a patient a 162 mg fixed dose of an anti-IL-6R antibody, wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively"* (claim 5)

NCT00965653 describes a study of "subcutaneously administered tocilizumab in patients." Ex. 1028 (NCT00965653) at 2. Tocilizumab is an anti-IL-6 receptor antibody. Ex. 1006 at 5:29-30 ("The invention also concerns subcutaneously administering an anti-IL-6R antibody (e.g. tocilizumab)."). 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 (NCT00965653) 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.* Thus, a POSA would have understood that the subcutaneous administration device contains and delivers to a patient a 162 mg fixed dose of an anti-IL-6R antibody. Ex. 1002 ¶101.

Furthermore, the anti-IL-6R antibody disclosed in NCT00965653 (i.e., tocilizumab) inherently 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 '677 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. 1006 ('677 patent) at 7:14-17 (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. 1007 ('677 Patent File History) at 181.

- During prosecution, the named inventors confirmed that tocilizumab has the claimed sequences. In an inventor declaration submitted to the Examiner in an effort to antedate Ohta 2010, the listed inventors admitted that tocilizumab has the claimed sequence: "MRA227 was a phase I/Il clinical study of the anti-IL-6 receptor antibody '***tocilizumab***' also called 'MRA' ***which we understand comprises the light chain and heavy chain amino acid sequences as in Figs. 7A-B*** of the above application." *Id.* at 257.[9]

- Chugai, one of the owners of the '977 patent, confirmed in a Request for Patent Extension that tocilizumab has the claimed amino acid sequences. *See* Ex. 1031 (Application for Patent Term Extension); Ex. 1003 ¶¶61-68.

- As explained by Dr. Levine, tocilizumab inherently has the claimed amino acid sequences for the heavy and light chains, which were disclosed in the prior art. Ex. 1003 ¶¶38-52.

[9] Likewise, the inventors made the same admission during prosecution of U.S. Patent No. 8,580,264, which shares the same specification as the '677 patent. Ex. 1005 ('264 Patent File History) at 1004, 1025-27.

For all of the reasons set forth above, the anti-IL-6R antibody included in the subcutaneous administration device of NCT00965653 discussed above inherently "comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively," as required by claim 5 of the '677 patent. Ex. 1002 ¶¶101-107; *see generally* Ex. 1003 (Levine Decl.). Accordingly, this limitation is also disclosed in NCT00965653.

B. Ground 2: Claims 1-8 Are Obvious Over NCT00965653 in view of Kivitz

As set forth above for Ground 1, claims 1 and 5 of the '677 patent are anticipated by NCT00965653, which discloses subcutaneous administration of a fixed dose of 162 mg of tocilizumab, and therefore implicitly discloses a subcutaneous administration device in accordance with claims 1 and 5. NCT00965653, however, does not identify which specific device (e.g., syringe or autoinjector) was used for subcutaneous administration. The remaining claims are directed to a specific device. Claims 2 and 6 are directed to the article of claims 1 and 5, respectively, "wherein the subcutaneous administration device is selected from the group consisting of a syringe, an injection device, an infusion pump, an injector pen, a needleless device, an autoinjector, and a subcutaneous patch delivery system." Claims 3 and 7 are directed to the article of claims 1 and 5, respectively, "wherein the subcutaneous administration device is a syringe, including a pre-filled syringe." Claim 4 and 8 are directed to the article of claims 1

and 5, respectively, "wherein the subcutaneous administration device is an autoinjector." All of these claims (including claims 1 and 5) would have been obvious to a POSA over NCT00965653 in view of Kivitz, which discloses successful use of a pre-filled syringe and autoinjector for an antibody used to treat RA patients.

Kivitz *et al.*, *HUMIRA® Pen: a novel autoinjection device for subcutaneous injection of the fully human monoclonal antibody adalimumab*, Expert Rev. Med. Devices, Vol. 4, No. 2, 2007 ("Kivitz") was published in in the journal, Expert Review of Medical Devices, and is therefore a printed publication as of 2007. Ex. 1070. Accordingly, Kivitz is prior art to the '677 patent under pre-AIA § 102(b).

Kivitz discloses that "[u]se of intravenous biological agents mandates administration by a healthcare professional in a clinical setting, whereas biological agents with a pharmacological composition that allows subcutaneous delivery can be administered at home by the patient or a caregiver." Ex. 1070 (Kivitz) at 2. "Self-administered injectables offer several advantages over intravenous injections (i.e., portability, convenience and flexible scheduling). In particular, patients with chronic, debilitating diseases may need a self-administered medication available in an easy-to-use and convenient delivery device that minimizes pain and facilitates adherence to therapy." *Id.* at 1.

Kivitz further discloses that Humira® (adalimumab), Enbrel® (etanercept), and Kineret® (anakinra) were all available to patients in either an autoinjector pen or pre-filled syringe for administration of a subcutaneous dose. *Id.* at 3. Although some patients preferred an autoinjector pen, "[t]o ensure the availability of options that meet the needs and preferences for all patients, both adalimumab and etanercept are still available in prefilled syringe." *Id*. at 6. Kivitz further states that "[b]iological therapies delivered by autoinjector pens may quickly become the treatment of choice in RA and related diseases." *Id.* at 7.

NCT00965653 itself would have motivated a POSA to use a "subcutaneous administration device," as recited in claims 1 and 5, to contain and deliver to a patient a subcutaneous 162 mg fixed dose of tocilizumab because it discloses subcutaneous administration of a fixed dose of 162 mg of tocilizumab. Ex. 1002 ¶116. Moreover, a POSA would have been motivated to use either a syringe or autoinjector, as recited in claims 2-4 and 6-8, in view of Kivitz to deliver and contain a subcutaneous 162 mg fixed dose of tocilizumab. *Id.*

The Patent Owners' own prior art disclosures would have further motivated a POSA to use a "subcutaneous administration device" for subcutaneously administering tocilizumab as disclosed in NCT00965653 to treat an RA patient. Ex. 1002 ¶117. While it was well known that intravenous (IV) administration of 4 mg/kg and 8 mg/kg tocilizumab every four weeks was safe and effective for

treating RA (Ex. 104 (Emery) at 7; Ex. 1014 (Smolen) at 1, 7-8; Ex. 1026 (Genovese) at 2-3), Chugai represented in its prior art patent 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"). Indeed, in February 2009, Chugai announced that it was in Phase II development of subcutaneous administration of Actemra® (tocilizumab). Ex. 1046 (Chugai 2009 Report) at 4. And, in June 2009, Roche announced to its investors that a "Subcutaneous dose form" of Actemra® was "in development," and that Actemra® had "[c]ontinued strong efficacy data" and had "[d]emonstrated long-term safety with increasing efficacy over time." Ex. 1045 (Roche 2009 Report) at 12.

Furthermore, a POSA's expectation that the 162 mg subcutaneous dosing regimens disclosed by NCT00965653 would successfully treat RA would have provided further motivation to a POSA to make and use the subcutaneous injection devices of claims 1-8 of the '677 patent. Ex. 1002 ¶¶118-122. A POSA would have expected that a subcutaneously-administered antibody would be at least as safe and effective as an equivalent intravenous amount. *Id.* ¶118. For example, Bonilla discloses that antibodies may be administered subcutaneously every week or every other week instead of intravenously every four weeks in an amount that "over time is generally equivalent." Ex. 1021 (Bonilla) at 15. Subcutaneous

administration provides the same mean serum levels along with fluctuations that are "much smaller" and therefore trough levels are higher and peak levels are lower than with intravenous administration. *Id.* For tocilizumab, it was known that the efficacy of tocilizumab depends upon maintaining adequate serum trough levels throughout treatment. Ex. 1033 (Nishimoto 2003) at 9. Therefore, a POSA would have reasonably expected that safety and efficacy would be maintained when using a subcutaneous dose equivalent to the known IV dose. Ex. 1002 ¶118.

A POSA would also have understood that the subcutaneous fixed dose of 162 mg disclosed in NCT00965653 as delivered weekly was equivalent to the known efficacious 8 mg/kg every four week IV dose. *Id.* ¶119. 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 this intravenous dose. *Id.*; Ex. 1021 (Bonilla) at 15. It was reported that the subcutaneous bioavailability of tocilizumab was 72%, which means administering 139% (i.e., 1/0.72 = 1.39) of the intravenous dosage subcutaneously would provide the same amount of tocilizumab over time. Ex. 1002 ¶119; Ex. 1019 (EMA Assessment Report) at 14. However, a POSA would have known 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 ¶119; Ex. 1021 (Bonilla) at 15-16; 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. 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 ¶119.

In assessing the equivalent subcutaneous dose for the known IV dose of 8 mg/kg every four weeks (known to be a safe and efficacious IV dose for treating RA), a POSA would have known that 8 mg/kg every four weeks amounts to 140 mg every week for a typical 70 kg patient. Ex. 1002 ¶120. A POSA would have understood that an equivalent subcutaneous dose would be somewhere between this amount and up to about 39% higher than the IV dose (see calculation in preceding paragraph), or approximately ~195 mg. *Id.* Because 162 mg every week falls squarely within this range, a POSA would have reasonably expected 162 mg tocilizumab administered subcutaneously every week to be safe and efficacious for treating RA. *Id.*

A POSA would also have reasonably expected that the 162 mg fixed dose of tocilizumab disclosed in NCT00965653 could be successfully contained and delivered to a patient in a "subcutaneous administration device." Ex. 1002 ¶¶123-124. Indeed, the patients in the NCT00965653 study were administered a 162 mg fixed dose of tocilizumab, so therefore a "subcutaneous administration device" was necessarily used. *Id.* ¶123. And a POSA would have reasonably expected that a syringe or autoinjector could be used to contain and deliver the 162 mg fixed dose of tocilizumab disclosed in NCT00965653. *Id.* ¶124. There is no reason why a 162 mg fixed dose of tocilizumab, which was known to be administered subcutaneously, would not have been suitable to administer in either a syringe or autoinjector. *Id*. Moreover, the success of Humira® (adalimumab), Enbrel® (etanercept), and Kineret® (anakinra)—all of which were available in a syringe or autoinjector—would have provided a POSA with a reasonable expectation that a 162 mg fixed dose of tocilizumab could also be used in either a syringe or autoinjector. *Id*.

C. Ground 3: Claims 1 and 5 Are Anticipated by Georgy

Georgy is an article titled "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," published in February 2010 in Clinical Pharmacology & Therapeutics, Vol. 87 Supp. 1. Ex. 1044. Georgy

is prior art to the '677 patent under pre-AIA § 102(a). Georgy was disclosed on an IDS, but was never cited by the Examiner during prosecution of the '677 patent.

1. Disclosure of Georgy

Georgy discloses a clinical study to assess the pharmacokinetics and pharmacodynamics of tocilizumab after a single dose of administration by subcutaneous and intravenous routes. Ex. 1044 (Georgy) at 3. Twelve patients received a 162 mg subcutaneous dose of tocilizumab. *Id.* "TCZ [tocilizumab] was well tolerated following 81 and 162 mg IV & SC administration." *Id.*

2. Claims 1 and 5 Are Anticipated by Georgy

a. "*[a]n article of manufacture comprising a subcutaneous administration device"* (claims 1 and 5)

Georgy describes a clinical study in which patients were administered subcutaneous tocilizumab. Ex. 1044 (Georgy) at 4. In order to administer tocilizumab subcutaneously, one must necessarily use a "subcutaneous administration device." Ex. 1002 ¶109. A POSA would have therefore understood Georgy to disclose a "subcutaneous administration device" for administering tocilizumab subcutaneously to patients. *Id.* This limitation is accordingly disclosed in Georgy. *See In re Baxter Travenol Labs*, 952 F.2d at 390.

b. *"which contains and delivers to a patient a 162 mg fixed dose of tocilizumab"* (claim 1)

Georgy discloses that twelve patients were administered subcutaneously a dose of 162 mg of tocilizumab. Ex. 1044 (Georgy) at 3. The 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.* A POSA would have therefore understood that the subcutaneous administration device disclosed by Georgy contains and delivers a 162 mg fixed dose of tocilizumab. Ex. 1002 ¶110. Therefore, Georgy discloses all limitations of claim 1.

c. *"which contains and deliver to a patient a 162 mg fixed dose of an anti-IL-6R antibody, wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively"* (claim 5)

As discussed above, Georgy discloses administration of a 162 mg fixed dose of tocilizumab subcutaneously to a patient. Tocilizumab is an anti-IL-6R antibody. Ex. 1006 ('677 patent) at 4:58-59 ("Preferably, the anti-IL-6R antibody is tocilizumab."); Ex. 1002 ¶111. And, as explained above, tocilizumab necessarily has the light and heavy chain sequences of SEQ. ID. Nos. 1 and 2, respectively. *See supra* p. 28-30. Therefore, Georgy discloses all limitations of claim 5.

D. Ground 4: Claims 1- 8 are Obvious over Georgy in view of Kivitz

As discussed above, Georgy discloses each and every limitation of claims 1 and 5. Georgy, however, does not identify a specific device (e.g., syringe or autoinjector) that was used for subcutaneous administration of the 162 mg of tocilizumab. All of the claims (including claims 1 and 5) would have been obvious

to a POSA over NCT00965653 in view of Kivitz, which discloses successful use of a pre-filled syringe and autoinjector for an antibody used to treat RA patients.

Georgy itself would have motivated a POSA to use a "subcutaneous administration device," as recited in claims 1 and 5, to contain and deliver to a patient a subcutaneous 162 mg fixed dose of tocilizumab because it discloses subcutaneous administration of a fixed dose of 162 mg of tocilizumab for treatment of RA. Ex. 1002 ¶132. Moreover, a POSA would have been motivated to use either a syringe or autoinjector, as recited in claims 2-4 and 6-8, in view of Kivitz to deliver and contain a subcutaneous 162 mg fixed dose of tocilizumab. *Id.*

For substantially the same reasons set forth above with respect to Ground 2, a POSA would have been further motivated to use a "subcutaneous administration device" for subcutaneously administering the 162 mg dose disclosed in Georgy in view of the prior teachings that subcutaneous administration was the "preferred form" of administration for tocilizumab, and the expectation that a 162 mg dose would be as safe and effective as the established IV regimens for treating RA patients. *See supra* Section IV.B; Ex. 1002 ¶133.

A POSA would have reasonably expected that the 162 mg fixed dose of tocilizumab disclosed in Georgy could be successfully contained and delivered to a patient in a "subcutaneous administration device." Ex. 1002 ¶¶134-136. Indeed, the patients in the clinical study disclosed in Georgy were administered a 162 mg

fixed dose of tocilizumab, so therefore a "subcutaneous administration device" was necessarily used. *Id.* ¶134. And a POSA would have reasonably expected that a syringe or autoinjector could be used to contain and deliver the 162 mg fixed dose of tocilizumab disclosed in Georgy. *Id.* ¶135. There is no reason why a 162 mg fixed dose of tocilizumab, which was known to be administered subcutaneously, would not have been suitable to administer in either a syringe or autoinjector. *Id*. Moreover, the success of Humira® (adalimumab), Enbrel® (etanercept), and Kineret® (anakinra)—all of which were available in a syringe or autoinjector—would have provided a POSA with a reasonable expectation that a 162 mg fixed dose of tocilizumab could also be used in either a syringe or autoinjector. *Id*.

E. Ground 5: Claims 1-8 Would Have Been Obvious over Maini 2006 and Kivitz in view of Bonilla and Wang

Claims 1-8 would also have been obvious from a combination of Maini 2006 and Kivitz in view of Bonilla and Wang. Ex. 1002 ¶¶143-166.

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

Maini 2006 discloses that tocilizumab administered by IV at a dose of 4 mg/kg and 8 mg/kg every four weeks was safe and effective for treating RA. The only difference between claims 1-8 of the '677 patent and Maini 2006 is that the claims recite a device for delivery of subcutaneous fixed dose of 162 mg for tocilizumab, whereas Maini 2006 discloses an intravenous dose of tocilizumab of 4

mg/kg to 8 mg/kg. As explained below, a POSA would have been motivated to combine Maini 2006 with Kivitz in view of Bonilla and Wang to arrive at the claimed devices with a reasonable expectation of success.

Bonilla, "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes," *Immunology & Allergy Clinics of North America*, Vol 28 ("Bonilla") was published in a printed publication as of 2008. Ex. 1021. Accordingly, Bonilla is prior art to the '677 patent under pre-AIA § 102(b). Bonilla discloses that it is preferable to administer an equivalent amount of an immunoglobulin as a subcutaneous dose every week rather than an IV dose every four weeks because it reduces serum concentration fluctuation around the same mean. Ex. 1021 (Bonilla) at 15. Bonilla also discloses that "SCIG leads to more physiologic IgG levels because the peaks and nadirs between infusions are blunted by slow absorption and maintenance of closer equilibrium between intra- and extravascular compartments," and that "[a]lthough SCIG is usually given weekly (sometimes more often), . . . a 2-week interval is also practical." *Id.* at 18.

In converting from an IV regimen to a more frequent subcutaneous regimen, Bonilla teaches that "the amount of [immunoglobulin] administered over time is generally equivalent," *i.e.*, the same total amount is given, but split over the shorter interval. *Id*. at 15; Ex. 1002 ¶146. To account for the potential lower

bioavailability associated with subcutaneous administration, Bonilla also discloses an alternative approach where the amount administered subcutaneously is the amount required to provide a "time averaged area under the curve that was equivalent to what had been obtained previously with" intravenous administration." *Id.* at 17; Ex. 1002 ¶146. Bonilla thus discloses that the of an antibody administered by subcutaneous injection should be between 100% of the IV dose and the amount necessary to provide 100% of the IV dose when accounting for the reduction in bioavailability. Ex. 1002 ¶146.

Wang et al., "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," *Pharmacokinetics & Pharmacodynamics*, Vol. 49 ("Wang") was published in September 2009. Ex. 1022. Accordingly, Wang is prior art to the '677 patent under pre-AIA § 102(b). Wang was not cited during examination of the '677 patent. Wang is directed to evaluating the relative advantages and disadvantages of weight-based and fixed dosing of monoclonal antibodies. Wang concludes that, all else being equal, monoclonal antibodies are preferably administered as a fixed dose rather than a weight-based dose due to its convenience, better compliance, less risk for medical errors, and cost-effectiveness. Ex. 1022 (Wang) at 7, 18 ("[W]hen there is no advantage of one dosing approach over another from a PK and PD perspective, fixed dosing is the approach of choice."). Wang also discloses that "[f]or drugs with a wide therapeutic window, a

fixed dosing approach is generally chosen for adult patients, regardless of the influence of body size on PK and PD properties due to its convenience, better compliance, less risk of medical errors, and cost-effectiveness." *Id.* at 7. Wang clarifies that "when a drug has a wide therapeutic window, an AUC difference more than ±20% may still be tolerated without additional safety issues." *Id.* at 17.

2. Motivation To Combine

A POSA would have been motivated to combine the teachings of Maini 2006 and Kivitz in view of Bonilla and Wang to arrive at the claimed devices for at least the following reasons. Ex. 1002 ¶¶148-154.

Maini 2006 discloses that 4 mg/kg of tocilizumab administered by IV every four weeks was safe and effective for treating RA. Ex. 1025 (Maini 2006) at 2. By June 2009, Chugai and Roche had also publicly disclosed their development of a subcutaneous tocilizumab. Ex. 1046 (Chugai 2009 Report) at 4; Ex. 1045 (Roche 2009 Report) at 12. A POSA would have been motivated to use a subcutaneous formulation of tocilizumab because Chugai had itself announced that subcutaneous was the "preferred" form of a drug that had been found to be safe and effective. Ex. 1011 (WO '621) at 4; Ex. 1002 ¶¶148-149.

A POSA would also have known that subcutaneous administration offers significant advantages over IV administration, including improved convenience, flexibility, reduced cost for patients, and reduced risk of medical errors in

preparing the dosage. Ex. 1002 ¶149; Ex. 1016 (Berger) at 12-13; Ex. 1070 (Kivitz) at 2; Ex. 1017 (Ochs) at 7. Bonilla discloses that immunoglobulins[10] are preferably administered by subcutaneous injection of an equivalent amount every other week instead of every four weeks by IV because it leads to more stable serum concentration levels. Ex. 1021 (Bonilla) at 8, 15-18. Hence, a POSA would have been motivated to administer tocilizumab subcutaneously, the "preferred form" of tocilizumab, every other week in an amount equivalent to the 4 mg/kg every four week dose disclosed by Maini 2006. Ex. 1002 ¶¶148-154.

To determine an equivalent subcutaneous dosing regimen based on the known effective IV regimens, a POSA would have looked to Bonilla and Wang. *Id.* ¶¶151-154. 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. *Id.* ¶151; 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. Ex. 1002 ¶151; Ex. 1002 (Wang) at 7. Tocilizumab was known in the prior art to be safe and effective over a wide range of doses, from 4 mg/kg to 8

[10] Although Bonilla discusses polyclonal human immunoglobulin IgG therapy, a POSA would understand that the same reasoning applies to IgG monoclonal antibodies like tocilizumab. Ex. 1002 ¶149, n.39.

mg/kg, despite the AUC for 8 mg/kg dose being more than double the AUC for the 4 mg/kg dose. Ex. 1025 (Maini 2006) at 2; Ex. 1033 (Nishimoto 2003) at 7. It had also been reported that an "almost two-fold" increase in tocilizumab's AUC "did not affect efficacy or safety parameters in a clinically relevant manner." Ex. 1019 (EMA Assessment Report) at 23-24; Ex. 1002 ¶151. 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 ¶151.

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.* ¶¶152-154. As taught by Bonilla, the equivalent amount of an antibody administered subcutaneously may be as low as the amount administered intravenously and as high as the amount necessary to account for the potential impact of reduced bioavailability of the subcutaneous mode of administration. *See* Ex. 1021 (Bonilla) at 16-17. The reported bioavailability of subcutaneously administered tocilizumab was 72%, which means that as much as 139% of the IV dose may be required to achieve the same area under the curve (AUC) if administered subcutaneously. *See* Ex. 1019 (EMA Assessment Report) at 18; Ex. 1002 ¶¶152-153 (an excess of 39% is required to account for a 72% bioavailability). However, because subcutaneous administration provides higher

trough concentrations than intravenous administration, the prior art taught that there may, in fact, be no need to increase the dose at all to maintain efficacy when converting to subcutaneous administration, notwithstanding the reduced bioavailability. Ex. 1021 (Bonilla) at 17; Ex. 1016 (Berger) at 6-7 (disclosing "no difference in … efficacy" whether an immunoglobulin was administered subcutaneously at the same total dose over time as the IV dose or at a higher dose to account for reduced bioavailability). Thus, a POSA would have understood that the optimal subcutaneous dose that would maintain safety and efficacy would be somewhere between 100% and 139% of the intravenous dose. Ex. 1002 ¶152.

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.[11] *Id.* ¶153. Accounting for the potential 39% increase, a POSA would have understood that an equivalent subcutaneous every other week regimen would require administering a fixed dose of between 140 mg and 195 mg. *Id.* A POSA would have arrived at the claimed 162 mg every other week subcutaneous regimen through routine optimization as 162 mg falls squarely within the range, and there is no evidence that the particular amount

[11] 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.

is critical. *Id.*; *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (finding claims requiring specific dosages obvious where "the experimentation needed to arrive at the claimed dosages was nothing more than routine"); *see also EI DuPont de NeNemours & Co. v. Synvina CV*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results, or other pertinent evidence of nonobviousness.").

Furthermore, a POSA would have known from Kivitz that subcutaneous delivery offered several advantages over intravenous injections (i.e., portability, convenience and flexible scheduling), and that several biologics were available to RA patients in a pre-filled syringe and an autoinjector. Ex. 1070 (Kivitz) at 3. Accordingly, a POSA would have been motivated to formulate the 162 mg fixed dose of tocilizumab with a pre-filled syringe and an autoinjector. Ex. 1002 ¶154.

3. Reasonable Expectation of Success

A POSA would have reasonably expected a 162 mg fixed subcutaneous dose of tocilizumab every other week to be successful at least because Maini 2006 taught that 4 mg/kg of tocilizumab administered by IV every four weeks was a safe and effective dose, and Bonilla taught that an equivalent subcutaneous dose would provide equivalent results. Ex. 1002 ¶159. As just discussed, a POSA would have

understood that 162 mg tocilizumab administered subcutaneously every other week was equivalent to 4 mg/kg administered by IV every four weeks for a typical 70 kg patient.

Furthermore, a POSA would have understood that the efficacy of tocilizumab depended upon maintaining trough concentrations above a minimum threshold. Ex. 1002 ¶156; 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 ¶157. 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 ¶157.

A POSA would have also reasonably expected this dose to be successful over a wide range of patient weights (i.e., as a fixed rather than weight-based dose). Ex. 1002 ¶157. Although it was known that tocilizumab's clearance was dependent upon body weight, and hence a fixed dose would result in heavier patients having a lower AUC than lighter patients, AUC was also known to vary significantly when tocilizumab was administered as a weight-based dose, with the

prior art reporting as much as a two-fold increase in AUC as between light and heavy patients. *Id.* ¶ 58; Ex. 1019 (EMA Assessment Report) at 23-24. This doubling of AUC was notably found to "not affect efficacy or safety in a clinically relevant manner." Ex. 1019 (EMA Assessment Report) at 23-24. A POSA would therefore have reasonably expected any AUC variation based on different clearance rates due to body weight to similarly not affect the safety or efficacy of the 162 mg dose. Ex. 1002 ¶158.

Moreover, several IgG antibodies and other proteins were approved in the prior art that were used in a subcutaneous fixed dose—e.g., etanercept (approved by FDA in 1998), adalimumab (approved by FDA in 2004), certolizumab (approved by FDA in April 2008), and golimumab (approved by FDA in April 2009). *See supra* § V.B. These approvals would have further reinforced to a POSA that a subcutaneous fixed dose of tocilizumab would have reasonably been expected to be successful. Ex. 1002 ¶159.

Finally, a POSA would have reasonably expected that a 162 mg fixed dose of tocilizumab could be successfully administered to a patient with a pre-filled syringe or autoinjector. *Id.* ¶155. As taught by Kivitz, by 2009 several biologics were available to patients in a pre-filled syringe and autoinjector, and a POSA would have expected that tocilizumab could also be successfully administered to patients using a pre-filled syringe or autoinjector. *Id.*; Ex. 1070 (Kivitz) at 3.

4. Application to the Claims

a. Claims 1 and 5

As discussed above, by combining Maini 2006 and Kivitz in view of Bonilla and Wang, a POSA would have arrived at a device for administering tocilizumab subcutaneously at a fixed dose of 162 mg. As discussed above, tocilizumab is an anti-IL-6 receptor antibody comprising the light and heavy chain amino acid sequences of SEQ ID NOS. 1 and 2, respectively. *See supra* p. 28-30. Accordingly, the combined method would have met each and every limitation of claims 1 and 5, and therefore these claims would have been obvious. Ex. 1002 ¶¶160-162.

b. Claims 2 and 6

Dependent claims 2 and 6 further recite "wherein the subcutaneous administration device is selected from the group consisting of a syringe, an injection device, an autoinjector, and a subcutaneous patch delivery system." A POSA would have been motivated to use one of the devices taught in Kivitz, including a syringes or autoinjector, for subcutaneous administration of tocilizumab. Ex. 1002 ¶¶163-164. Claims 2 and 6 would therefore also have been obvious.

c. Claims 3 and 7

Dependent claims 3 and 7 further recite "wherein the subcutaneous administration device is a syringe, including a pre-filled syringe." As explained

above, Kivitz discloses subcutaneous administration of antibodies through syringes, including pre-filled syringes. *See supra* p. 32-33. It would therefore have been obvious to use a syringe, including pre-filled syringes, to administer the 162 mg fixed dose of tocilizumab. Ex. 1002 ¶165. Claims 3 and 7 would therefore also have been obvious.

d. Claims 4 and 8

Dependent claims 4 and 8 further recite "wherein the subcutaneous administration device is an autoinjector." As explained above, Kivitz discloses subcutaneous administration of antibodies through an autoinjector. *See supra* p. 32-33. It would therefore have been obvious to use an autoinjector to administer the 162 mg fixed dose of tocilizumab. Ex. 1002 ¶166. Claims 4 and 8 would therefore also have been obvious.

F. Secondary Considerations

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

X. Section 325(d) Should Not Prevent Institution

Section 325(d) provides discretion to deny institution where (1) the same or substantially the same art or arguments were previously presented to the patent office; and (2) the petitioner has failed to demonstrate that the Examiner erred in a

manner material to the claims. *Sony Interactive Entertainment LLC v. Bot M8, LLC*, 2020 WL 5924211, at *2 (PTAB Oct. 6, 2020). The so-called *Becton Dickinson* factors are applied to aid in answering these questions. These factors include: "(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Becton, Dickinson & Co. v. B. Braun Melsungen, AG*, IPR 2017-01586, Paper 8, at 17-18 (PTAB Dec. 15, 2017).

A. Grounds 1 and 2

With regards to Ground 1 and 2, Petitioners rely upon NCT00965653, which discloses treating patients with a subcutaneous fixed dose of 162 mg to treat rheumatoid arthritis. Although NCT00965653 was disclosed on an IDS during prosecution, it was never substantively evaluated by the Examiner. *See supra* p.

22. Mere inclusion of a reference on an IDS does not mean that it was involved or evaluated during prosecution. *See Fox Factory, Inc. v. SRAM, LLC*, IPR 2016-01876, 2017 WL 1240081, at *3 (PTAB April 3, 2017). Even more critically, the Applicant's description of NCT00965653 omitted the "First Posted" date of August 25, 2009 (*see supra* p. 22), 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 more than one year before the earliest claimed priority date of the '677 patent. *See supra* Section IX.A.2. 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. v. E-ImageData Corp.*, IPR 2017-00178, Paper 6, at 12-13 (P.T.A.B. April 25, 2017).

Factors (e) and (f) also strongly support institution. As discussed above, NCT00965653 discloses and enables each and every limitation of all claims 1 and 5 of the '677 patent. The Examiner's failure to appreciate that a single § 102(b) reference was publicly available and anticipates these claims reflects a plain error

in evaluating the prior art (factor (e)) and the arguments set forth in Petitioners' Grounds 1 and 2 reflect additional evidence and facts presented in the Petition that warrant reconsideration of the prior art (factor (f)). *See Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR 2017-01884, 2018 WL 924243, at *4-5 (PTAB Feb. 15, 2018) (Paper 14) (finding that "because the Examiner did not have the benefit of Petitioner's additional experimental evidence relating to competition, we are not persuaded that the same or substantially the same prior art or arguments were previously presented to the Office").

B. Grounds 3 and 4

Ground 3 and 4 assert that all claims of the '677 patent are anticipated and/or obvious in view of Georgy. Although Georgy was disclosed on an IDS during prosecution, it was never substantively evaluated by the Examiner. Georgy contains a similar disclosure to Ohta 2010, which was before the Examiner, of a 162 mg fixed subcutaneous dose of tocilizumab. During prosecution of the '677 patent, the Examiner rejected all of the claims as either anticipated by or obvious over Ohta 2010. Ex. 1007 ('677 Patent File History) at 181. The applicant overcame these rejections by submitting a declaration from two of the four named inventors—Xiaoping Zhang and Kimio Terao—that alleged that "[p]rior to September 2010 we had conceived of and reduced to practice the invention of said claims." *Id.* at 257-73, 325-326. Georgy, however, was published in February

2010, whereas Ohta 2010 was published in September 2010, and therefore there is no evidence that Applicant can antedate Georgy. For that reason alone, discretionary denial of institution is inappropriate for Grounds 3 and 4 under Section 325(d).

Furthermore, the Examiner fundamentally erred in finding that the applicant had established prior inventorship over Ohta 2010. 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 the 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. Furthermore, nothing in the Synopsis suggests that any of the named inventors were even involved in the clinical study. The Synopsis identifies several individuals involved with the clinical study—including the lead author of Ohta 2010—but the purported inventors' names are noticeably absent. Ex. 1007 ('677 Patent File History) at 257-73. 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 for this additional reason, discretionary denial of institution is inappropriate for Grounds 3 and 4 under Section 325(d). *See Boehringer Ingelheim Pharms., Inc. v. Genentech, Inc.*, IPR2017-02032, 2018 WL 1605268, at *4 (Mar. 29, 2018) (declining to exercise discretion under § 325(d) to deny institution ground where an inventor declaration submitted during prosecution could not antedate a reference).

C. Ground 5

Ground 5 asserts that all claims of the '677 patent are obvious in view of Maini 2006, Bonilla and Wang. None of these references were before the Examiner during prosecution of the '677 patent, much less cited as a basis for a rejection. Maini 2006 discloses successful Phase III clinical trial results for

intravenous tocilizumab at 4 mg/kg and 8 mg/kg dosages. Ex. 1025 (Maini 2006) at 3, 11. Although Emery discloses similar results and was cited in an IDS, it was never substantively evaluated by the Examiner. Mere inclusion of a reference on an IDS does not mean that it was involved or evaluated during prosecution. *See Fox Factory, Inc. v. SRAM, LLC*, IPR 2016-01876, Paper 8, at 7-9 (PTAB April 3, 2017). Therefore, factors (a)-(c) favor institution.

Furthermore, at no point during prosecution did the Examiner issue an obviousness rejection based on a reference disclosing that intravenous tocilizumab at 4 mg/kg and 8 mg/kg dosages was effective in treating RA. Instead, the Examiner relied upon Ohta 2010 as a primary reference, which discloses that subcutaneous tocilizumab was effective at a fixed dose of 162 mg.[12] Moreover, the 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. *See supra* Section IX.E. Therefore, (c) and (d) also favor institution. *Oticon Medical AB v. Cochlear Ltd.*, IPR 2019-00975, 2019 WL

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

5237817, at *8 (PTAB Oct. 16, 2019) (declining to deny institution where examiner failed to consider specific teachings in the prior art).

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

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

XI. CONCLUSION

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

Dated: August 18, 2021

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 10,874,677 complies with the type-volume limits of 37 C.F.R. §42.24(a)(1)(i) because it contains 12,063 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: August 18, 2021

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,874,677** and the exhibits cited therein by Federal Express Next Business Day Delivery on this day, August 18, 2021, on the Patent Owner's correspondence address of record for the subject patent as follows:

Genentech, Inc.
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Dated: August 18, 2021

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