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.

IPR2022-00201
Patent No. 9,750,752

Title: SUBCUTANEOUSLY ADMINISTERED ANTI-IL-6 RECEPTOR ANTIBODY

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 9,750,572

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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. 9,750,752 ("the '752 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	Prosecution File History of U.S. Patent No. 9,750,752 ("'752 Patent File History")
Ex. 1005	Prosecution File History of U.S. Patent No. 8,580,264 ("'264 Patent File History")[1]
Ex. 1006	Provisional Application No. 61/411,015 ("the '015 Application")
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	Hagihara et al., "Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica," *The Journal of Rheumatology* 37(5):1075-76 (May 2010) ("Hagihara")

[1] Ex. 1005 is a copy of the certified file history for the '264 patent, dated November 23, 2020. This exhibit does not include filings in 2021 relating to a Certificate of Correction that issued on August 17, 2021.

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1011	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. 1012	Seitz et al., "Rapid induction of remission in large vessel vasculitis by IL-6 blockage," *Swiss Medical Weekly* 141:w13156 (January 17, 2011) ("Seitz")
Ex. 1013	Chugai Pharmaceutical Co., "Product Overview of Actemra" (May 22, 2008) ("Product Overview of Actemra")
Ex. 1014	Savage et al., "ABC of Arterial and Vascular Disease Vasculitis," *BMJ* 320:1324-28 (May 13, 2000) ("Savage")
Ex. 1015	Salvarini et al., "Polymyalgia rheumatica and giant-cell arteritis," *Lancet* 372:234-45 (2008) ("Salvarini")
Ex. 1016	Melvin Berger, "Subcutaneous Administration of IgG," *Immunology and Allergy Clinics of North America* 28:779-802 (2008) ("Berger")
Ex. 1017	Hans D. Ochs et al., "Safety and Efficacy of Self-Administered Subcutaneous Immunoglobulin in Patients with Primary Immunodeficiency Diseases," *Journal of Clinical Immunology* 26(3):265-73 (2006) ("Ochs")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1018	Pharmaceuticals and Medicals Devices Agency of Japan, Annual Report FY 2008, https://www.pmda.go.jp/files/000232775.pdf ("PMDA 2008 Report")
Ex. 1019	Archived European Medicines Agency, Assessment Report for Ro-Actemra (July 7, 2009) (pgs. 5-59), with Affidavit of Duncan Hall, Internet Archive (pgs. 1-4) ("EMA Assessment Report")
Ex. 1020	Food and Drug Administration, BLA 125276 Approval Letter for Actemra® (January 8, 2010), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/125276s000ltr.pdf ("BLA Approval Letter")
Ex. 1021	Francisco A. Bonilla, "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes," *Immunology and Allergy Clinics of North America* 28:803-19 (2008) ("Bonilla")
Ex. 1022	Diane D. Wang et al., "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," *Journal of Clinical Pharmacology* 49:1012-24 (Sept. 2009) ("Wang")
Ex. 1023	Humira® (adalimumab) Package Insert (Dec. 2002), available at the FDA website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/adalabb123102LB.htm ("2002 Humira FDA Label")
Ex. 1024	"CIMZIA (certolizumab pegol)," *Physicians' Desk Reference* (63rd ed. 2009) ("2009 PDR – Cimzia")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1025	R. N. Maini et al., "Double-Blind Randomized Controlled Clinical Trial of the Interleukin-6 Receptor Antagonist, Tocilizumab, in European Patients with Rheumatoid Arthritis Who Had an Incomplete Response to Methotrexate," *Arthritis & Rheumatism* 54(9):2817-29 (2006) ("Maini 2006")
Ex. 1026	Weyand et al., "Vascular Dendritic Cells in Giant Cell Arteritis," *Ann. N.Y. Acad. Sci.* 1062:195-208 (2005) ("Weyand 2005")
Ex. 1027	Nishimoto et al., "Successful Treatment of a Patient With Takayasu Arteritis Using a Humanized Anti–Interleukin-6 Receptor Antibody," *Arthritis & Rheumatism* 58(4):1197-1200 (April 2008) ("Nishimoto 2008")
Ex. 1028	FDA Label for Actemra® (tocilizumab) from January 4, 2011, available at the FDA website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125276s007s010s011lbl.pdf ("2011 FDA Actemra® Label")
Ex. 1029	Nishimoto et al, "Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti–IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease," *Blood* 112(10):3959-64 (Nov. 15, 2008) (" Nishimoto 2008B")
Ex. 1030	Lobo et al., "Antibody Pharmacokinetics and Pharmacodynamics," *J. of Pharmaceutical Sciences*, Vol. 93, No. 11 (Nov. 2004) ("Lobo")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1031	Application for Patent Term Extension Under 35 U.S.C. § 156 to the PTO for U.S. Patent. No. 5,795,965
Ex. 1032	September 17, 2013 PTO Notice of Final Determination and Requirement for Election for U.S. Patent No. 5,795,965
Ex. 1033	Norihiro Nishimoto et al., "Toxicity, Pharmacokinetics, and Dose-Finding Study of Repetitive Treatment with the Humanized Anti-Interleukin 6 Receptor Antibody MRA in Rheumatoid Arthritis. Phase I/II Clinical Study," *The Journal of Rheumatology* 30:1426-35 (2003) ("Nishimoto 2003")
Ex. 1034	Certificate of Translation (pg. 1), Translation (pgs. 2-183) & Original (pgs. 184-364) of PCT International Publication No. WO2009/041621 A1 ("WO '621")
Ex. 1035	Sequence Listing for WO2009/041621 A1
Ex. 1036	"TNF Blocker Wins Approvals," *Internal Medicine News*, Vol. 42, No. 11 (2009) ("TNF Blocker Wins Approval")
Ex. 1037	Christidis et al., "Successful use of tocilizumab in polymyalgic onset biopsy positive GCA with large vessel involvement," *BMJ Case Reports* (June 2011) ("Christidis")
Ex. 1038	Provisional Application No. 61/542/615 ("the '615 Application")
Ex. 1039	Reserved

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1040	Guidance for Industry: *Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)*, U.S. Dept. of Health and Human Services, Food and Drug Administration, February 1999 ("1999 FDA Guidance")
Ex. 1041	Thompson, "FDA approves tocilizumab to treat rheumatoid arthritis," *Am. J. Health-Syst. Pharm.*, Vol. 67 (Feb. 15, 2010) ("Thompson")
Ex. 1042	Beyer et al., "Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis," *Annals of the Rheumatic Diseases* (published online on April 24, 2011 and in print on October 1, 2011) ("Beyer")
Ex. 1043	Warrington et al., "Management Guidelines and Outcome Measures in Giant Cell Arteritis (GCA)," *Clinical and Experimental Rheumatology* (2007) ("Warrington")
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	Center for Drug Evaluation and Research Approval Package for ORENCIA, Application Number 125118Orig1s122 ("Orencia Approval Package")
Ex. 1046	*Annals of the Rheumatic Diseases*, Vol. 70, Issue 10, Table of Contents (October 2011) ("ARD TOC")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1047	Schmalzing et al., "Tocilizumab in Large Vessel Vasculitis – Different Routes of Administration," *The Open Rheumatology Journal* 12:152-59 (2018) ("Schmalzing")
Ex. 1048	Park et al., "Serum Cytokine and their correlations with disease activity in Takayasu's arteritis," *Rheumatology* 45:545-548 (Dec. 13, 2005) ("Park")
Ex. 1049	Simponi (golimumab) Package Insert (Apr. 2009), available at the FDA website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s000lbl.pdf ("2009 Simponi FDA Label")
Ex. 1050	World Intellectual Property Office, WO2009041621, available at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009041621&tab=PCTDOCUMENTS
Ex. 1051	Reserved
Ex. 1052	William E. Werner et al., "The removal of pyroglutamic acid from monoclonal antibodies without denaturation of the protein chains," *Analytical Biochem.* 342:120-25 (2005) ("Werner")
Ex. 1053	Certificate of Translation (pg. 1), Translation (pgs. 2–27), & Original (pg. 28-52) of PCT International Publication No. WO2005/090405 A1 ("WO2005090405")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1054	Lawrence W. Dick et al., "Determination of the origin of the N-terminal pyro-glutamate variation in monoclonal antibodies using model peptides," *Biotechnology & Bioengineering* 97(3):544-53 (November 10, 2006) ("Dick")
Ex. 1055	Dick Chelius et al., "Formation of Pyroglutamic Acid from N-terminal glutamic acid In immunoglobulin gamma antibodies," *Analytical Chemistry* 78:2370-76 (April 1, 2006) ("Chelius")
Ex. 1056	Y. Diana Liu et al., "N-terminal glutamate to pyroglutamate conversion in vivo for human IgG2 antibodies," *J. of Biol. Chem.* 286(13):11211-17 (April 1, 2011) ("Liu")
Ex. 1057	U.S. Patent No. 5,795,965 ("'965 patent")
Ex. 1058	Excerpt of Physicians' Desk Reference, 65th Edition (2011) for Actemra® (tocilizumab)
Ex. 1059	Certificate of Translation (pg. 1), Translation (pgs. 2–6), & Original (pgs. 7–10) of Norihiro Nishimoto, *Anti-IL-6 Receptor Antibodies, Usefulness and Issues in Rheumatoid Arthritis*, ChiryoGaku 36(12):1264-67 (2002) ("Nishimoto 2002")
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FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1061	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. 1062	Pei-Show Juo, *Concise Dictionary of Biomedicine and Molecular Biology* (2002, 2nd ed.) ("Concise Dictionary of Biomedicine")
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Ex. 1064	Alan Kivitz et al., "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. 1066	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. 1067	Form 8-K, Abbott Laboratories (April 9, 2003) ("Abbott 8K")

FRESENIUS EXHIBIT NO.	DESCRIPTION
Ex. 1068	FDA Approves New Therapy for Rheumatoid Arthritis, Dec. 31, 2002, available at www.fda.gov/bbs/topics/ANSWERS/2002/ANS01186.html, with Affidavit of Duncan Hall (Internet Archive) ("FDA Talk Paper")
Ex. 1069	Products Approved for Marketing during 1998, Editorial, *Journal of Clinical Pharmacology* 39:439-441 (1999) ("1999 J. Clinical Pharm")
Ex. 1070	Excerpt of Physicians' Desk Reference, 54th Edition (2000) for Enbrel® (etanercept) ("2000 PDR Excerpt – Enbrel")
Ex. 1071	Mazumdar et al., "Golimumab," *mAbs* 1(5):422-31 (September/October 2009) ("Golimumab")
Ex. 1072	Reserved
Ex. 1073	Roche et al., Correlation of Interleukin-6 Production and Disease Activity in Polymyalgia Rheumatic and Giant Cell Arteritis, *Arthritis & Rheumatism*, Vol. 36, No. 9, Sept. 1993 ("Roche")
Ex. 1074	Blockmans et al., Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients, *Rheumatology*, Vol. 46 (2007) ("Blockmans")
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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 1-16 of U.S. Patent No. 9,750,752 ("the '752 patent"). Petitioners' request is supported by the Expert Declarations of Thomas M. Zizic, M.D. (Ex. 1002) and Howard L. Levine, Ph.D. (Ex. 1003), and the other exhibits submitted herewith.

The claims of the '752 patent are directed to methods of treating a patient with giant cell arteritis (GCA) by subcutaneous (SC) administration of a 162 mg fixed dose of tocilizumab every week or every other week. Although the '752 patent purports to claim priority to a provisional application filed on November 8, 2010, there is no description whatsoever in that application for treatment of GCA. The earliest application to which the '752 patent claims priority that even mentions GCA was filed on October 3, 2011. Thus, the '752 patent claims are entitled to a priority date no earlier than October 3, 2011.

[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.

GCA is a type of vasculitis that affects large- and medium-sized blood vessels, with clinical manifestations of headaches, visual impairment, fever and weight loss. By 2010, tocilizumab had been shown to be effective in treating many interleukin-6 (IL-6) mediated diseases, including rheumatoid arthritis (RA), and tocilizumab at an intravenous dosage of 8 mg/kg every four weeks had been approved by FDA for the treatment of RA. GCA was also known to be an IL-6 mediated inflammatory disease, with elevated IL-6 levels correlating with disease activity, leading researchers to treat GCA and the closely related condition, polymalygia rheumatica (PMR) with tocilizumab regimens that had been shown to be effective for treating RA. By the October 3, 2011 priority date, the prior art had disclosed that GCA was effectively treated with the approved 8 mg/kg intravenous tocilizumab dosing regimen.

The prior art also disclosed subcutaneous administration of tocilizumab as a preferable alternative to the intravenous method. Specifically, the prior art disclosed that RA patients could be safely and effectively treated with subcutaneous tocilizumab, administered as a 162 mg fixed dose every week or every other week. Following the same approach that had been shown to successfully treat GCA—*i.e.*, using the same dose and frequency that had been shown to be useful for treating RA—the next logical step would have been to employ the preferred subcutaneous tocilizumab regimen to treat GCA. The ’752

patent claims are obvious because a POSA would have been motivated to combine these disclosures to arrive at the claimed methods for treating GCA with a reasonable expectation of success.

The claims of the '752 patent were allowed only because the Examiner credited the applicant's alleged evidence of unexpected results. However, the applicant did not compare the claimed subject matter to the closest prior art—intravenous treatment of GCA with tocilizumab—but rather to treatment with an entirely different drug, prednisone. These results were therefore not relevant.

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 '752 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 '752 patent is available for IPR and that Petitioners are not barred or estopped from requesting IPR on the grounds raised in this petition. Moreover, neither Petitioners nor their privies or the real parties-in-interest have filed or been served with any complaint alleging

infringement or invalidity of the ’752 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 ’752 patent is not currently the subject of any litigation or post-grant proceedings.

The ’752 patent claims priority to Application No. 13/390,266, which issued as U.S. Patent No. 8,580,264 (“the ’264 patent”). On August 18, 2021, Petitioners filed a petition seeking *inter partes* review of claims 1-3 and 6-11 of the ’264 patent. *See* IPR 2021-01288. On September 24, 2021, Petitioners filed a petition seeking *inter partes* review of claims 4, 5, and 12 of the ’264 patent. *See* IPR 2021-01542.

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

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

Elizabeth J. Holland (lead counsel) Reg. No. 47,657 Daniel P. Margolis (backup counsel) to seek *pro hac vice* admission Goodwin Procter LLP 620 Eighth Avenue, New York, NY 10018, T: (212) 459 7236 Fax: (212) 658 9563	Daryl Wiesen (backup counsel) to seek *pro hac vice* admission Emily Rapalino (backup counsel) to seek *pro hac vice* admission Kevin J. DeJong (backup counsel) Reg. No. 64,762 Goodwin Procter LLP 100 Northern Ave. Boston, MA 02210 T: (617) 570 1156 Fax: (617) 649 1430

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

D. Service Information (§ 42.8(b)(4))

This Petition is being served by Federal Express Next Business Day Delivery to the correspondence address of record for the '752 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. Giant Cell Arteritis (GCA) and Other IL-6 Mediated Disorders

GCA, also called temporal arteritis, is a type of vasculitis that affects large- and medium-sized blood vessels, particularly the cranial branches derived from the carotid artery. Ex. 1002 ¶¶32-33; Ex. 1015 (Salvarini) at 1. The clinical manifestations range from headache, scalp tenderness, visual involvement or stroke, to less specific manifestations such as fever, malaise, or weight loss. Ex. 1014 (Savage) at 1; Ex. 1015 (Salvarini) at 4. A new-onset headache is the most frequent symptom. Ex. 1015 (Salvarini) at 4. Partial or complete loss of vision occurs in around 20% of patients. *Id.* GCA typically affects individuals aged above 50 years and is more common in women than men. *Id.* at 1.

Takayasu's arteritis is a variant of GCA chiefly affecting young females. Ex. 1012 (Seitz) at 1. In Takayasu's arteritis, the inflammation damages the large and medium-sized arteries, primarily the aorta, the large artery that carries blood

from the heart to the rest of the body, and its major branches. Ex. 1027 (Nishimoto 2008) at 1. The disease can lead to narrowed or blocked arteries, or to weakened artery walls that may bulge (aneurysm) and tear. Ex. 1002 ¶34. It can also lead to arm or chest pain, high blood pressure, and eventually heart failure or stroke. *Id.* Ongoing inflammation causes severe vascular damage and formation of stenoses and aneurysms, both of which may lead to fatal vascular accidents. *Id.*

PMR is another vascular disorder closely related to GCA, and the two frequently occur together. *Id.* ¶35; Ex. 1073 (Roche) at 1. Whereas GCA mainly involves the large- and medium-sized arteries, PMR is characterized by pain and stiffness in the neck, shoulder, and pelvic girdles. Ex. 1015 (Salvarini) at 2, 4;. Patients typically have shoulder pain that radiates distally toward the elbows. *Id.* at 4. Approximately 20% of patients with PMR also have GCA, and PMR is present in 40-60% of patients with GCA. *Id.* at 2; Ex. 1002 ¶36.

By 2010, it was well known that each of these vascular disorders—GCA, Takayasu's arteritis, and PMR—was characterized by increased levels of interleukin-6 (IL-6), a pro-inflammatory cytokine. Ex. 1002 ¶39. In 1993, it was reported that IL-6 plasma concentrations were increased in both PMR and GCA patients, and that "[t]he close correlation of plasma IL-6 concentrations with clinical symptoms suggests a direct contribution of this cytokine to the disease manifestations." Ex. 1073 (Roche) at 1; *see also* Ex. 1026 (Weyand 2005) at 3.

And in 1996, it was reported that IL-6 levels were elevated in patients with Takayasu's arteritis, and that IL-6 contributes to the pathogenesis of the disorder. Ex. 1048 (Park) at 1.

The IL-6 pathway was also recognized by 2010 as a pivotal pathway involved in immune regulation of many other diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and Castleman's disease. Ex. 1002 ¶¶40-44; Ex. 1066 (March 6, 2008 Report) at 1, 4–5; Ex. 1018 (PMDA 2008 Report) at 124; Ex. 1029 (Nishimoto 2008B) at 1. Notably, targeting of the IL-6 pathway with tocilizumab had become an established treatment for these IL-6-mediated disorders by 2010. In January 2009, the European Medicine Agency (EMA) approved tocilizumab for the treatment of RA based on pivotal clinical trials using 8 mg/kg every four weeks. Ex. 1019 (EMA Assessment Report) at 11, 27. And in January 2010, the FDA approved tocilizumab at dosages of 4 mg/kg and 8 mg/kg every four weeks for the treatment of RA. Ex. 1063 (2010 FDA Actemra Label) at 2; Ex. 1020 (BLA Approval Letter) at 1. Tocilizumab had also been approved in Japan at an intravenous dose of 8 mg/kg for treatment of not only RA, but also polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and Castleman's disease, all of which were known to be IL-6 mediated disorders. Ex. 1066 (March 6, 2008 Report) at 1, 4-5; Ex. 1018 (PMDA 2008 Report) at 124; Ex. 1029 (Nishimoto 2008B) at 1.

This wide-spread success of tocilizumab in treating IL-6 mediated disorders led naturally to its use in treating PMR, GCA, and Takayasu's arteritis. For example, an 8 mg/kg every four week intravenous dose of tocilizumab was shown to be effective in treating patients with PMR, and, because of the known clinical relationship between PMR and GCA, it was "anticipated that tocilizumab may become a treatment option for GCA." Ex. 1010 (Hagihara) at 3. This was confirmed in a subsequent study, wherein five patients with GCA and two with Takayasu's arteritis were treated with monthly tocilizumab infusions at 8 mg/kg , and each patient "achieved a rapid and complete clinical response" with "no relapse and no drug-related side effects." Ex. 1012 (Seitz) at 1. Thus, by 2010, the prior art had established that GCA could be treated by administering tocilizumab in accordance with regimens known to be safe and effective for treating other IL-6 mediated disorders, like RA. Ex. 1002 ¶44.

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

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, such as increased independence 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. For tocilizumab specifically, subcutaneous was considered the "preferred form of administration." Ex. 1011 (WO '621) at 4.

It was known in the prior art that it was preferable to administer an equivalent amount of an immunoglobulin,[3] like tocilizumab, as a subcutaneous dose every week or every other week, rather than an IV dose every four weeks, because it reduces serum concentration fluctuation around the same mean. Ex. 1002 ¶46; Ex. 1021 (Bonilla) at 15. Moreover, a fixed subcutaneous dose (i.e., not based on the weight of the patient) was considered preferable for monoclonal antibodies "when there is no advantage of one dosing approach over another from a PK [pharmacokinetic] and PD [pharmacodynamic] perspective," as it provides "better compliance, less risk for medical errors, and cost-effectiveness." Ex. 1022 (Wang) at 7, 18. Fixed dosing can also avoid or reduce errors that may occur in calculating and preparing individualized weight-based doses for patients. *Id*. Indeed, in view of these known advantages, by 2010 there were several biologics approved by FDA for subcutaneous administration using a fixed dose:

[3] Immunoglobulins are also referred to as antibodies. Ex. 1030 (Lobo 2004) at 1–3.

- Enbrel® (etanercept), approved in 1998 for treatment of RA. Ex. 1069 (1999 J. Clinical Pharm) at 3; Ex. 1070 (2000 PDR Excerpt – Enbrel) at 5.
- Humira® (adalimumab), approved in 2002 for treatment of RA. Ex. 1023 (2002 Humira FDA Label) at 7, 14, 16; Ex. 1067 (Abbott 8K) at 5; Ex. 1068 (FDA Talk Paper) at 5.
- Cimzia® (certolizumab pegol), approved in 2008 for treatment of Crohn's disease. Ex. 1024 (2009 PDR - Cimzia) at 4–5.
- Simponi® (golimumab), approved in April 2009 for the treatment of RA, among other indications. Ex. 1036 (TNF Blocker Wins Approval) at 1; Ex. 1071 (Golimumab) at 1; Ex. 1049 (2009 Simponi FDA Label) at 1, 4.

A Phase I/II clinical trial was accordingly initiated in 2009 to evaluate a 162 mg subcutaneous dose of tocilizumab, administered weekly or every other week as an alternative to the prior, intravenous method. Ex. 1011 (Ohta 2010) at 2. The study was carried out in RA patients, and the results were published in Ohta et al., which concluded that treatment with 162 mg weekly and every other week was "well tolerated" and "associated with good clinical response." Ex. 1011 (Ohta 2010) at 3.

VI. THE ’752 PATENT

A. Challenged Claims

Petitioners challenge claims 1–16 of the ’752 patent. The two independent claims (1 and 8) recite a “method of treating giant cell arteritis” by administering a fixed dose of 162 mg of tocilizumab, or an anti-IL-6R antibody, every week or every two weeks:

Independent Claims	Dependent Claims
1. A method of treating giant cell arteritis (GCA) in a patient comprising administering an anti-IL-6 receptor (IL-6R) antibody to the patient in an amount effective to treat the GCA, wherein the anti-IL-6R antibody is administered subcutaneously as a fixed dose of 162 mg per dose every week or every two weeks, and wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively.	2. The method of claim 1 wherein the fixed dose is administered every week. 3. The method of claim 1 wherein the fixed dose is administered every two weeks. 4. The method of claim 1 further comprising administering an initial course of corticosteroid to the patient. 5. The method of claim 1 wherein the effective amount reduces GCA signs and symptoms, maintains clinical remission, and/or reduces or stops corticosteroid to be administered to the patient.

	6. The method of claim 1 wherein the GCA is new onset GCA. 7. The method of claim 1 wherein the GCA is refractory GCA.
8. A method of treating giant cell arteritis in a patient comprising administering tocilizumab to the patient, wherein the tocilizumab is administered subcutaneously as a fixed dose of 162 mg per dose every week or every two weeks.	9. The method of claim 8 wherein the fixed dose is administered every week. 10. The method of claim 8 wherein the fixed dose is administered every two weeks. 11. The method of claim 8 further comprising administering an initial course of corticosteroid to the patient. 12. The method of claim 8 wherein the treatment reduces giant cell arteritis signs and symptoms in the patient. 13. The method of claim 8 wherein the treatment maintains clinical remission in the patient.

	14. The method of claim 8 wherein the treatment reduces or stops corticosteroid to be administered to the patient. 15. The method of claim 8 wherein the giant cell arteritis (GCA) is new onset GCA. 16. The method of claim 8 wherein the giant cell arteritis (GCA) is refractory GCA.

B. Prosecution History

On December 2, 2015, the Examiner rejected the then-pending claims as obvious in view of Christidis et al. The Examiner stated that Christidis teaches "a method of treating giant cell arteritis (GCA) by administering intravenous tocilizumab (TCZ) and an initial dose of prednisone corticosteroid" and "administering 8 mg/kg monthly intravenous infusions." Ex. 1004 ('752 Patent FH) at 725. The Examiner further stated that, "[a]bsent unexpected results, at the time the instant invention was made, one of skill in the art would have been motivated from the teachings of the reference to optimize the dosage and times of administration of the active ingredient, TCZ antibody, in the composition to obtain the best results." *Id.* at 726–27.

In response, the applicant argued that Christidis discloses intravenous administration of tocilizumab, not subcutaneous administration; that Christidis does not disclose a fixed dose of 162 mg; and that Christidis discloses monthly infusions, not every week or every two weeks. *Id*. at 754–55. The applicant also argued that Christidis "failed to provide a reasonable expectation that the presently claimed invention would be successful prior to the presently filed patent application" because "[t]here was nothing in Christidis et al. to provide the skilled person with a reasonable expectation of success before the present application was filed that non-intravenous administration (subcutaneous administration) of TCZ would reproduce the IL-6 serum levels achieved by intravenous administration of TCZ; or that non-intravenously administered TCZ could accomplish a therapeutic effect in large-sized and medium-sized arteries." *Id.* at 755 (emphasis omitted).

On June 7, 2016, the Examiner maintained the rejection over Christidis. The Examiner stated that the applicant "failed to show unexpected results by subcutaneous administration of the same IL-6R antibody administered in the prior art, and the results would have been expected by one of ordinary skill in the art for treatment of GCA." *Id*. at 767.

In response to the Examiner's renewed obviousness rejection based on Christidis, the applicant submitted a Declaration from Dr. John Stone, who asserted that the invention "addressed a long-felt and unmet medical need that

existed in 2011, and is also associated with results that would have been unexpected or surprising as of 2011." *Id*. at 904. According to Dr. Stone, the claimed invention achieved "surprise results" in comparison with prednisone. *Id.* at 901–04. Relying on Dr. Stone's declaration, the Examiner allowed the claims, stating that the declaration "provides evidence of the efficacy, advantage and surprising result of subcutaneous administration of 162 mg tocilizumab every week or every other week for the treatment of giant cell arteritis (GCA)." *Id*. at 913.

Notably, the Examiner failed to substantively consider during prosecution any reference which disclosed subcutaneous administration of 162 mg of tocilizumab in treating IL-6 mediated disorders (e.g., Ohta 2010). And, as explained *infra* Section IX.D, the Examiner incorrectly credited applicant's purported evidence of unexpected results—the applicant did not provide any evidence that subcutaneous treatment of GCA with tocilizumab provided unexpected results compared to the closest prior art, which was intravenous treatment with tocilizumab, not prednisone.

VII. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art ("POSA") to whom the '752 patent is directed would have been an individual with an M.D. specializing in the treatment of autoimmune and inflammatory disorders and having several years of experience treating patients with such disorders, including GCA and RA, or having several

years of experience researching treatments for autoimmune and inflammatory disorders, including GCA and RA. Ex. 1002 ¶30.

VIII. PRIORITY DATE

The '752 patent claims priority to Provisional Application No. 61/411,015 ("the '015 Application"), filed on November 8, 2010. However, all of the claims of the '752 patent are directed to treating GCA with tocilizumab, and the '015 Application does not disclose administering tocilizumab to a patient with GCA. Ex. 1006 ('015 Application); Ex. 1002 ¶¶60–63.

For a patent to claim priority to the filing date of its provisional application, the provisional must "'contain a written description of the invention . . . in such full, clear, concise, and exact terms,' 35 U.S.C. § 112 ¶ 1, to enable an ordinarily skilled artisan to practice the invention *claimed* in the *non-provisional* application." *Purdue Pharma L.P. v. Iancu*, 767 F. App'x 918, 923 (Fed. Cir. 2019) (internal citations omitted). To satisfy the written description requirement, the disclosure of the provisional application must "reasonably convey to those skilled in the art that as of the claimed priority date the inventor was in possession of the later claimed subject matter." *L.A. Biomed. Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057-58 (Fed. Cir. 2017). The '015 Application identifies a number of IL-6 mediated disorders that may be treated with tocilizumab, but GCA is notably absent. *See, e.g.*, Ex. 1006 ('015

Application) at 20, 28, 41.[4] The specification filed with the '015 Application contained five Examples, none of which relate to treatment of GCA. *Id.* at 45-69; Ex. 1002 ¶61. In fact, GCA is not mentioned anywhere in the '015 Application. Ex. 1002 ¶61. Thus, the specification of the '015 Application does not reasonably convey to a POSA that the inventors were in possession of the subject matter claimed in the '752 patent. *Id.*; *Purdue Pharma L.P.*, 767 F. App'x at 923 ("[S]imply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses . . . Such 'laundry list' disclosures do not provide adequate specificity to constitute written description support."), Because there is no written description support for the '752 patent claims in the '015 Application, the claims are not entitled to priority to November 8, 2010.

[4] While the '015 Application identifies PMR among the list of conditions that may be treatable with an IL-6 receptor antibody (Ex. 1006 at 28), and, as discussed below, a POSA would have found it obvious to treat GCA based on the known relationship between GCA and PMR and the prior art disclosure that tocilizumab effectively treats PMR, "[e]ntitlement to a filing date extends only to the subject matter that is disclosed; not to that which is obvious." *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 870 (Fed. Cir. 2010).

GCA was not identified by the applicant as being treatable with tocilizumab until the second-filed provisional application, No. 61/542,615, filed on October 3, 2011 ("the '615 Application"). With the '615 Application, the applicant added GCA to the list of IL-6 mediated disorders that may be treated with tocilizumab, and added four new examples, Examples 6–9, that appear in the specification of the '752 patent. Ex. 1038 ('615 Application) at 49, 103-117; Ex. 1002 ¶64. Example 9 describes a protocol for the treatment of GCA by subcutaneously administering 162 mg tocilizumab either weekly or every other week.[5] Ex. 1038 ('615 Application) at 115-117; Ex. 1002 ¶64. No clinical results are reported, yet Example 9 of the '615 Application nevertheless states that "[i]t is anticipated that subcutaneously administered TCZ as disclosed herein will effectively treat GCA, for example by reducing GCA signs and symptoms, maintaining clinical remission, and/or reducing or stopping corticosteroid use in the patient with GCA." Ex. 1038 at 117. Thus, the '752 patent claims are entitled to a priority date no earlier than October 3, 2011.

[5] The '615 Application included two examples titled "Example 8." Ex. 1038 at 112, 115. The example related to GCA was later renamed as Example 9, which is how it appears in the specification of the '752 patent.

IX. CLAIM CONSTRUCTION

In an IPR, the terms of challenged claims are construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," just as they are in district court. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). For the purpose of this proceeding, any term not expressly discussed should be given its ordinary and customary meaning to a POSA as of the time of the alleged invention, which Petitioners assume for purposes of this IPR only to be October 3, 2011.[6]

A. "fixed dose" (claim 1 and 8)

The term "fixed dose" is defined in the specification as "a dosage of a drug, such as an anti-IL-6R antibody which is administered without regard to the patient's weight or body surface area (BSE), i.e., it is not administered as either a mg/kg or mg/m^2 dose." Ex. 1001 at 15:22–25.

[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 Chugai, or court rulings. Petitioners do not waive any argument concerning indefiniteness or invalidity under 35 U.S.C. § 112.

B. "new onset GCA" (claims 6 and 15)

The term "new onset GCA" refers to GCA in a patient that has not previously been treated. *See* Ex. 1001 at 55:31–33 ("Patients may be either new onset or refractory (i.e. GCA patients who have responded inadequately to previous therapy with corticosteroids (CS)."); Ex. 1002 ¶118.

C. "refractory GCA" (claims 7 and 16)

The term "refractory GCA" refers to GCA in a patient that has responded inadequately to previous therapy with corticosteroids. *See* Ex. 1001 at 55:31–33 ("Patients may be either new onset or refractory (i.e. GCA patients who have responded inadequately to previous therapy with corticosteroids (CS)."); Ex. 1002 ¶119.

X. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claims 1–16 of the '752 patent under § 103 for the reasons explained in this petition, which are summarized as follows:

Ground No	Claims and Basis
1	Claims 1–16 are obvious over Seitz and Ohta 2010
2	Claims 1–16 are obvious over Hagihara and Ohta 2010

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

Seitz is an article titled "Rapid induction of remission in large vessel vasculitis by IL-6 blockage," published in *Swiss Medical Weekly, The European Journal of Medical Sciences*, on January 17, 2011. Ex. 1012 (Seitz). Seitz is prior art under pre-AIA § 102(a). Seitz discloses a study in which five patients with GCA were treated with tocilizumab intravenous infusions at 8 mg/kg. Ex. 1012 (Seitz) at 1. Tocilizumab was given every other week for the first month and once monthly thereafter. *Id.* All patients in the study "achieved a rapid and complete clinical response and normalization of the acute phase protein" and "[n]o relapse and no drug-related side effects were noted." *Id.* The authors concluded that "[c]ollectively the data suggest that IL-6 blockade using tocilizumab qualifies as a therapeutic option to induce rapid remission in large vessel vasculitides," including "not only for patients with newly diagnosed GCA but also for patients with relapse of the disease at moderate to high doses of GCs." *Id.* at 1, 4.

Ohta 2010 is an abstract published online on September 28, 2010 on the American College of Rheumatology (ACR) website, and in ACR's print journal, *Arthritis & Rheumatism*, in October 2010. Founded in 1934, the ACR is a not-for-profit, professional association committed to advancing the specialty of rheumatology and serves over 7,700 physicians, health professionals, and scientists

worldwide who work in the medical subspecialty of rheumatology. Ex. 1002 ¶103 n.40. During prosecution of the '677 patent,[7] the applicant represented that the "Ohta et al. abstract was first published [on] September 28, 2010 on the ACR website." Ex. 1007 ('677 Patent File History) at 325. Applicant also submitted correspondence from the Editorial Coordinator for ACR, responding to applicant's attorney's inquiry as to the publication date of Ohta 2010, stating that "I checked on this for you and I can confirm that the abstract you refer to, [Ohta 2010], was first published on September 28, 2010 on the ACR website."[8] *Id.* at 289–90. Ohta 2010 is therefore prior art to the '752 patent under pre-AIA § 102(b) because it was publicly available more than one year before the October 3, 2011 priority date. *Constant v. Advanced Micro-Devices Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness.").

[7] The '677 patent shares the same specification as the '752 patent, and also claims priority to the same '015 and '615 provisional applications.

[8] As explained by Dr. Zizic, the ACR website is a publicly available resource for both physicians and patients, providing up to date information on education, research, and practice support related to the treatment of rheumatic disorders. Ex. 1002 ¶103 n.40.

Ohta 2010 discloses an open-label, multi-center clinical study "[t]o evaluate the safety, pharmacokinetics and efficacy of tocilizumab subcutaneous injection." Ex. 1011 (Ohta 2010) at 2. The abstract teaches that "[i]nterleukin-6 (IL-6) plays pathologic roles in immune-inflammatory disease as rheumatoid arthritis," and that "[t]ocilizumab is a humanized monoclonal antibody which inhibits IL-6 signal transduction by binding with both soluble and membranous IL-6 receptor." *Id.* Ohta 2010 also states that, while "[i]t has been shown IL-6 inhibition therapy by tocilizumab is effective in RA, JIA and Castleman's disease," tocilizumab has previously been administered "by one hour infusion." *Id.* Ohta 2010 further explains that subcutaneous administration was being evaluated because of its "ease of use." *Id*. Patients received a fixed dose of 162 mg tocilizumab subcutaneously either weekly or every other week for the treatment of RA. *Id.* at 2–3. Ohta 2010 reports that both regimens were "well tolerated" and "associated with good clinical response." *Id.* at 3.

The only difference between the '752 patent claims and the treatment regimen disclosed in Seitz is that the claims are directed to a 162 mg subcutaneous dose every week or every other week to treat GCA, whereas Seitz reports treating GCA with an intravenous dose of 8 mg/kg once per month. As set forth below for Ground 1, a POSA would have been motivated to combine the disclosure in Seitz—that GCA can be effectively treated by administering tocilizumab— with

the subcutaneous dosing regimens disclosed in Ohta 2010 as safe and effective for treating RA (i.e., a fixed dose of 162 mg administered subcutaneously weekly or every two weeks), to arrive at the claimed methods for treatment of GCA.

The claims are also obvious in view of Hagihara and Ohta 2010. Hagihara is an article titled "Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica," published in *The Journal of Rheumatology*, in May 2010. Ex. 1010. Hagihara is prior art to the '752 patent under pre-AIA § 102(b). Hagihara states that "[s]ince interleukin-6 (IL-6) has been shown to play a major role in sustaining disease activity in PMR, treatment of a patient with PMR refractory to corticosteroids was initiated with the humanized anti-IL-6 receptor antibody tocilizumab." *Id.* at 3. The patient was treated with infusion of tocilizumab 8 mg/kg every 4 weeks. *Id.* Hagihara reports that the tocilizumab treated "ended clinical symptoms," and allowed prednisolone to be reduced to 6 mg/day. *Id.*

Hagihara further discloses that "[i]n the literature, the clinical relationship between PMR and GCA has been established, since 16%–21% of patients with PMR also had GCA, and PMR was reportedly present in 40%–60% of patients with GCA." *Id.* Based on this known clinical relationship, and the success of tocilizumab in treating PMR, Hagihara concluded that it is "anticipated that tocilizumab may become a treatment option for GCA." *Id.*

The only difference between the '752 patent claims and the treatment regimen disclosed in Hagihara is that the claims are directed to a 162 mg subcutaneous dose every week or every other week for treatment of GCA, whereas Hagihara reports an intravenous dose of 8 mg/kg every four weeks for the treatment of PMR, and suggests that it would also be useful for treating GCA. As set forth below for Ground 2, a POSA would have been motivated to combine the disclosure in Hagihara with the subcutaneous dosing regimens disclosed in Ohta 2010 as safe and effective for treating RA (i.e., a fixed dose of 162 mg administered subcutaneously weekly or every two weeks), to arrive at the claimed methods for treatment of GCA.

B. Ground 1: Claims 1–16 Are Obvious Over Seitz and Ohta 2010

Independent claims 1 and 8 are directed to a method of treating GCA by administering a subcutaneous fixed dose of 162 mg of an anti-IL-6 receptor (IL-6R) antibody (claim 1) or tocilizumab (claim 8), every week or every two weeks. A POSA would have been motivated by Seitz and Ohta 2010 to treat a GCA patient with a fixed dose of 162 mg of tocilizumab (an anti-IL-6 receptor antibody) every week or every two weeks, with a reasonable expectation of success.

1. A POSA Would Have Been Motivated to Combine Seitz and Ohta 2010

The prior art reported that RA and GCA were both known to be IL-6 mediated inflammatory diseases, with elevated IL-6 levels correlating with disease

activity. Ex. 1012 (Seitz) at 2; Ex. 1011 (Ohta 2010) at 2. By the time the study reported in Seitz had begun, the IL-6 inhibitor, tocilizumab, had a long history of successful use in treating RA, and skilled artisans were using the known tocilizumab regimens to treat other IL-6 mediated disorders. *See*, *e.g.*, Nishimoto 2008 at 1198; Ex. 1002 ¶131. Accordingly, the 8 mg/kg intravenous tocilizumab monthly dosing regimen administered by Seitz to treat GCA was essentially identical to the regimen known at that time to be optimally safe and effective for treating RA. *See* Ex. 1027 (Nishimoto 2008) at 2 ("8 mg/kg every four weeks is an optimal dosage for maintaining appropriate serum levels of the drug."); Ex. 1002 ¶125. As discussed above, Seitz disclosed that this regimen safely and effectively treated GCA patients. *Supra* § IX.A.

Shortly after the patients in the Seitz study were treated, Ohta 2010 was published, disclosing a subcutaneous tocilizumab dosing regimen as an alternative to the known intravenous regimen. Ohta 2010 reports that "[t]ocilizumab subcutaneous injection is well tolerated up to 162 mg QW and is associated with good clinical response both 162 mg Q2W and QW." Ex. 1011 (Ohta 2010) at 3. Moreover, "[n]o treatment related serious adverse event were observed, and there are also no serious injection site reaction." *Id.* In fact, the results reported in Ohta 2010 showed that tocilizumab administered subcutaneously at a fixed dose of 162 mg every week or every other week resulted in a greater improvement in disease

indicators in RA patients than had been previously observed with intravenous tocilizumab. Ex. 1002 ¶126. For example, the efficacy as measured by ACR 20/50/70 scores,[9] was higher for both 162 mg subcutaneous regimens than had been reported for the intravenous regimen of tocilizumab for the treatment of RA, as shown below:

	Dosage	ACR20 (%)	ACR50 (%)	ACR70 (%)
Ohta 2010	Subcutaneous 162 mg	83.3 (Q2W) 91.7 (QW)	83.3 (Q2W) 83.3 (QW)	58.3 (Q2W) 66.7 (QW)
Actemra Label	IV 8 mg/kg every four weeks	70	44	28
Maini 2006	IV 8 mg/kg every four weeks	63	41	16

Ex. 1011 (Ohta 2010) at 3; Ex. 1063 (2010 Actemra FDA Label) at 17 (Table 3); Ex. 1058 at 6; Ex. 1025 (Maini 2006) at 6.

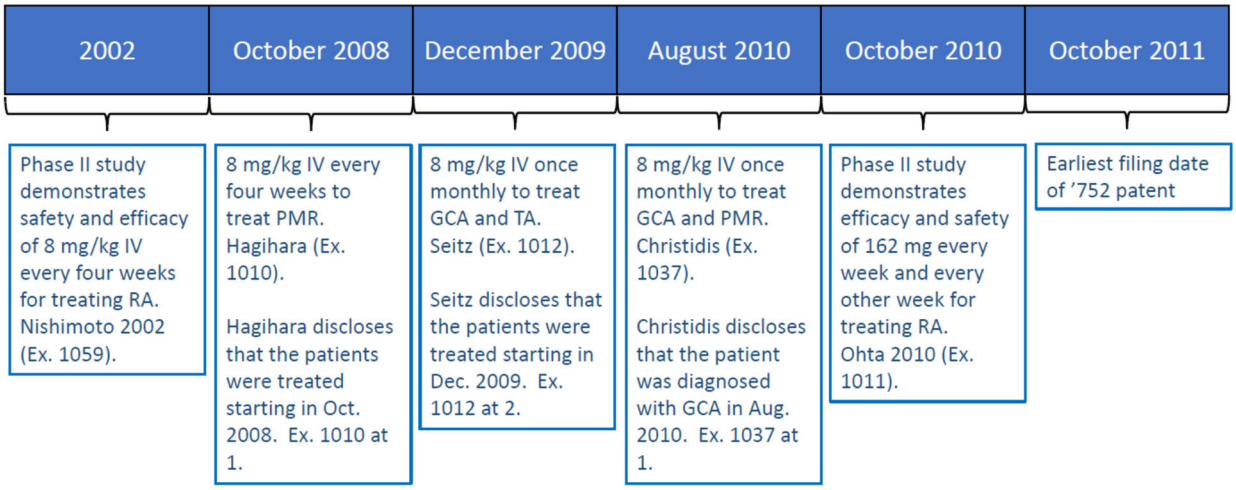
Even beyond this potential improvement in efficacy, it was well known that subcutaneous administration is generally preferred over intravenous administration. Subcutaneous administration offers significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered therapy. Ex. 1002 ¶45; Ex.

[9] ACR20/50/70 responses are measurements of efficacy for RA treatment. Ex. 1001 at 33:52–63.

1016 (Berger) at 11–13; Ex. 1070 (Kivitz) at 2. Indeed, Chugai had itself announced in the prior art that subcutaneous was the "preferred" form of tocilizumab. Ex. 1034 (WO '621) at 4. Furthermore, the prior art reported that more frequent administration of an equivalent amount of an immunoglobulin by subcutaneous injection instead of by IV advantageously provides more stable serum concentration levels. Ex. 1021 (Bonilla) at 15. The prior art also disclosed that a fixed subcutaneous dose was considered preferable to a weight-based dose for monoclonal antibodies in the absence of a specific reason to the contrary, as the former provides "better compliance, less risk of medical errors, and cost effectiveness." Ex. 1022 (Wang) at 7, 18; Ex. 1002 ¶127. Moreover, there were several antibodies and similar biologics 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), reinforcing to a POSA that subcutaneous administration of an antibody was not only well known, but preferred for many patients. *Supra* § IV.B; Ex. 1002 ¶48.

In summary, while tocilizumab had been used to successfully treat GCA at the intravenous dose known to be useful for treating RA, by the time of the alleged invention of the '752 patent, it was also known that subcutaneous tocilizumab was preferred and that it could be administered subcutaneously at a fixed dose of 162

mg every week or every two weeks to treat RA while still achieving "good clinical response." Ex. 1011 (Ohta 2010) at 3. The following timeline illustrates these developments:



Ex. 1002 ¶129. Thus, following the same approach that was used by Seitz and others—i.e., using the tocilizumab dose and frequency that had been shown to be useful for treating RA to treat GCA—the next logical step would have been to employ the new and "preferred" subcutaneous tocilizumab regimen to treat GCA. Ex. 1002 ¶130. More specifically, a POSA would have been motivated to combine the disclosure in Seitz—that GCA can be effectively treated by administering tocilizumab in accordance with known dosing amounts and frequencies for treating RA— with the subcutaneous dosing regimens disclosed in Ohta 2010 as safe and effective for treating RA (i.e., a fixed dose of 162 mg administered subcutaneously weekly or every two weeks), to arrive at the claimed methods for treatment of GCA. *Id.* ¶¶120-130.

2. A POSA Would Have Had a Reasonable Expectation of Success

A POSA would have reasonably expected the claimed subcutaneous treatment regimen to successfully treat GCA in view of the prior success in using known intravenous tocilizumab RA regimens to treat IL-6 mediated disorders, generally, including GCA. Ex. 1002 ¶¶By 2010, tocilizumab had received regulatory approval for treatment of various IL-6 mediated disorders. Ex. 1002 ¶¶131-137. In 2005, tocilizumab was approved in Japan for treatment of Castleman's disease, an IL-6 mediated disorder, with an 8 mg/kg intravenous dosage. Ex. 1013 (Product Overview) at 4. In 2008, Japan also approved tocilizumab at 8 mg/kg for treatment of RA, polyarticular-course juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. Ex. 1066 (March 6, 2008 Report) at 1, 4–5. In January 2010, the FDA approved tocilizumab at a dosage of 4 or 8 mg/kg every four weeks for the treatment of rheumatoid arthritis, noting that "[t]ocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6 mediated signaling through these receptors." Ex. 1063 (2010 Actemra FDA Label) at 12; Ex. 1028 (2011 Actemra FDA Label) at 13; Ex. 1058 (2011 PDR-Actemra) at 5; Ex. 1041 (Thompson) at 1.

It had also been reported in several prior art articles that GCA patients were successfully treated with the same 8 mg/kg intravenous dose of tocilizumab known

to be useful for treating RA and other IL-6 mediated disorders. Seitz discloses that five patients with GCA were successfully treated with 8 mg/kg once a month, with each patient achieving "a rapid and complete clinical response." Ex. 1012 (Seitz) at 1. While Seitz acknowledges that the study was not designed to conclusively establish efficacy,[10] the rapid and complete clinical response in all tested patients, particularly in view of tocilizumab's well-established efficacy in treating other IL-6 disorders, would have provided a POSA with at least a reasonable degree of certainty that the treatment regimen was efficacious for treating GCA. Ex. 1002 ¶132. Likewise, Christidis discloses that a patient with GCA was successfully treated with intravenous infusions of tocilizumab at 8 mg/kg every four weeks, and "within 24 [hours] of the first infusion, the patient reported excellent response with resolution of pain in her shoulders and pelvic girdle." Ex. 1037 (Christidis) at 2. And Beyer discloses that three patients with GCA were treated with 8 mg/kg every

[10] Seitz states that "[t]hree limitations have to be mentioned. First, the non-experimental study design, which does not allow efficacy to be inferred in the absence of a control group; second, the small number of patients, and third, the short observation time. Nevertheless, the fact that all patients responded to this IL-6 targeting strategy argues for interesting therapeutic potential." Ex. 1012 (Seitz) at 3.

four weeks of tocilizumab, and "[a]ll patients tolerated tocilizumab well and showed a rapid clinical response with normalization of symptoms and inflammation markers (CRP, serum amyloid A)." Ex. 1042 (Beyer) at 1. Thus, the prior art taught that tocilizumab regimens that were used to treat RA, another IL-6 mediated disorder, could also be used to treat GCA. Because Ohta 2010 taught that RA could be safely and effectively treated with a 162 mg fixed dose administered subcutaneously weekly or every other week, a POSA would have reasonably expected that these subcutaneous regimens could also be used to successfully treat GCA, another IL-6 mediated disorder for which tocilizumab had been shown to be effective. Ex. 1002 ¶133.

The published pharmacokinetic properties of tocilizumab would have further led a POSA to reasonably expect that subcutaneous administration of a 162 mg fixed dose of tocilizumab would be as safe and effective for treating GCA as the intravenous regimen employed by Seitz. Ex. 1002 ¶134. The prior art reported that subcutaneously administered tocilizumab inhibited the effects of IL-6 to a similar extent as intravenous administration of an equivalent amount of the drug. *Id.* Georgy reports results of an open-label study on the pharmacokinetics and pharmacodynamics after subcutaneous and intravenous administration of tocilizumab, and concludes that "the sIL-6R-TCZ complex levels and CRP response were comparable following 162 mg SC and IV administration." Ex. 1044

(Georgy) at 3. These markers were known to reflect levels of tocilizumab sufficient to inhibit IL-6. Ex. 1029 (Nishimoto 2008B) at 4–5 ("CRP is therefore a useful surrogate marker for tocilizumab levels that are high enough to inhibit the effects of IL-6 in patients"); Ex. 1002 ¶134. The prior art also taught that an antibody may be administered subcutaneously every week or every other week instead of every four weeks intravenously in an amount that, "over time is generally equivalent," and that more frequent subcutaneous dosing would provide the same mean serum levels, but with higher troughs and lower peaks. Ex. 1021 (Bonilla) at 15.

For an average patient weighing 70 kg, an intravenous dosage of 8 mg/kg every month of tocilizumab corresponds to approximately 560 mg/every four weeks, or 140 mg/week. A POSA would therefore have reasonably expected that the 162 mg dose of tocilizumab every week disclosed by Ohta 2010 would have been at least as efficacious as an 8 mg/kg monthly intravenous dose for treating GCA. Ex. 1002 ¶135. And, as noted above, Ohta 2010 disclosed that a 162 mg every week subcutaneous dose was "well tolerated." Ex. 1012 (Ohta 2010) at 3. Furthermore, a POSA would have expected that this dose could be administered to a patient regardless of weight (i.e., as a fixed dose). Ex. 1002 ¶135. The prior art taught that large differences in tocilizumab AUC "did not affect efficacy or safety in a clinically relevant manner," and fixed dosing was known to be preferable to

weight-based dosing for drugs with such a large therapeutic window. Ex. 1019 (EMA Assessment Report) at 24; Ex. 1022 (Wang) at 7, 17. Accordingly, a POSA would have reasonably expected that a 162 mg fixed subcutaneous dosage of tocilizumab every week would successfully treat GCA. Ex. 1002 ¶135.

A POSA would also have reasonably expected that a 162 mg fixed subcutaneous dose of tocilizumab *every other week* would also successfully treat GCA. The prior art disclosed that the intravenous tocilizumab dosage administered to a GCA patient could be reduced to 4 mg/kg every four weeks once clinical symptoms were under control, and that the patient remained in remission after treatment at the lower dose. Ex. 1037 (Christidis) at 2; Ex. 1002 ¶136. A POSA would also have known that tocilizumab was approved by the FDA for treatment of RA at a 4 mg/kg every four week dose. Ex. 1063 (2010 Actemra FDA Label); Ex. 1041 (Thompson) at 1. For an average patient weighing 70 kg, a 4 mg/kg every four week dosage of tocilizumab corresponds to a dose of 280 mg/every four weeks, or 140 mg every other week. Thus, a POSA would have understood that a 162 mg dose every other week would be at least as efficacious as an 4 mg/kg every four week intravenous dose for an average patient. Ex. 1002 ¶137. Accordingly, a POSA would have reasonably expected that a fixed 162 mg subcutaneous dosage of tocilizumab every other week would also successfully treat GCA. Ex. 1002 ¶137.

Notably, the '752 patent specification does not contain any clinical results for the treatment of GCA using the claimed subcutaneous treatment regimens. And yet, the named inventors stated in the specification that "[i]t is anticipated that subcutaneously administered TCZ as disclosed herein will effectively treat GCA." Ex. 1001 at 56:63–64. Therefore, Patent Owner cannot credibly contend that a POSA would not have had a reasonable expectation of success. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) (affirming obviousness based on inventors' admissions in specification: "Nor is there any unfairness in holding the inventors to the consequences of their admissions."); *see also Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1381 (Fed. Cir. 2019) (a specification that "provide[s] nothing more than the mere claim that [the claimed invention] might work, even though persons of ordinary skill in the art would not have thought it would work" is invalid for lack of written description).

3. Application to the Claims

a) Claims 1 and 8

By combining Seitz and Ohta 2010, a POSA would have arrived at a method of treating GCA in a patient comprising administering tocilizumab (an anti-IL-6R antibody) subcutaneously as a fixed dose of 162 mg every week or every other week, as recited in claims 1 and 8. Ex. 1002 ¶139. As explained above, a POSA

would have been motivated to combine Seitz and Ohta 2010 in this manner, and would have had a reasonable expectation that the treatment regimen would have been successful in treating GCA. *Supra* §§ IX.B.1-B.2.

Claim 1 further recites that the anti-IL-6R antibody "comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively." Ohta 2010 discloses administration of tocilizumab, which comprises the light chain and heavy chain amino acid sequences of SEQ ID. Nos. 1 and 2, respectively. The following evidence—including Patent Owner Chugai's and the '752 patent inventors' own admissions—makes clear that tocilizumab has the claimed amino acid sequences:

- The '752 patent specification confirms that tocilizumab has the claimed amino acid sequences: "FIGS. 7A and 7B depict the amino acid sequences of the ***light chain*** (FIG. 7A: SEQID NO: 1) ***and heavy chain*** (FIG. 7B: SEQID NO:2) ***of Tocilizumab***." Ex. 1001 at 7:1–3 (emphasis added).
- During prosecution of the '752 patent, the Examiner stated that, "[a]lthough [Christidis 2011] does not teach the sequences for the heavy and light chains of TCZ, the sequences recited in claim 1 of the instant application are intrinsic properties of the TCZ antibody of the reference." Ex. 1004 ('752 Patent File History) at 726. The applicant did not disagree with the Examiner's conclusion.

- During prosecution of parent and child patents, the listed inventors also confirmed that tocilizumab has the claimed sequences. During prosecution of the parent '264 patent, the Examiner rejected claims as anticipated by Ohta 2010 which discloses tocilizumab, asserting that the "amino acid sequence characteristics would be inherent in the antibody of the prior art." Ex. 1005 ('264 Patent File History) at 1004. The applicant did not disagree with the Examiner's conclusion that tocilizumab inherently has the claimed amino acid sequences. Instead, the applicant submitted an inventor declaration to antedate Ohta 2010. In the declaration, 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 1025, 1027. Likewise, during prosecution of U.S. Patent No. 10,874,677 ("'677 patent"), the inventors again admitted in a declaration that tocilizumab "comprises the light chain and heavy chain amino acid sequences as in Figs. 7A-B of the above application." Ex. 1007 ('677 Patent File History) at 257.
- As explained by Dr. Levine, tocilizumab inherently has the claimed amino acid sequences for the heavy and light chains. S*ee generally* Ex. 1003.

Therefore, the tocilizumab disclosed in Ohta 2010 is an "anti-IL-6R antibody compris[ing] the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively," as set forth in claim 1 of the '752 patent. *See generall*y Ex. 1003; Ex. 1002 ¶147. And for the reasons set forth above, the treatment regimen recited in claim 1 is obvious. *Supra* §§ IX.B.1-B.2.

b) Claims 2 and 9 Are Obvious

Claim 2 depends from claim 1 and further requires that "the fixed dose is administered every week." Likewise, claim 9 depends from claim 8, and also further requires that "the fixed dose is administered every week."

As discussed above, a POSA would have been motivated to combine Seitz and Ohta 2010 to arrive at a method of treating GCA comprising administering tocilizumab subcutaneously at a fixed dose of 162 mg every week, and would have had a reasonable expectation in so doing. *Supra* §§ IX.B.1-B.2. Thus, claims 2 and 9 are also obvious. Ex. 1002 ¶151.

c) Claims 3 and 10 Are Obvious

Claim 3 depends from claim 1, and further recites "wherein the fixed dose is administered every two weeks." Likewise, claim 10 depends from claim 8, and further recites "wherein the fixed dose is administered every two weeks."

As discussed above, a POSA would have been motivated to combine Seitz and Ohta 2010 to arrive at a method of treating GCA comprising administering

tocilizumab subcutaneously at a fixed dose of 162 mg every other week, and would have had a reasonable expectation of success in so doing. *Supra* §§ IX.B.1-B.2; Ex. 1002 ¶153. Thus, claims 3 and 10 are also obvious. Ex. 1002 ¶153.

d) Claims 4 and 11 Are Obvious

Claim 4 depends from claim 1, and further recites "administering an initial course of corticosteroid to the patient." Likewise, claim 11 depends from claim 8, and further recites "administering an initial course of corticosteroid to the patient."

Seitz discloses that the GCA patients had each been administered prednisone, the most commonly used corticosteroid, before infusion with tocilizumab. Ex. 1012 (Seitz) at 2; Ex. 1002 ¶¶154-155. Therefore, by combining Seitz and Ohta 2010, a POSA would have arrived at a method of treating GCA using an initial course of corticosteroids, following by administration with tocilizumab subcutaneously at a fixed dose of 162 mg every week or every other week. Ex. 1002 ¶155. Moreover, a POSA would have known that corticosteroids were the cornerstone therapy for treating GCA and should be started immediately to prevent severe consequences of the disease, such as blindness. Ex. 1043 (Warrington) at 2 ("[G]lucocorticosteroid therapy should be initiated promptly after a diagnosis of GCA is suspected.").

Accordingly, a POSA would have been motivated to administer a 162 mg subcutaneous fixed dose of tocilizumab to treat a GCA patient following an initial

course of corticosteroid, and would have had a reasonable expectation of success in so doing, for substantially the same reasons as set forth with respect to claims 1 and 8. Ex. 1002 ¶157. Therefore, claims 4 and 11 are also obvious.

e) Claims 5, 12-14 Are Obvious

Claim 5 depends from claim 1, and further recites "wherein the effective amount reduces GCA signs and symptoms, maintains clinical remission, and/or reduces or stops corticosteroid to be administered to the patient." Similarly, claim 12 depends from claim 8, and further recites "wherein the treatment reduces giant cell arteritis signs and symptoms in the patient"; claim 13 depends from claim 8, and further recites "wherein the treatment maintains clinical remission in the patient"; and claim 14 depends from claim 8, and further recites "wherein the treatment reduces or stops corticosteroid to be administered to the patient."

Seitz discloses that treatment with tocilizumab caused a reduction in GCA signs and symptoms, maintained clinical remission, and allowed a reduction in corticosteroids to be administered to the treated patients. Ex. 1012 (Seitz) at 2. Accordingly, a POSA would have reasonably expected the claimed treatment regimen—which, as discussed above, a POSA would have reasonably expected to be similarly effective as the 8 mg/kg every four week intravenous regimen—to similarly "reduce[] GCA signs and symptoms, maintain[] clinical remission, and/or reduce[] or stop[] corticosteroid to be administered to the patient," as recited in

claim 5. Ex. 1002 ¶162. Likewise, a POSA would have reasonably expected the claimed treatment regimen to "reduce[] giant cell arteritis signs and symptoms in the patient," as recited in claim 12, to "maintain[] clinical remission in the patient," as recited in claim 13, and to "reduce[] or stop[] corticosteroid to be administered to the patient," as recited in claim 14. *Id.*

The limitations in dependent claims 5, and 12–14 are also inherently disclosed in the prior art. "[T]he prior art need only meet the inherently disclosed limitation to the extent the patented method does." *King Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010). In *King Pharm.*, the Federal Circuit concluded that a claimed bioavailability result was inherent in practicing the prior art because the patent at issue disclosed nothing more than the exact steps disclosed in the prior art. *Id.*; *see also Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001) ("A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations.").

The '752 patent does not explain how to achieve the claimed results beyond the simple act of administering the treatment regimen of 162 mg of tocilizumab to a GCA patient. Example 9 is the only example in the patent that relates to treatment of GCA. Ex. 1001 at 55:20–56:67. The example describes a "protocol for treating patients with GCA" in which patients would be subcutaneously

administered two doses of 162 tocilizumab every week or every other week. *Id.* But the example provides no clinical results. Indeed, the patent merely states that "[i]t is anticipated that subcutaneously administered TCZ as disclosed herein will effectively treat GCA, for example by reducing GCA signs and symptoms, maintaining clinical remission, and/or reducing or stopping corticosteroid use in the patient with GCA." *Id.* at 56:63–68. Therefore, like the bioavailability limitation deemed inherent by the Federal Circuit in *King Pharm.*, the functional result limitations of claims 5, and 12–14 merely reflect the "natural result" of administering the claimed regimen, and are inherently disclosed by the combination of Seitz and Ohta 2010. *See also Persian Pharm. v. Alvogen Malta Oper.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) ("[I]nherency may supply a missing claim limitation in an obviousness analysis where the limitation at issue is the natural result of the ***combination of prior art elements***.").

f) Claims 6–7 and 15–16 Are Obvious

Claim 6 depends from claim 1, and further recites "wherein the GCA is new onset GCA." Likewise, claim 15 depends from claim 8, and further recites "wherein the giant cell arteritis (GCA) is new onset GCA." Claim 7 depends from claim 1, and further recites "wherein the GCA is refractory GCA." Likewise, claim 16 depends from claim 8, and further recites "wherein the giant cell arteritis (GCA) is refractory GCA."

A POSA would have been motivated to treat both new onset GCA patients and refractory GCA patients with the recited treatment regimen, and would have reasonably expected that it would be effective to treat both groups of patients.

Seitz discloses effective treatment of seven patients with GCA or Takayasu's arteritis, a variant of GCA. "Of the seven patients three were ***newly diagnosed*** and four showed GC resistance, i.e. GC could not be lowered to less than 7.5 mg/day." Ex. 1012 (Seitz) at 1 (emphasis added). All seven patients exhibited a reduction in active symptoms, and "[c]ontinuous reduction of GCs over time was achieved in all patients without any signs of clinical or laboratory relapse of LVV after the fourth TCZ infusion." *Id.* at 2–3. Thus, Seitz disclosed that tocilizumab effectively treated both new onset and refractory GCA patients. *Id.* at 3 ("[T]he fact that all patients responded to this IL-6 targeting strategy argues for interesting therapeutic potential, not only for patients with newly diagnosed GCA but also for patients with relapse of the disease at moderate to high doses of GCs."). Accordingly, a POSA would have been motivated to administer the claimed treatment regimen to treat both new onset GCA and refractory GCA with a reasonable expectation of success for substantially the same reasons set forth with respect to claims 1 and 8, and therefore claims 6–7 and 15–16 are also obvious. Ex. 1002 ¶¶164, 167.

C. Ground 2: Claims 1–16 Are Obvious Over Hagihara and Ohta 2010

A POSA would also have been motivated to use the claimed methods, with a reasonable expectation of success, in view of Hagihara and Ohta 2010. Ex. 1002 ¶¶168-177. Hagihara discloses the successful treatment of patients with PMR by intravenous administration of 8 mg/kg tocilizumab (an anti-IL-6 receptor antibody) every four weeks. Ex. 1010 (Hagihara) at 3. Hagihara discloses that "[s]ince interleukin 6 (IL-6) has been shown to play a major role in sustaining disease activity in PMR, treatment of a patient with PMR refractory to corticosteroids was initiated with the humanized anti-IL-6 receptor antibody tocilizumab." *Id.* Hagihara also states that "the clinical relationship between PMR and GCA has been established, since 16%–21% of patients with PMR also had GCA, and PMR was reportedly present in 40%–60% of patients with GCA." *Id*.

1. A POSA Would Have Been Motivated to Combine Hagihara and Ohta 2010

A POSA would have been motivated to combine the disclosure of Hagihara—that PMR can be effectively treated with tocilizumab—with the subcutaneous dosing regimen disclosed in Ohta 2010 of 162 mg of tocilizumab weekly or every other week to arrive at the claimed methods for treatment of GCA. Ex. 1002 ¶170. Hagihara itself discloses that the "clinical relationship between

PMR and GCA has been established," and "[i]t is thus anticipated that tocilizumab may become a treatment option for GCA." Ex. 1010 (Hagihara) at 3.

Because PMR and RA were both known to be IL-6 mediated diseases, the intravenous 8 mg/kg tocilizumab dosing regimen administered in Hagihara in October 2008 to treat PMR was identical to the regimen known at that time to be optimally safe and effective for treating RA. *See* Ex. 1027 (Nishimoto 2008) at 2 ("8 mg/kg every four weeks is an optimal dosage."). A POSA would have therefore been motivated to administer tocilizumab in accordance with known RA regimens to treat GCA in view of Hagihara's reported success in administering 8 mg/kg every four weeks to treat PMR, its disclosure of the clinical relationship between PMR and GCA, and its express suggestion that tocilizumab would be similarly useful for treating GCA. Ex. 1002 ¶170.

However, after October 2008, treatment of RA with tocilizumab had advanced to also include subcutaneous administration. Specifically, Ohta 2010 described a Phase I/II clinical study for treatment of RA patients with subcutaneous administration of 162 mg every week or every other week of tocilizumab "for ease of use." Ex. 1011 (Ohta 2010) at 2. The results reported in Ohta 2010 showed that tocilizumab administered subcutaneously at a dose of 162 mg every week or every other week resulted in improvement in disease indicators in RA patients as compared to the 8 mg/kg intravenous regimen. As explained

supra § IX.B.1, the ACR 20/50/70 scores were in fact higher for both 162 mg subcutaneous regimens than had been reported for the intravenous regimen of tocilizumab for the treatment of RA.

As discussed above, it was well known that subcutaneous injection is generally a preferred method of administration for many patients. *Supra* § IV.B. In view of this preference for subcutaneous administration of antibodies, a POSA would have been motivated to treat GCA by administering the weekly and every other week 162 mg fixed subcutaneous regimen disclosed in Ohta 2010 as useful for treating RA. Ex. 1002 ¶174.

2. A POSA Would Have Had a Reasonable Expectation of Success

Based on successful treatment with other IL-6 mediated disorders, a POSA would have reasonably expected that administration of a 162 mg fixed dose of tocilizumab subcutaneously once a week or every other week would be successful in treating GCA. Ex. 1002 ¶175. By 2010, tocilizumab had received regulatory approval for treatment of various IL-6 mediated disorders, including RA. *Supra* § IX.B.2. Hagihara disclosed that the same dosing regimen used to treat RA—8 mg/kg intravenously every four weeks—could safely and effectively treat PMR, a disorder known to have a close clinical relationship with GCA. Ex. 1002 ¶175. A POSA would therefore have reasonably expected that GCA could also be treated with the same tocilizumab regimens as used for treating RA. *Id.*

Also, as discussed above, Ohta 2010 taught that a 162 mg fixed dose administered weekly or every other week was at least as safe and effective as the 8 mg/kg every four week intravenous regimen for treating RA, and a POSA would have expected the same would be true for GCA, since they are both IL-6 mediated disorders. *Supra* § IX.A; Ex. 1002 ¶175.

More generally, the prior art reported that subcutaneously administered tocilizumab inhibited the effects of IL-6 to a similar extent as intravenous administration of an equivalent amount of the drug. Ex. 1044 (Georgy) at 3. And, the prior art also taught that an antibody may be administered subcutaneously every week or every other week instead of every four weeks intravenously in an amount that, "over time is generally equivalent." Ex. 1021 (Bonilla) at 15. The 8 mg/kg every four week dose disclosed in Hagihara would equate to 140 mg every week for an average 70 kg patient, and therefore a POSA would have understood that the 162 subcutaneous weekly fixed dose disclosed in Ohta 2010 would be at least as safe and effective as the intravenous regimen, reinforcing the expectation that the subcutaneous regimen would be successful in treating GCA. Ex. 1002 ¶176.

A POSA would also have known that tocilizumab was approved by the FDA for treatment of rheumatoid arthritis at a 4 mg/kg every four week dose, and that this dose had also been shown to be effective for treating GCA. Ex. 1063 (2010

Actemra FDA Label) at 2; Ex. 1041 (Thompson) at 1. Accordingly, a POSA would have reasonably expected that a 4 mg/kg every four week intravenous dosage would have also been successful in treating GCA. Ex. 1002 ¶177. Because this dose equates to 140 mg every other week for an average 70 kg patient, a POSA would have reasonably expected that the 162 mg fixed dose administered every other week disclosed in Ohta 2010 to be safe and effective for treating GCA. *Id.*

3. Application to the Claims

a) Claims 1 and 8

As discussed above, a POSA would have been motivated to combine Hagihara and Ohta 2010 and arrive at a method of treating GCA to a patient comprising administering tocilizumab (an anti-IL-6R antibody) subcutaneously at a fixed dose of 162 mg every week or every other week, as recited in claims 1 and 8, and would have had a reasonable expectation that the treatment regimen would have been successful in treating GCA. *Supra* §§ IX.C.1-C.2.

Claim 1 further recites that the anti-IL-6R antibody "comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively." As explained above, the tocilizumab disclosed in the prior art inherently has the claimed amino acid sequences. *Supra* § IX.B.3. Accordingly, claims 1 and 8 would have been obvious for the reasons set forth above. *Supra* §§ IX.C.1-C.2.

b) *Claims 2 and 9*

Claim 2 depends from claim 1 and further requires that "the fixed dose is administered every week." Likewise, claim 9 depends from claim 8, and also further requires that "the fixed dose is administered every week."

As discussed above, a POSA would have been motivated to combine Hagihara and Ohta 2010 to arrive at a method of treating GCA comprising administering tocilizumab subcutaneously at a fixed dose of 162 mg every week, and would have had a reasonable expectation in so doing. *Supra* §§ IX.C.1-C.2. Thus, claims 2 and 9 are also obvious. Ex. 1002 ¶184.

c) Claims 3 and 10

Claim 3 depends from claim 1, and further recites "wherein the fixed dose is administered every two weeks." Likewise, claim 10 depends from claim 8, and further recites "wherein the fixed dose is administered every two weeks."

As discussed above, a POSA would have been motivated to combine Hagihara and Ohta 2010 to arrive at a method of treating GCA comprising administering tocilizumab subcutaneously at a fixed dose of 162 mg every other week, and would have had a reasonable expectation of success in so doing. Thus, claims 3 and 10 are also obvious. Ex. 1002 ¶186.

d) Claims 4 and 11

Claim 4 depends from claim 1, and further recites "administering an initial course of corticosteroid to the patient." Likewise, claim 11 depends from claim 8, and further recites "administering an initial course of corticosteroid to the patient."

Hagihara discloses that a patient with PMR was initially treated with corticosteroids, and then was administered tocilizumab. Ex. 1010 (Hagihara) at 3. The treatment "ended clinical symptoms, so that prednisone could be reduced to 6 mg/day." *Id.* Hagihara also states that, due to the close clinical relationship between PMR and GCA, "tocilizumab may become a treatment option for GCA." Ex. 1010 (Hagihara) at 3. By combining Hagihara and Ohta 2010, a POSA would have arrived at a method of treating GCA using an initial course of corticosteroids, following by administration with tocilizumab subcutaneously at a fixed dose of 162 mg every week or every other week. Ex. 1002 ¶188.

A POSA would also have known that corticosteroids were the cornerstone of medical therapy in GCA and should be started immediately to prevent severe consequences of the disease, such as blindness. Ex. 1043 (Warrington) at 2; Ex. 1002 ¶189. As explained above, a POSA would also have reasonably expected that the claimed treatment regimen would have been successful in treating GCA, and therefore claims 4 and 11 are also obvious. *Supra* §§ IX.C.1-C.2.

e. Claims 5, 12–14

Claim 5 depends from claim 1, and further recites "wherein the effective amount reduces GCA signs and symptoms, maintains clinical remission, and/or reduces or stops corticosteroid to be administered to the patient." Similarly, claim 12 depends from claim 8, and further recites "wherein the treatment reduces giant cell arteritis signs and symptoms in the patient"; claim 13 depends from 8, and further recites "wherein the treatment maintains clinical remission in the patient"; and claim 14 depends from claim 8, and further recites "wherein the treatment reduces or stops corticosteroid to be administered to the patient."

Hagihara discloses the successful treatment of patients with PMR. Ex. 1010 (Hagihara) at 3. After 1 injection of tocilizumab, serum CRP and SAA levels became normal and pain in the shoulders and pelvic girdle improved. *Id.* Moreover, "continued tocilizumab treatment ended clinical symptoms, so that prednisone could be reduced to 6 mg/day." *Id.* Therefore, in view of the known close clinical relationship between PMR and GCA, a POSA would have reasonably expected that the claimed treatment regimen would cause a reduction in GCA signs and symptoms, maintain clinical remission, and allow a reduction in corticosteroids to be administered to the patient. Ex. 1002 ¶192. A POSA would also have reasonably expected that the claimed treatment regimen would reduce GCA signs and symptoms, maintain clinical remission, and reduce or stop corticosteroids to be administered to a patient with GCA, based on successful

treatment of RA, Castleman's disease, and Takayasu's arteritis, similar IL-6 mediated disorders. *Id.* ¶193.

Moreover, as explained above for Ground 1, the functional results recited in claims 5 and 12–14 would inherently result from administration of a 162 mg subcutaneous every week or every other week dose of tocilizumab. *Supra* § IX.B.3. By combining Hagihara and Ohta 2010, a POSA would have arrived at a method of treating GCA that meets each and every limitation of claims 5 and 12–14, and therefore the claims are obvious for the same reasons set forth above. *Supra* §§ IX.C.1-C.2.

e) Claims 6-7 and 15–16

Claim 6 depends from claim 1, and further recites "wherein the GCA is new onset GCA." Likewise, claim 15 depends from claim 8, and further recites "wherein the giant cell arteritis (GCA) is new onset GCA." Claim 7 depends from claim 1, and further recites "wherein the GCA is refractory GCA." Likewise, claim 16 depends from claim 8, and further recites "wherein the giant cell arteritis (GCA) is refractory GCA."

A POSA would have been motivated to use a 162 mg fixed dose of tocilizumab every week or every other week to treat both new onset GCA patients and refractory GCA patients, and would have reasonably expected that the treatment regimen would have been effective. Ex. 1002 ¶¶196-198. As discussed

above, a POSA would have been motivated to combine Hagihara and Ohta 2010 to arrive at a method of treating GCA patients with a 162 mg tocilizumab every week or every other week. The patient treated in Hagihara had inadequately responded to treatment with corticosteroids, and a POSA would therefore have been motivated to administer the combined regimen to treat refractory GCA patients with a reasonable expectation of success for substantially the same reasons as set forth above. Ex. 1010 (Hagihara) at 3; Ex. 1002 ¶198.

A POSA would also have been motivated to treat new onset GCA patients with this same regimen, and would have also expected it to be successful. Ex. 1002 ¶ 196. A POSA would have known that, GCA, if left untreated, could cause devastating permanent effects, like blindness, and therefore, as discussed with respect to claims 4 and 11, would have been motivated to aggressively treat a new onset GCA patient. *Id.* Hagihara discloses that tocilizumab may be administered simultaneously with corticosteroids, and so, in addition to being motivated to administer an initial course of corticosteroids prior to tocilizumab, a POSA would also have been motivated to initially administer tocilizumab in combination with corticosteroids to a new onset GCA patient, and would have had a reasonable expectation of success in so doing. *Id.* Therefore, claims 6 and 15–16 are also obvious. *Id.* ¶¶196-198.

D. 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.

During prosecution, the applicant argued that the alleged inventions claimed in the '752 patent provided unexpected results compared to use of prednisone for the treatment of GCA. Ex. 1004 at 818. However, by the earliest effective priority date, prednisone was not the closest prior art for the treatment of GCA. The prior art had already disclosed intravenous administration of tocilizumab for treatment of GCA (*see supra* § IX.A), which is closer prior art to the claimed subject matter than use of prednisone for treatment of GCA. For example, Seitz discloses a method of treating GCA comprising administering the exact same compound recited by each of the claims of the '752 patent, the only difference being the mode of administration. The prednisone treatment to which the applicants compared their alleged invention differs from the claims not only in the administration regimen, but also the drug itself, and thus cannot plausibly be the closest prior art. Ex. 1004 at 780–83, 850–82, 902–03. For at least that reason, the applicant's assertion of unexpected results was fundamentally flawed. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014) (legal

error in not comparing claimed compound with closest prior art to determine whether results are unexpected). Petitioners are not aware of any evidence that subcutaneous administration of tocilizumab for treatment of GCA provides superior efficacy, in comparison with intravenous administration of tocilizumab.

Furthermore, even if prednisone treatment were the closest prior art, the results applicants relied upon were not unexpected. Ex. 1002 ¶¶200–01. The study relied upon by applicants compared GCA patients treated with subcutaneous tocilizumab combined with tapered prednisone to GCA patients treated with tapered prednisone alone, and found a greater percentage of the patients treated with tocilizumab achieved sustained remission at 12 months. Ex. 1004 at 780–83. But, the prior art had already disclosed that relapses occur in GCA patients when glucocorticoids (*e.g.*, prednisone) are tapered; and, by contrast, tocilizumab allowed for sustained remission even after withdrawal from treatment. Ex. 1012 (Seitz) at 1, 3. As discussed above, a POSA would have expected to achieve comparable safety and efficacy treating GCA patients with the claimed subcutaneous regimen instead of the prior art intravenous regimen. *Supra* §§ IX.B,

IX.C. Thus, applicants' proffered results are entirely consistent with the teachings of the prior art, and would not have been unexpected. Ex. 1002 ¶201.[11]

Applicant's assertion that the alleged inventions addressed a long-felt unmet medical need in 2011 is also erroneous. For evidence of long-felt need to be probative of non-obviousness, there must be a nexus to the novel features of the claimed invention. *Magseis FF LLC v. Seabed Geosolutions (US) Inc*., 850 Fed. App'x 746, 751-52 (Fed. Cir. July 29, 2021) (affirming PTAB's finding of no nexus in fact because the evidence of secondary considerations was not tied to the

[11] The applicants' suggestion that the FDA's granting of breakthrough designation and priority review for subcutaneous tocilizumab implies that the results of the claimed invention are "surprising" is baseless. *See* Ex. 1004 at 818, 902–03. Neither breakthrough designation nor priority review requires the FDA to conclude the treatment is in any way surprising; just that it is "intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy" or would provide "significant improvements in the safety or effectiveness of the treatment … when compared to standard applications." *Id.* at 824-826. These designations are therefore irrelevant to whether or not the results of the claimed invention were "unexpected" for secondary considerations purposes.

"claimed invention's unique characteristics"). By 2010, tocilizumab was FDA-approved and available to a POSA in a form suitable to intravenous injection, and the prior art disclosed that intravenous administration of tocilizumab was effective for treatment of GCA. *Supra* § IV. Thus, to the extent there was a long-felt need for a new GCA treatment, that need was met before the claimed invention by the prior art intravenous tocilizumab treatment regimen. Ex. 1002 ¶203. Therefore, there is no nexus between satisfaction of a long-felt need for an effective treatment for GCA and the claimed methods. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1102 (Fed. Cir. 2015).

XI. 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*, IPR2020-00726, Paper 13, at 6-7 (PTAB Oct. 6, 2020). The so-called *Becton Dickinson* factors are applied to aid in answering these questions. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17-18 (PTAB Dec. 15, 2017) (precedential).

For Ground 2, Petitioners rely on Hagihara, which was not before the Examiner. Indeed, the Examiner did not consider any prior art, like Hagihara, that

disclosed that tocilizumab was effective in treating PMR, which was known to share a clinical relationship with GCA. For those reasons alone, the Board should proceed to institution.

For Grounds 1 and 2, Petitioners rely on Ohta 2010, which discloses treating patients with a subcutaneous fixed dose of 162 mg to treat RA. Although Ohta 2010 was disclosed on an IDS, it was never substantively evaluated by the Examiner. *Supra* § V.B. "The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharma., Inc.*, IPR2019-00739, Paper 15, at 58-59 (PTAB Aug. 30, 2019) (collecting cases). Nothing in the prosecution history suggests that the Examiner appreciated that Ohta 2010 or anything else in the prior art had disclosed the claimed subcutaneous dose and administration schedule. By contrast, Grounds 1 and 2 herein each allege obviousness based upon a prior art reference disclosing the claimed dosing regimen, a position never evaluated by the Examiner. Factors (a), (b), (c), and (d) therefore favor institution.

The remaining factors demonstrate that the Examiner erred in a material way by failing to reject the claims over Ohta 2010, and strongly counsel against denying institution. The Examiner's failure to appreciate that a reference was publicly available that discloses the claimed 162 mg subcutaneous tocilizumab

weekly and every other week dose reflects a plain error in evaluating the prior art (factor (e)), as does the Examiner's crediting applicants' proffered unexpected results, notwithstanding those results failed to compare the claimed invention to the closest prior art. *Supra* § IX.D. Indeed, the Examiner expressly acknowledged that the claims were only allowable because of the "efficacy, advantage, and surprising results of subcutaneous administration of a fixed dose of 162 mg tocilizumab every week or every other week." Ex. 1004 at 913. The Examiner's failure to address Ohta 2010's disclosure of the exact same subcutaneous regimen, and improperly crediting the proffered evidence of unexpected results, therefore demonstrate a material error in the Examiner's consideration of the prior art. 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.*, IPR2017-01884, Paper 14, at 12-13 (PTAB Feb. 15, 2018).

XII. *NHK SPRING* AND *FINTIV* ARE INAPPOSITE

In response to Petitions filed on other patents claiming methods of treating by administering tocilizumab, Patent Owner has argued that the Board should decline to institute under *NHK Spring* and *Fintiv*. IPR2021-01024 at Paper 8; IPR2021-01025 at Paper 8. Those cases do not control here. In both cases, the Board declined to institute under § 314(a) where instituting an IPR would have

been inefficient in view of pending district court litigation in an advanced stage involving the same prior art or arguments. Here, there is no pending litigation, much less one in an advanced stage.

In *NHK Spring*, the Board noted that "[t]he district court proceeding, in which Petitioner asserts the same prior art and arguments, is nearing its final stages, with expert discovery ending on November 1, 2018, and a 5-day jury trial set to begin on March 25, 2019," whereas an IPR trial would not have concluded until September 2019. *NHK Spring Co., Ltd. v. Intri-Plex Techs. Inc.*, IPR 2018-00752, Paper 8, at 19-20 (PTAB. Sept. 20, 2018) (precedential on May 7, 2019). And in *Fintiv*, the Board declined to institute where a trial date had been set for two months before an IPR decision would have been due, a *Markman* hearing had already been conducted, the parties had already exchanged initial and final infringement and invalidity contentions, fact discovery was underway, and the same prior art was at issue in the district court. *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15, at 11-15 (PTAB May 13, 2020). These cases are applicable when there is an ongoing, parallel district court litigation. They do not, however, provide any basis to decline institution under § 314(a) where, as here, there is no such pending litigation.

Patent Owner has argued that the statutory scheme governing biosimilars like Petitioners' copy of Actemra® all but guarantees patent litigation between

Petitioners and Patent Owner. IPR2021-01024 at Paper 8; IPR2021-01025 at Paper 8. Even if true, this is beside the point. Fresenius has not yet filed an application with FDA for a biosimilar tocilizumab product, a prerequisite for the commencement of litigation under the BPCIA. *See* 42 U.S.C. § 262(*l*). No complaint has even been filed at this time, much less a trial date set, and Patent Owner's purported analysis of the relevant factors under *NHK Spring*/*Fintiv* is pure speculation. The Board routinely grants institution in cases much further along than this one. *See*, *e.g.*, *Oticon Medical AB v. Cochlear Ltd*., IPR 2019-00975, Paper 15, at 23-24 (PTAB Oct. 6, 2019) (precedential on March 24, 2020) (deciding not to exercise discretion under § 314(a) and granting institution despite concurrent litigation where no trial had been scheduled by the district court); *see also Zonar Sys., Inc. v. Innovative Global Sys., LLC*, No. IPR2020-00155, Paper 15, at 9 (PTAB May 12, 2020) (declining to deny institution where an "assessment of the state of the parallel district court proceeding requires substantial speculation as to several factors").

Patent Owner has also argued that, because Fresenius would not agree to hold off serving its notice of intent to market until this proceeding concludes, Petitioners virtually guarantee that the court and the Board will be addressing the

challenged patents in parallel.[12] Again, even if true, this is of no moment. The timing of Fresenius's notice of commercial marketing has no bearing on the trial date of a theoretical litigation between the parties to this proceeding—although it may impact the timing of a preliminary injunction hearing, that is not a final resolution on the merits. *See* 42 U.S.C. § 262(*l*)(8-9). Nevertheless, Patent Owner has not alleged that such an interlocutory decision would be rendered by a district court prior to a decision on the merits in this proceeding; only that there will eventually be a co-pending proceeding. Of course, the mere existence of a co-pending district court litigation is, in and of itself, insufficient to support a discretionary denial under *NHK Spring/Fintiv*, which instead requires an analysis of several specific factors.

Consideration of the *Fintiv* factors confirms that discretionary denial would be improper. As litigation is not pending, there is no stay, nor any evidence that a court will grant a stay (factor 1). There is no trial date, and no realistic way in which trial in district court could occur before a final written decision in this proceeding (factor 2). Neither the parties nor any court has invested any effort

[12] Under the BPCIA, a biosimilar applicant must give a reference product sponsor a Notice of Commercial Marketing at least 180 days before market launch of the biosimilar. *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052, 1066 (Fed. Cir. 2016).

whatsoever in a related parallel proceeding (factor 3). And it is far too soon to speculate on what, if any, overlap there might be in a parallel proceeding (factor 4). Although the parties to this IPR may be the same as in a district court proceeding (factor 5), that too remains to be seen.

"Other circumstances" (factor 6) also weigh against declining to institute. Patent Owner has argued that Fresenius should have filed IPRs as early as 2017, when its clinical development began, in order to avoid the potential for overlapping district court litigation. But if Fresenius had filed an IPR in 2017 and the Board upheld the validity of the patent in a final written decision, then Fresenius may not have had standing to appeal because its biosimilar product would not yet have been approved by FDA. *Pfizer, Inc. v. Chugai Pharm. Co., Ltd.*, 812 Fed. App'x. 979, 981 (Fed. Cir. 2020) (holding that Pfizer had no standing to appeal adverse final decision from the PTAB because, at the time the appeal was filed, Pfizer had not yet received FDA approval for its biosimilar product). Simply put, Fresenius should not be expected to file an IPR when it may have no opportunity to appeal an adverse final written decision.

As stated in *Fintiv*, the underlying rationale behind denial of institution was "whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding." *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, at 6 (PTAB March 20, 2020)

(precedential on May 5, 2020). Patent Owner can only speculate as to whether efficiency supports the denial of institution. As for fairness, extending *NHK Spring*/*Fintiv* to situations where there is no pending litigation would be profoundly unfair to biosimilar developers because the IPR procedure would be effectively closed as a viable option for them to challenge patent validity. And on the merits, Petitioners have made a strong showing that the claims of the '752 patent are invalid as obvious. For all the reasons set forth above, Petitioners respectfully request that the Board decline to exercise its discretion to deny institution under *NHK Spring*/*Fintiv*.

XIII. 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: November 24, 2021

Respectfully submitted,

By: */Elizabeth J. Holland/*

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

Kevin J. DeJong (Reg. No. 64,762)
Goodwin Procter LLP
100 Northern Avenue

Boston, MA 02210
Tel: (617) 570 1156
Fax: (617) 649 1430
kdejong@goodwinlaw.com

Counsel for Petitioners

CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 9,750,752 contains 13,703 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: November 24, 2021

By: */Elizabeth J. Holland/*

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

Counsel for Petitioners

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,750,752** and the exhibits cited therein by Federal Express Next Business Day Delivery on this day, November 24, 2021 on the Patent Owner's correspondence address of record for the subject patent as follows: Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

Dated: November 24, 2021

By: */Elizabeth J. Holland /*

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

Counsel for Petitioners