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.

IPR2022-01065
U.S. Patent No. 10,231,981

Title: SUBCUTANEOUSLY ADMINISTERED ANTI-IL-6 RECEPTOR ANTIBODY FOR TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,231,981

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

Other Authorities

LIST OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 10,213,981
1002	Declaration of Thomas M. Zizic, M.D. in Support of Fresenius's Petition for Inter *Partes* Review of U.S. Patent No. 10,213,981
1003	Declaration of Howard Levine, Ph.D. in Support of Fresenius's Petition For Inter *Partes* Review of U.S. Patent No. 10,231,981
1004	Declaration of Robert Paarlberg in Support of Fresenius's Petition for Inter *Partes* Review of U.S. Patent No. 10,231,981
1005	File History for U.S. Patent No. 8,580,264
1006	File History for U.S. Patent No. 10,213,981
1007	File History for U.S. Patent No. 10,874,677
1008	Thomas M. Zizic, M.D., *Curriculum Vitae*
1009	Howard L. Levine, Ph.D., *Curriculum Vitae*
1010	Robert A. Paarlberg, *Curriculum Vitae*
1011	Troels Herlin, *Tocilizumab: The evidence for its place in the treatment of juvenile idiopathic arthritis*, 4 CORE EVIDENCE 181 (2009)
1012	N. Kutukculer, S. Caglayan & F. Aydogdu, *Study of Pro-Inflammatory (TNF-α, IL-lα, IL-6) and T-Cell-Derived (IL-2, IL-4) Cytokines in Plasma and Synovial Fluid of Patients with Juvenile Chronic Arthritis: Correlations with Clinical and Laboratory Parameters*, 17 CLINICAL RHEUMATOLOGY 288 (1998)
1013	Tomoyuki Imagawa et al., Annual Scientific Meeting Presentation No. 268, *Efficacy and safety of tocilizumab, an Anti-IL-6 Receptor Monoclonal Antibody, in Patients with Polyarticular or Oligoarticular Onset Juvenile Idiopathic Arthritis*, AM. COLLEGE OF RHEUMATOLOGY (2006)

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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.*,[1] petition for *inter partes* review ("IPR") of claims 1-14 of U.S. Patent No. 10,231,981 ("'981 patent") (Ex. 1001). Petitioners' request is supported by the Expert Declarations of Thomas M. Zizic, M.D. (Ex. 1002), Howard L. Levine, Ph.D. (Ex. 1003), Mr. Robert Paarlberg (Ex. 1004), and the other exhibits submitted herewith.

The '981 patent claims are directed to methods of treating juvenile idiopathic arthritis ("JIA") with a subcutaneous fixed dose of 162 mg of tocilizumab, an anti-IL6 receptor antibody. Although the '981 patent purports to claim priority to several applications, none of the priority applications provide written description support for the full scope of the '981 patent claims. Each claim of the '981 patent is directed to methods of treating JIA by subcutaneous administration of a 162 mg fixed dose of tocilizumab every week, every other week, or every 3 weeks, but the priority applications do not describe a 3-week treatment frequency. And, claims 6-7 and 13-14 have an additional problem—

[1] 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.

none of the priority applications describe treatment of polyarticular-course JIA ("pcJIA" or "pJIA") with an administration frequency based on a patient's weight, as required by claims 6-7 and 13-14. Thus, all of the claims are entitled to a priority date no earlier than August 3, 2017, the filing date of the application that became the '981 patent.

Each claim of the '981 patent is anticipated by intervening prior art. U.S. Patent No. 8,580,264 ("'264 patent") issued on November 12, 2013, and is therefore prior art under § 102(a)(1) and does not qualify for the one-year exception under § 102(b)(1). The '264 patent, which shares essentially the same specification as the '981 patent, discloses methods for treating systemic JIA ("sJIA") and pcJIA using the claimed treatment regimens. A clinical study protocol, NCT02165345, was published in 2014, and likewise discloses methods for treating sJIA and pcJIA using the claimed treatment regimens.

All of the claims of the '981 patent are also obvious in view of the prior art, no matter what priority date the claims are afforded. JIA, the most common type of arthritis in children, generally refers to a group of conditions involving joint inflammation (arthritis), and was understood to be an interleukin-6 (IL-6) mediated disorder. Tocilizumab is a recombinant, humanized monoclonal antibody that binds to the IL-6 receptor blocking the IL-6 signal transmission. By 2010 (before the earliest possible priority date of the '981 patent claims), tocilizumab had been

shown to be effective in treating many IL-6 mediated diseases, including JIA, rheumatoid arthritis ("RA"), Castleman's disease, and giant cell arteritis, among others, and it was well known that JIA patients could be safely and effectively treated with an 8 mg/kg intravenous tocilizumab dosing regimen.

The prior art also disclosed that subcutaneous administration of tocilizumab was preferable to intravenous administration. 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 RA, the next logical step would have been to employ the preferred subcutaneous tocilizumab regimen to treat JIA patients. The '981 patent claims are obvious because a POSA would have been motivated to combine these disclosures to arrive at the claimed methods for treating JIA with a reasonable expectation of success.

The Board should institute review because there is 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 '981 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 '981 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 '981 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 '981 patent is not currently the subject of any litigation or post-grant proceedings.

The '981 patent claims priority to Application No. 14/062,025, which issued as U.S. Patent No. 9,750,752 ("'752 patent"), and to Application No. 13/390,266, which issued as U.S. Patent No. 8,580,264 ("'264 patent"). On November 24, 2021, August 18, 2021, and September 24, 2021, respectively, Petitioners filed petitions seeking *inter partes* review of claims 1-16 of the '752 patent (IPR2022-00201),

claims 1-3 and 6-11 of the ’264 patent (IPR2021-01288), and claims 4, 5, and 12 of the ’264 patent (IPR2021-01542).

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* IPR2021-01336.

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

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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: elizabeth.holland@allenovery.com; daniel.margolis@allenovery.com; christopher.galligan@allenovery.com; FreseniusIPR@allenovery.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 '981 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 604184.

V. TECHNICAL BACKGROUND

A. Tocilizumab for Treatment of Juvenile Idiopathic Arthritis and Other IL-6 Mediated Disorders

JIA, the most common type of arthritis in children, generally refers to a group of conditions involving joint inflammation (arthritis) that first appears before the age of 16. Ex. 1002 ¶32. JIA is an autoimmune disease, meaning that the immune system attacks the body's cells and tissues; inflammatory chemicals are released and attack the synovium (tissue lining around a joint), cells, and various other connective tissues throughout the body. *Id.* It typically causes joint pain and inflammation in the hands, knees, ankles, elbows and/or wrists. An inflamed synovium may make a joint feel painful or tender, look red or swollen, or difficult to move. *Id.*

JIA is classified according to the onset of the disease into several subtypes, with the three most common being oligoarticular, polyarticular-course (pcJIA), and systemic JIA (sJIA). Oligoarticular JIA is the most common type of JIA, and affects four or fewer joints, typically the large ones (knees, ankles, elbows). Polyarticular-course JIA, representing about 25% of JIA patients, affects five or more joints, often on both sides of the body (both knees, both wrists, etc.). Systemic JIA affects the entire body (joints, skin and internal organs) and includes other symptoms, including a high spiking fever (103°F or higher) that can last several weeks. Ex. 1011 at 2. Children with systemic JIA may also have a skin

rash or enlargement of the lymph nodes (lymphadenopathy), liver (hepatomegaly), or spleen (splenomegaly). *Id.*

By 2010, it was well known that JIA was an IL-6 mediated disorder. For example, in 1998, it was reported that "[i]t has long been recognized that the activity of JCA[2] is reflected in a systemic acute response characterized by increased concentrations of a variety of different plasma proteins," and that elevated plasma IL-6 concentrations may be used as a marker for disease activity. Ex. 1012 at 4. In 2006, the American College of Rheumatology reported that "targeted blockade of IL-6 signal represents an effective approach to the treatment of pJIA." Ex. 1013 at 1. Similarly, in 2009, Herlin reported that "[s]ubstantial evidence shows that the proinflammatory cytokine interleukin-6 (IL-6) plays a pivotal role in systemic JIA." Ex. 1011 at 1.

Tocilizumab, also known as MRA, is a humanized anti-IL-6 receptor monoclonal antibody of the IgG1 subclass. Tocilizumab inhibits the binding of IL-6 to its receptors, and thus reduces the cytokine's pro-inflammatory activity by competing for both the soluble and membrane-bound forms of the human IL-6

[2] The terms "juvenile chronic arthritis" (JCA) and "juvenile rheumatoid arthritis" were replaced with the single nomenclature of "juvenile idiopathic arthritis." Ex. 1002 ¶34; Ex. 1014 at 1.

receptor. Ex. 1015 at 8.

By 2010, the efficacy and safety of tocilizumab in treating JIA had been well established in the prior art. In a clinical study published in 2008, 56 children with systemic JIA were treated with tocilizumab at 8 mg/kg intravenously every two weeks. Ex. 1016 at 2. The investigators concluded that "[t]ocilizumab is effective in children with systemic-onset juvenile idiopathic arthritis," and that "the results of this placebo-controlled and open-label extension study with tocilizumab in children with systemic-onset juvenile idiopathic arthritis show a sustained clinical improvement and a favourable risk-benefit profile." *Id.* at 2, 10. Likewise, the prior art reported that intravenous tocilizumab at 8 mg/kg every four weeks was effective in treating pcJIA. For example, clinical investigators reported in 2006 that "[c]onsistent with improvements observed in adult RA patients, tocilizumab demonstrated significant improvements in signs and symptoms of pJIA of polyarticular or oligoarticular onset, and was generally well-tolerated." Ex. 1013 at 1; *see also* Ex. 1017 at 1.

The successful results of tocilizumab in treating JIA followed earlier successes in treating RA, another IL-6 mediated disorder with the same drug. By 2010, it was also well known that IL-6 played a pivotal role in the pathogenesis of RA, a chronic, immune-mediated, systemic disease characterized by pain, swelling and progressive destruction of the small joints of the hands and feet.

Overproduction of IL-6 and its interaction with its receptor, IL-6R, which is expressed on effector cells, was known to cause and prolong inflammation associated with RA. Ex. 1018 at 3-4.

In March 2008, intravenous tocilizumab was approved in Japan for treating RA, pcJIA, and sJIA, with a recommended dosage of 8 mg/kg every four weeks for treating RA and pcJIA, and 8 mg/kg every two weeks for treating sJIA. Ex. 1019 at 1, 3-4. By 2010, tocilizumab at 8 mg/kg IV had been approved in over 70 countries for use in treating RA, including the United States, Japan and Europe. Ex. 1001 at 2:34-35; Ex. 1020 at 9. In the United States, intravenous tocilizumab (4 mg/kg and 8 mg/kg) had been approved in RA patients who have had an inadequate response to anti-TNF agents. Ex. 1001 at 2:35-38; Ex. 1020 at 9; Ex. 1022. On April 15, 2011, FDA approved tocilizumab for the treatment of sJIA at 12 mg/kg every two weeks for patients less than 30 kg and 8 mg/kg every two weeks for patients at or above 30 kg. Ex. 1001 at 2:40-44; Ex. 1021 at 2-3. And in April 2013, FDA approved tocilizumab for treatment of pcJIA at 10 mg/kg every four weeks for patients less than 30 kg, and 8 mg/kg every four weeks for patients at or above 30 kg. Ex. 1023 at 1.

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 ¶39; Ex. 1024 at 12-13; Ex. 1025 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 at 1. For tocilizumab specifically, subcutaneous was considered the "preferred form of administration." Ex. 1026 at 4. 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. 1027 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*. In view of these known advantages, by 2010 there were several biologics approved by FDA for subcutaneous administration using a fixed dose, including for treatment of JIA. *See, e.g.*, Ex. 1030 at 4 (Enbrel, approved for JIA and RA); Ex. 1034 (Humira, approved for JIA and RA); Ex. 1035 at 4-5 (Cimzia, approved for Crohn's disease); Ex. 1036 at 1, 4 (Simponi, approved for RA).

Subcutaneous tocilizumab, using the claimed 162 mg dosage, was also

known in the prior art. A Phase I/II clinical trial was 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. 1039 at 2. The study was carried out in RA patients, and the results were published in Ohta 2010, which concluded that treatment with 162 mg weekly and every other week was "well tolerated" and "associated with good clinical response." Ex. 1039 at 3. By 2013, FDA had approved this 162 mg tocilizumab subcutaneous fixed dose, administered either weekly or every other week, for the treatment of RA. Ex. 1059.

Following the successful results with a 162 mg dosage for treatment of RA, further studies were conducted with the same dosage for treatment of JIA. By 2016, before the priority date for the claims of the '981 patent, clinical trials were underway for treatment of both systemic JIA and pcJIA, using a subcutaneous 162 mg fixed dose of tocilizumab at the exact dosage frequency recited in the claims. Ex. 1084; Ex. 1041; Ex. 1042; Ex. 1043; Ex. 1044.

VI. THE '981 PATENT

A. Challenged Claims

Petitioners challenge claims 1-14 of the '981 patent. The two independent claims (1 and 8) recite a "method of treating juvenile idiopathic arthritis" by administering a fixed dose of 162 mg of tocilizumab, or an anti-IL-6R antibody, every week, every two weeks, or every three weeks:

Independent Claims	Dependent Claims
1. A method of treating juvenile idiopathic arthritis (JIA) in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient in an amount effective to treat the JIA, wherein the anti-IL-6R antibody is administered as a fixed dose of 162 mg per dose every week, every two weeks, or every three 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 JIA is systemic JIA (sJIA). 3. The method of claim 2 wherein the fixed dose is administered every week if the patient's weight is ≥30 kilograms. 4. The method of claim 2 wherein the fixed dose is administered every two weeks if the patient's weight is <30 kilograms. 5. The method of claim 1 wherein the JIA is polyarticular course juvenile idiopathic arthritis (pcJIA). 6. The method of claim 5 wherein the fixed dose is administered every two weeks if the patient's weight is ≥30 kilograms. 7. The method of claim 5 wherein the fixed dose is administered every three weeks if the patient's weight is <30 kilograms.

Independent Claims	Dependent Claims
8. A method of treating juvenile idiopathic arthritis (JIA) in a patient comprising subcutaneously administering tocilizumab to the patient, wherein the tocilizumab is administered subcutaneously as a fixed dose of 162 mg per dose every week, every two weeks, or every three weeks.	9. The method of claim 8 wherein the JIA is systemic JIA (sJIA). 10. The method of claim 9 wherein the tocilizumab is administered every week if the patient's weight is ≥30 kilograms. 11. The method of claim 9 wherein the tocilizumab is administered every two weeks if the patient's weight is <30 kilograms. 12. The method of claim 8 wherein the JIA is polyarticular course juvenile idiopathic arthritis (pcJIA). 13. The method of claim 12 wherein the tocilizumab is administered every two weeks if the patient's weight is ≥30 kilograms. 14. The method of claim 12 wherein the tocilizumab is administered every three weeks if the patient's weight is <30 kilograms.

VII. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art ("POSA") to whom the '981 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 juvenile idiopathic rheumatoid arthritis, or having several years of experience researching treatments for autoimmune and inflammatory disorders, including juvenile idiopathic rheumatoid arthritis. Ex. 1002 ¶30.

VIII. PRIORITY DATE

"In order for a patent to be entitled to priority based on an earlier application or chain of applications, each previous application in the chain must comply with the written description requirement of 35 U.S.C. § 112(a)." *Los Angeles Biomedical Rsch. Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057 (Fed. Cir. 2017). To satisfy the written description requirement, the disclosure of the priority 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." *Id.* at 1057-58.

The '981 patent claims priority to two provisional applications, Application No. 61/411,015 ("'015 Application") (Ex. 1047), filed on November 8, 2010, and Application No. 61/542,615 ("'615 Application") (Ex. 1048), filed on October 3,

2011. The '981 patent claims also claims priority to Application No. 13/290,366 (Ex. 1052), filed on November 7, 2011, which issued as U.S. Patent No. 8,580,264, as well as Application No. 14/062,026 (Ex. 1051), filed on October 24, 2013, which issued as U.S. Patent No. 9,750,752.

As explained in detail below, the '981 patent claims are not entitled to the benefit of the priority date of any of the foregoing applications. Thus, all of the claims have a priority date, at the earliest, of August 3, 2017, the filing date of the application that issued as the '981 patent.

A. The Priority Applications Do Not Describe a Three-Week Administration Frequency

Claims 1-14 are all directed to methods of treating JIA that include administering a 162 mg fixed dose of tocilizumab (or an anti-IL-6R antibody) every three weeks. Specifically, independent claims 1 and 8 are directed to a method in which an anti-IL-6R antibody (claim 1) / tocilizumab (claim 8) is administered "as a fixed dose of 162 mg per dose every week, every two weeks, ***or every three weeks***." (emphasis added).

None of the dependent claims limit the frequency of administration for all patients within the scope of the claims. Claims 2, 5, 9, and 12 do not limit the administration frequency at all, and instead only limit the recited methods to categories of JIA, either sJIA or pcJIA. The remaining claims (claims 3-4, 6-7, 10-

11 and 12-14) introduce conditional limitations that only limit the administration frequency for some patients, depending on their weight. For example, claim 3 recites the "method of claim 2 wherein the fixed dose is administered every week ***if the patient's weight is ≥ 30 kilograms***." (emphasis added). In other words, if a patient weighs ≥ 30 kilograms, then the administration frequency is every week. But if the patient weighs less than 30 kilograms, the administration frequency can be either every week, every two weeks, or every three weeks (as set forth in claim 1, from which claims 2 and 3 depend). As the PTAB recently stated, "a method claim that includes a conditional step can be thought of as covering two methods—one method where the condition for the step is met and the step is performed, and the second method where the condition is *not* met and the step is *not* performed." *Microsoft Corp. v. Uniloc 2017 LLC*, No. IPR2019-01187, 2021 WL 189216, at *8 (P.T.A.B. Jan. 19, 2021). Here, dependent claims 3-4, 6-7, 10-11 and 12-14 recite conditional limitations that limit the administration frequency only when the condition is met; if the condition is not met, the administration frequency can be every week, every two weeks, or every three weeks, as recited in independent claims 1 and 8. Accordingly, all the '981 patent claims recite a three-week administration frequency for at least some patients.

The priority applications to the '981 patent do not disclose administering a 162 mg fixed dose of tocilizumab or an anti-IL-6R antibody ***every three weeks*** for

treatment of JIA. At most, the priority applications describe a treatment frequency with a 162 mg dose of every week or every two weeks. Ex. 1047 at 20; Ex. 1048 at 48; Ex. 1052 at 24; Ex. 1051 at 27; Ex. 1002 ¶¶51-53. While the priority applications also disclose an every four week treatment frequency, that is with higher doses of 324 mg and 648 mg, not 162 mg. Ex. 1002 ¶51; Ex. 1047 at 20; Ex. 1048 at 48; Ex. 1052 at 24; Ex. 1051 at 27. A dosage of 324 mg or 648 mg every four weeks amounts to 162 mg every two weeks or every week, respectively—not every three weeks. A POSA would not have understood these disclosures to convey that the named inventors were in possession of administering tocilizumab or an anti-IL-6R antibody every three weeks for treatment of JIA. Ex. 1002 ¶¶51-53.[3] Accordingly, claims 1-14 lack written description support in any

[3] As the Federal Circuit has made clear, "[t]he disclosure of a broad range of values does not by itself provide written description support for a particular value within that range. Instead, where a specification discloses a broad range of values and a value within that range is claimed, the disclosure must allow one skilled in the art to 'immediately discern the limitation at issue in the claims.'" *Gen. Hosp. Corp. v. Sienna Biopharms., Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018) (quoting *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000)). Here, the priority applications to the '981 patent do not even disclose administering 162 mg

application in the priority chain, and therefore are entitled only to a priority date of August 3, 2017, the filing date of the application that issued as the '981 patent. *See Los Angeles*, 849 F.3d at 1058 (holding that method of treatment claims were not entitled to priority date of parent application, where parent application did not explicitly disclose the claimed dosage).

B. None of the Priority Applications Disclose Administering to pcJIA Patients a Different Frequency Depending on the Patient's Weight, as Recited in Claims 6-7 and 13-14

As explained above, none of the claims are entitled to a priority date earlier than August 3, 2017 because the priority applications do not describe a three-week administration frequency. Claims 6-7 and 13-14 also are not entitled to the benefit of the priority date of any priority application for an additional reason—the priority applications describe the same frequency for all pcJIA patients regardless of a patient's weight. Claims 6 and 13 are directed to a method of treating pcJIA "wherein the fixed dose is administered every two weeks if the patient's weight is ≥ 30 kilograms," and claims 7 and 14 are directed to a method of treating pcJIA "wherein the fixed dose is administered every three weeks if the patient's weight is

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with a range of frequencies that would include a 3-week frequency, much less provide any disclosure that would allow a POSA to immediately discern the 3-week administration frequency.

< 30 kilograms."

The priority applications do not describe administering tocilizumab or an anti-IL-6R antibody for treatment of pcJIA wherein the frequency of administration is based on a patient's weight. The first-filed provisional application, the '015 Application, does not disclose a weight-based frequency for treatment of any IL-6 mediated disorder, much less one for the treatment of pcJIA. Ex. 1047; Ex. 1002 ¶55. In the second-filed provisional application, the '615 Application, the applicant added, *inter alia*, Example 7, titled "SQ Administered Anti-IL6R Antibody for pcJIA," that describes a clinical study in which ***all patients*** (regardless of patient weight) were treated with 162 mg every two weeks. Ex. 1002 ¶56; Ex. 1048 at 107-112 ("SC dose of 162 mg Q2W for both BW < 30 kg and BW ≥ 30 kg patients appears to be appropriate to maintain TCZ serum concentration above 1 μg/mL for all patients."). The applicant also added subject matter disclosing treatment of sJIA wherein the frequency of administration is based on a patient's weight (i.e., once a week if a patient's weight is ≥ 30 kg, and every 10 +/1 day if a patient's weight is < 30 kg), but there is no analogous disclosure for treatment of pcJIA. Ex. 1048 at 74-75; Ex. 1002 ¶¶56, 60. A POSA would not understand the disclosure of a weight-based frequency of administration of treatment of ***sJIA*** to convey that the named inventors were also in possession of administering ***pcJIA*** using a weight-based frequency, particularly since the

disclosures explicitly state that a 162 mg should be used for treatment of pcJIA for ***all patients*** regardless of weight, and the claimed pcJIA methods require a different weight-based frequency than that disclosed as useful for treating sJIA. Ex. 1002 ¶¶56-58. None of the later-filed applications provide any further disclosure concerning weight-based administration for the treatment of pcJIA. Ex. 1002 ¶57. Accordingly, claims 6-7 and 13-14 lack written description support to any application in the priority chain, and therefore for this additional reason are entitled, at the earliest, to a priority date of August 3, 2017.[4] *See Los Angeles*, 849 F.3d at 1058.

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

[4] Claims 3-4 and 10-11, which recite weight-based limitations for the treatment of sJIA, are analogously not entitled to priority to the first-filed Provisional Application because that application fails to disclose weight-based treatment of sJIA patients, as explained above. Ex. 1002 ¶¶55, 59-60. Therefore, even if the Board were to find that these claims do not encompass every three week administration, they would nevertheless not be entitled to priority earlier than the October 3, 2011 filing date of the second Provisional Application.

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, 1312-13 (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.[5]

A. "fixed dose" (claims 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 (BSA), i.e., it is not administered as either a mg/kg or mg/m^2 dose." Ex. 1001 at 15:22-25.

X. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Petitioners request review and cancellation of claims 1-14 of the '981 patent under §§ 102 and 103 for the reasons explained in this petition, which are summarized as follows:

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

Ground No.	Claims and Basis
1	Claims 1-14 are anticipated by the ’264 patent
2	Claims 1-14 are anticipated by NCT02165345
3	Claims 1-14 are obvious in view of NCT02165345
4	Claims 1-14 are obvious in view of Herlin and Ohta 2010

A. Ground 1: Claims 1-14 Are Anticipated by the ’264 Patent

Claims 1-14 are entitled to a priority date no earlier than August 3, 2017. *Supra* § VIII. The ’264 patent issued on November 12, 2013, and therefore is prior art under AIA § 102(a)(1) and does not qualify for an exception under section 102(b)(1). As set forth below, and as explained by Dr. Zizic, the claims are anticipated by the ’264 patent. Ex. 1002 ¶¶100-113.

1. Claims 1 and 8

Claim 1 recites “[a] method of treating juvenile idiopathic arthritis (JIA) in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient in an amount effective to treat the JIA, wherein the anti-IL-6R antibody is administered as a fixed dose of 162 mg per dose every week, every two weeks, or every three 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.” Claim 8 recites “[a] method of treating juvenile idiopathic arthritis (JIA) in a patient comprising subcutaneously administering tocilizumab to the

patient, wherein the tocilizumab is administered subcutaneously as a fixed dose of 162 mg per dose every week, every two weeks, or every three weeks."

The '264 patent discloses a method of treating JIA by subcutaneously administering a fixed dose of 162 mg of tocilizumab every week or every two weeks. Specifically, the '264 patent discloses:

> [T]he invention concerns a method of treating an IL-6-mediated disorder in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient, wherein the anti-IL-6R antibody is administered as a fixed dose of 162 mg per dose (e.g. administered every week or every two weeks). Embodiments of the disorder include: rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis, and Castleman's disease. Preferably, the anti-IL-6R antibody is tocilizumab.

Ex. 1050 at 4:33-41. Furthermore, the '264 patent discloses that "the light chain and heavy chain amino acid sequences of Tocilizumab comprise SEQ ID NOs. 1 and 2, respectively (see FIGS. 7A-B)." *Id.* at 8:43-46.

The '264 patent further states that it was expected that the 162 mg subcutaneous dosage would be effective in treating sJIA and pcJIA patients when administered at a frequency of every week (for sJIA) and every two weeks (for pcJIA):

> It is anticipated that the anti-IL-6R antibody (TCZ) will be effective in sJIA patients with body weight ≥ 30 kg when administered as a fixed dose of 162 mg every week (QW) by SQ administration, e.g., for up to 14 weeks.
>
> . . .
>
> It is anticipated that the anti-IL-6R antibody (TCZ) will be effective in pcJIA patients when administered as 162 mg dose every 2 weeks (Q2W) by SQ administration, e.g., for up to 14 weeks.

Ex. 1050 at 51:5-14, 53:31-35. Thus, the '264 patent anticipates claims 1 and 8 of the '981 patent. Ex. 1002 ¶¶101-107.[6]

[6] To the extent that Patent Owner alleges that the '264 patent does not anticipate any of the challenged claims because it does not expressly disclose that the treatment regimens were effective, efficacy is inherent in the prior art regimens. As the Federal Circuit has explained, "[t]o anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *See King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010). In *King*, the Federal Circuit explained that the patent at issue provided nothing more than the prior art with respect to how to carry out the claimed method, and "to the extent such a method increases the bioavailability of metaxalone, the identical

2. Claims 2-4 and 9-11

Claims 2 and 9 are directed to the methods of claims 1 and 8, respectively, with the further limitation that the "JIA is systemic JIA (sJIA)." Claims 3 and 10 depend from claims 2 and 9, respectively, and further recite "wherein the [fixed dose] (claim 3) / [tocilizumab] (claim 10) is administered every week if the patient's weight is ≥ 30 kilograms." Claims 4 and 11 depend from claims 2 and 9, respectively, and further recite "wherein the [fixed dose] (claim 4) / [tocilizumab] (claim 11) is administered every two weeks if the patient's weight is <30 kilograms."

As discussed above with respect to claims 1 and 8, the '264 patent discloses a method of treating sJIA in a patient comprising subcutaneously administering tocilizumab (an anti-IL-6 receptor antibody having the light and heavy chain amino acid sequences of SEQ ID NOs 1 and 2, respectively) to the patient as a fixed dose of 162 mg every week, and that such administration was expected to be effective to treat the sJIA. *Supra* § X.A.1. The '264 patent further discloses treating sJIA patients with "162 mg of the antibody (e.g. of tocilizumab) every week if the

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prior art method does as well." *Id*. As in *King*, the '981 patent claims are directed to the same method disclosed by the prior art, and to the extent the claimed method provides effective treatment, then the prior art method does as well.

patient's weight is ≥ 30 kilograms," and "[i]n an alternative embodiment, the SJIA patient whose weight is < 30 kilograms is treated with 162 mg of the antibody (e.g. of tocilizumab) every week or every two weeks." Ex. 1050 at 26:21-29. Thus, claims 2-4 and 9-11 are also anticipated by the '264 patent. Ex. 1002 ¶¶108-110.

3. Claims 5-7 and 12-14

Claims 5 and 12 are directed to the methods of claims 1 and 8, respectively, with the further limitation that the "JIA is polyarticular course juvenile idiopathic arthritis (pcJIA)." As discussed above with respect to claims 1 and 8, the '264 patent discloses a method of treating pcJIA in a patient comprising subcutaneously administering tocilizumab (an anti-IL-6 receptor antibody having the light and heavy chain amino acid sequences of SEQ ID NOs 1 and 2, respectively) to the patient as a fixed dose of 162 mg every two weeks, and that such administration was expected to be effective to treat the pcJIA. *Supra* § X.A.1. Thus, the '264 patent discloses all elements of claims 5 and 12, and therefore anticipates both claims. Ex. 1002 ¶¶111-112.

Claims 6 and 13 depend from claims 5 and 12, respectively, and further recite "wherein the [fixed dose] (claim 6) / [tocilizumab] (claim 13) is administered every two weeks if the patient's weight is ≥ 30 kilograms." With respect to treating pcJIA, the '264 patent discloses that a subcutaneous "dose of 162 mg Q2W for both BW<30 kg and BW ≥30 kg patients appear to be

appropriate," and therefore discloses that the subcutaneous dose for treating pcJIA "is 162 mg Q2W for all patients," which a POSA would have understood includes patient weighing at least 30 kg. Ex. 1050 at 52:62-67; Ex. 1002 ¶112. The '264 patent further discloses that "[i]t is anticipated that the anti-IL-6R antibody (TCZ) will be effective in pcJIA patients when administered as 162 mg dose every two weeks (Q2W) by SQ administration." Ex. 1050 at 53:31-34. Thus, because the '264 patent discloses subcutaneously administering a 162 mg fixed dose of tocilizumab to treat pcJIA if the patient's weight is ≥ 30 kg, claims 6 and 13 are also anticipated by the '264 patent. Ex. 1002 ¶¶111-112.

Claims 7 and 14 depend from claims 5 and 12, respectively, and further recite "wherein the [fixed dose] (claim 7) / [tocilizumab] (claim 12) is administered every three weeks if the patient's weight is <30 kilograms." These claims recite a conditional limitation: "***if***" a pcJIA patient weighs less than 30 kilograms, the patient is administered a dose every three weeks. But if the recited condition is not met, i.e., a patient weighs ≥ 30 kilograms, the patient can be administered a dose every week, every two weeks, or every three weeks, as recited in claim 5 and 12 (via their dependency on claims 1 and 8, respectively) and still fall within the scope of claims 7 and 14.

As the PTAB has held, "if a method's conditional step does not need to be performed, it does not need to be shown to invalidate the method claim."

Microsoft, 2021 WL 189216, at *8; *Cybersettle, Inc. v. National Arbitration Forum*, 243 F. App'x 603, 607 (Fed. Cir. 2007) ("If the condition for performing a contingent step is not satisfied, the performance recited by the step need not be carried out in order for the claimed method to be performed."). As just discussed, the '264 patent discloses administering a 162 mg fixed dose of tocilizumab every two weeks to patients that weigh ≥ 30 kilograms. Ex. 1050 at 4:33-5:62. Thus, because the '264 patent discloses treatment methods that fall within the scope of claims 7 and 14, those claims are also anticipated by the '264 patent.[7] Ex. 1002 ¶113.

B. Ground 2: Claims 1-14 are Anticipated by NCT02165345

NCT02165345 is a clinical trial protocol, entitled "Extension Study Evaluating the Safety and Efficacy of Subcutaneous Tocilizumab

[7] The '264 patent would have enabled a POSA to practice the challenged claims of the '981 patent. As a preliminary matter, prior art patents and publications are presumed enabled, and at this stage (prior to institution), Petitioners are entitled to rely upon that presumption to establish invalidity. *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x 443, 450 (Fed. Cir. 2021). Moreover, although not necessary to enable the method of treatment claims, the '264 patent discloses several exemplary formulations for subcutaneous administration. Ex. 1050 at Table 2.

(RoActemra/Actemra) Administration in Systemic and Polyarticular Course Juvenile Idiopathic Arthritis," published on ClinicalTrials.gov. Ex. 1084; Ex. 1079; Ex. 1100 at 951-52. Claims 1-14 are entitled to a priority date no earlier than August 3, 2017. *Supra* § VIII. NCT02165345 was publicly available on ClinicalTrials.gov as early as 2014, more than one year before the earliest priority date. Ex. 1004 ¶¶25-37; Ex. 1002 ¶¶78-83, 114. Therefore, NCT02165345 is prior art under AIA § 102(a)(1) and does not qualify for an exception under § 102(b)(1).

1. Disclosure of NCT02165345

NCT02165345 is an extension clinical study "designed to evaluate the long term safety and efficacy of subcutaneous (SC) tocilizumab treatment in patients with polyarticular-course and systemic juvenile idiopathic arthritis (pJIA and sJIA)." Ex. 1084 at 2. The NCT02165345 clinical trial was an "open-label extension" of the JIGSAW studies, meaning that participants had already participated in the JIGSAW studies.[8] Ex. 1004 ¶27; Ex. 1084 at 2. As stated in the

[8] The JIGSAW studies refers to two open-label, multicenter clinical studies evaluating the pharmacokinetics, pharmacokinetics and safety of subcutaneously administered tocilizumab in patients with JIA. One was for an evaluation of pcJIA

protocol, "[p]articipants from the 2 JIGSAW studies will continue to receive 162 milligrams (mg) of SC tocilizumab according to arthritis subtype and body weight." Ex. 1084 at 2. More specifically, NCT02165345 discloses the following treatment regimens for JIA patients: "pJIA participants less than (<) 30 kilograms (kg): every 3 weeks; pJIA participants greater than or equal to (>=) 30 kg: every 2 weeks; sJIA participants <30kg: every 2 weeks; sJIA participants >/= 30 kg: once weekly." Ex. 1084 at 4.

2. NCT02165345 Was Publicly Available as Early as 2014

NCT02165345 is a prior art printed publication, which was available on ClinicalTrials.gov as early as 2014. Ex. 1004 ¶¶25-37; Ex. 1002 ¶¶78-83, 114. The study record for NCT02165345 was "First Posted" on ClinicalTrials.gov on June 17, 2014, and therefore was publicly available at least as of that date. Ex. 1004 ¶28; Ex. 1084 at 2. As Mr. Robert Paarlberg explains, ClinicalTrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials, and NCT02165345 was publicly accessible more than one year before the earliest claimed priority date. Ex. 1004 ¶¶25-37.

In 1997, the FDA Modernization Act required that the National Institutes of

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patients (NCT01904279) and the other was for evaluation of sJIA patients (NCT01904292). Ex. 1041; Ex. 1042.

Health ("NIH") establish a database of information on clinical trials conducted in the United States for drugs for serious or life threatening diseases and conditions. *Id.* ¶12. The National Library of Medicine, under the NIH, launched ClinicalTrials.gov in February 2000, providing the public with access to information on clinical studies. *Id.* ¶13. The database is intended to provide "patients, families and members of the public ***easy access to information***." Ex. 1053 at 1 (emphasis added). The FDA Amendments Act of 2007 later expanded the database by requiring additional submission information, mandating searchable categories in the database, and imposing a fine for failure to submit information within 21 days of first patient enrollment. Ex. 1004 ¶¶15-16.

The ClinicalTrials.gov database provides key publication dates for each study submitted. According to the NIH, the "First Posted" date is "[t]he date on which the study record was first available on ClinicalTrials.gov." Ex. 1054 at 7. The study record for NCT02165345 was "First Posted" on June 17, 2014. Ex. 1084 at 2. Thus, although the current version of the protocol was updated as recently as November 10, 2021, as Mr. Paarlberg explains, the "First Posted" date is sufficient to indicate that the posting was available to the public in 2014. Ex. 1004 ¶28. Moreover, an article published in September 2014 cites to NCT02165345 which provides further confirmation that it was publicly accessible to a POSA in 2014. Ex. 1055 at 5 ("Subcutaneous use of abatacept and of

tocilizumab (clinical trial # NCT01844518 and NCT02165345) are currently being studied in JIA."). Furthermore, although Patent Owners neglected to disclose NCT02165345 to the Examiner during prosecution of the '981 patent, they not only disclosed it during prosecution of another patent on September 8, 2015—i.e., more than one year before the August 3, 2017 priority date applicable here—they also represented its publication date as June 13, 2014. Ex. 1100 at 788-93; 951-52. That version was "Last Updated" on July 1, 2015, and indicates a download date of July 13, 2015. *Id.* at 951-52. In short, Patent Owners cannot credibly dispute that NCT02165345 was publicly accessible to a POSA more than one year prior to the earliest possible priority date to which the claims of the '981 patent are entitled.[9]

[9] Hoffmann-La Roche, one of the patent owners, sponsored the NCT02165345 clinical study, and therefore likely has documents reinforcing that the study was publicly available on ClinicalTrials.gov before August 2017. Indeed, as explained above, in September 2015, Hoffman-La Roche provided a copy to the Examiner. To the extent Hoffman-La Roche disputes whether the ClinicalTrials.gov posting is prior art, Petitioners should be entitled to "routine discovery" and/or "additional discovery" from Hoffmann-La Roche that is inconsistent with that position. *See* PTAB Trial Practice Guide (Nov. 2019) at 23-24 (providing for "routine

As Mr. Paarlberg explains, the versions of NCT02165345 publicly available beginning in 2014 (as well as every version since that time) disclosed the drug ("tocilizumab"), as well as the dosage amount and delivery route—"162 mg will be administered by subcutaneous injection"—and the following treatment regimen for pcJIA patients: "pJIA participants less than (<) 30 kilograms (kg): every 3 weeks; pJIA participants greater than or equal to (>=) 30 kg: every 2 weeks." Ex. 1004 ¶¶25-37; Ex. 1084 at 4; Ex. 1100 at 951-52; Ex. 1079 at 8; Ex. 1082 at 8; Ex. 1078 at 8. By no later than March, 2016 (and in all subsequent versions), NCT02165345 disclosed the following treatment regimen for sJIA patients: "sJIA participants < 30 kg: every 2 weeks; sJIA participants >/= 30 kg: once weekly." *Id*. Ex. 1004 ¶¶38-56; Ex. 1079 at 8; Ex. 1082 at 8; Ex. 1084 at 4.[10] While there have been changes made to the study status (e.g., "recruiting" vs. "completed," updated study locations, etc.), none of the changes altered the treatment protocol for pcJIA or sJIA patients weighing at least 30 kg since the original 2014 posting, nor have there been any changes to the treatment protocol for sJIA patients weighing less

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

[10] Prior to March, 2016, the frequency identified in NCT02163453 for treatment of sJIA patients weighing less than 30 kg was "every 10 days." Ex. 1004 ¶41.

than 30 kg. Ex. 1004 ¶¶38-56. In short, the pcJIA and sJIA treatment protocols disclosed in the latest version of NCT02165345 are identical to the version which would have been publicly available more than one year before the August 3, 2017 priority date applicable to the '981 patent claims. *Id.* Therefore, insignificant differences aside, the current version of NCT021653453 reflects the clinical trial protocol as it was publicly available to a POSA before the priority date. *Id.*

The totality of the evidence, including the indicia on the face of the documents, the citation of the protocol in other prior art documents, Patent Owner's disclosure of the protocol to the Patent Office, and the testimony of Mr. Paarlberg, establishes that NCT021653453 was a publicly accessible printed publication more than one year before the earliest claimed priority date. *See, e.g.*, *Grunenthal GmbH v. Antecip Bioventures II, LLC.*, PGR 2019-00003, 2020 WL 2203740, at *7-8 (P.T.A.B. May 5, 2020) (finding a protocol available on ClinicalTrials.gov to have been publicly available as of its "first posting" date and therefore a "prior art printed publication").

3. NCT02165345 Discloses All Elements of Claims 1-14

a) Claims 1 and 8

Claim 1 recites "[a] method of treating juvenile idiopathic arthritis (JIA) in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient in an amount effective to treat the JIA, wherein the anti-IL-

6R antibody is administered as a fixed dose of 162 mg per dose every week, every two weeks, or every three 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." Claim 8 recites "[a] method of treating juvenile idiopathic arthritis (JIA) in a patient comprising subcutaneously administering tocilizumab to the patient, wherein the tocilizumab is administered subcutaneously as a fixed dose of 162 mg per dose every week, every two weeks, or every three weeks."

NCT02165345 is a clinical study "designed to evaluate the long term safety and efficacy of subcutaneous (SC) tocilizumab treatment in patients with polyarticular-course and systemic juvenile idiopathic arthritis (pJIA and sJIA)." Ex. 1084 at 2; Ex. 1079 at 7; Ex. 1100 at 951. Patients were administered a 162 mg fixed dose, i.e., a fixed amount without regard to a patient's weight or body surface area. Ex. 1084 at 4; Ex. 1079 at 8; Ex. 1100 at 952. The protocol required treatment of patients with tocilizumab, an anti-IL-6R antibody,[11] at the following intervals: "pJIA participants less than (<) 30 kilograms (kg): every 3 weeks; pJIA participants greater than or equal to (>=) 30 kg: every 2 weeks; sJIA participants < 30 kg: every 2 weeks; sJIA participants >/= 30 kg: once weekly." Ex. 1084 at 4;

[11] Ex. 1001 at 5:29-30 ("The invention also concerns subcutaneously administering an anti-IL-6R antibody (e.g., tocilizumab).").

Ex. 1079 at 8; Ex. 1100 at 951.[12] Thus, NCT02165345 discloses multiple treatment regimens within the scope of claims 1 and 8, whether one considers the prior art protocol as reflected in the current version, the 2016 version, or the 2015 version. Ex. 1002 ¶¶116-126.

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." NCT02165345 discloses administration of tocilizumab, which comprises the light chain and heavy chain amino acid sequences of SEQ ID. Nos. 1 and 2, respectively. Ex. 1002 ¶¶120-125. The patent specification confirms that tocilizumab comprises the claimed sequences: "FIGS. 7A and 7B depict the amino acid sequences of the **light chain** (FIG. 7A: **SEQID NO: 1**) and **heavy chain** (FIG. 7B: **SEQID NO:2**) **of Tocilizumab**." Ex. 1001 at 7:14-16 (emphasis added). And Chugai and the patent inventors have admitted that tocilizumab has

[12] As discussed above, the current version of the NCT02165345 reflects the disclosure available to a POSA as of the priority date of the '981 patent claims. The 2015 version of the NCT02165345 protocol submitted by Patent Owner during prosecution of a different patent discloses the same dosing regimens as the current version with the exception that sJIA patients weighing less than 30 kg were administered the drug every ten days rather than every two weeks.

the claimed amino acid sequences. Ex 1005 at 1025-1027; Ex. 1007 at 181, 257; Ex. 1031 at 2; Ex. 1003 ¶¶53-60. Furthermore, as explained by Dr. Levine, tocilizumab inherently has the claimed amino acid sequences for the heavy and light chains. Ex. 1003 ¶¶50-52.

NCT02165345 also discloses that the protocol was effective in treating sJIA and pcJIA patients. NCT02165345 is an extension study in which patients continued to receive the same treatment they were provided in the prior JIGSAW studies. NCT02165345 expressly states that an inclusion criteria is "[c]ompletion of either of the JIGSAW studies, study WA28117 (for participants with pJIA) or study WA28118 (for participants with sJIA)," and that patients must have had "[a]dequate disease control with the use of SC tocilizumab (TCZ)." Ex. 1084 at 5; Ex. 1079 at 10; Ex. 1100 at 952.[13] Thus, a POSA would have understood from the express disclosures in NCT02165345 that the disclosed treatment was effective in

[13] Study WA28117 involved subcutaneously administering 162 mg tocilizumab every three weeks to pcJIA patients weighing less than 30 kg and every two weeks to patients weighing greater than or equal to 30 kg. Ex. 1041 at 3; Ex. 1004 ¶41. Study WA28118 involved subcutaneously administering 162 mg tocilizumab every two weeks to sJIA patients weighing less than 30 kg and every week to patients weighing greater than or equal to 30 kg. Ex. 1042 at 3.

treating sJIA and pcJIA patients.[14] Ex. 1002 ¶¶117-118. Accordingly, claims 1 and 8 are anticipated by NCT02165345.

b) Claims 2-4 and 9-11

Claims 2 and 9 depend from claims 1 and 8, respectively, and further require that "the JIA is systemic JIA (sJIA)." Claims 3 and 10 depend from claims 2 and 9, respectively, and further recite "wherein the [fixed dose] (claim 3) / [tocilizumab] (claim 10) is administered every week if the patient's weight is ≥ 30 kilograms." Claims 4 and 11 recite methods of treating sJIA, and depend from claims 2 and 9, respectively, and further recite "wherein the fixed dose is administered every two weeks if the patient's weight is < 30 kilograms."

As discussed above with respect to claims 1 and 8, NCT02165345 discloses treating sJIA patients by subcutaneously administering a fixed dose of 162 mg

[14] To the extent Patent Owner alleges that NCT02165345 does not expressly disclose that the treatment regimens are efficacious, such efficacy is inherently disclosed. *See King*, 616 F.3d at 1275-76 ("[t]o anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does"). The '981 patent claims are directed to the same method disclosed by the prior art, and to the extent the claimed method provides effective treatment, then the prior art method does as well.

tocilizumab every week to patients weighing at least 30 kg and every two weeks to patients weighing less than 30 kg, and that these regimens were effective for treating sJIA. *Supra* § X.B.3.a. Accordingly, claims 2-4 and 9-11 are anticipated by NCT02165345 for substantially the same reasons as set forth with respect to claims 1 and 8, whether one considers the current version of the protocol or the 2016 version. Ex. 1002 ¶128.

Furthermore, as discussed above, claims 4 and 11 encompass administering 162 mg tocilizumab every week to sJIA patients weighing at least 30 kg (i.e., those patients that do not meet the conditional limitation of weighing less than 30 kg). *Supra* § X.A.2. NCT02165345 discloses treating "sJIA participants >/= 30 kg: once weekly," and therefore anticipates these claims for this additional reason, even if one considers only the 2015 version. Ex. 1100 at 951-52; Ex. 1002 ¶¶127-128; *Microsoft*, 2021 WL 189216, at *8 ("[I]f a method's conditional step does not need to be performed, it does not need to be shown to invalidate the method claim.").

c) Claims 5-7 and 12-14

Claims 5 and 12 depend from claims 1 and 8, respectively, and further recite "wherein the JIA is polyarticular course juvenile idiopathic arthritis (pJIA)." Claims 6 and 13 depend from claims 5 and 12, respectively, and further recite that the "fixed dose is administered every two weeks if the patient's weight is ≥ 30

kilograms." Claims 7 and 14 depend from claims 5 and 12, respectively, and further recite that the "fixed dose is administered every three weeks if the patient's weight is < 30 kilograms."

As discussed above with respect to claims 1 and 8, NCT02165345 discloses treating pcJIA patients by subcutaneously administering a fixed dose of 162 mg tocilizumab every two weeks to patients weighing at least 30 kg or every three weeks to patients weighing less than 30 kg, and that these regimens were effective for treating pcJIA. *Supra* § X.B.3.a. Accordingly, claims 5-7 and 12-14 are anticipated by NCT02165345 for substantially the same reasons as set forth with respect to claims 1 and 8. Ex. 1002 ¶¶129-130.

4. NCT02165345 Is Enabled

In related proceedings, Patent Owners have asserted that prior art clinical trial references are not enabled, notwithstanding that they disclose the exact same dosing regimens recited by the claims. IPR2021-01288, Paper 10 at 21-26. As a preliminary matter, "[i]t is well-established that prior art patents and printed publications . . . are presumed enabling," and, at this stage (prior to institution), Petitioners are entitled to rely upon that presumption to establish invalidity. *Apple*, 861 F. App'x at 450 (holding that the Board erred in shifting the burden to petitioner to provide evidence, before institution, that a prior art was enabled).

Patent Owners have previously argued that prior art references disclosing

clinical trials are not enabled because they do not instruct on how to prepare a stable formulation. But the challenged claims here require subcutaneously ***administering*** an IL-6R antibody at a specific dose and a specific frequency, and do not require use of any particular formulation or that the formulation be stable. In short, NCT02165345 is enabled because it recites the precise claimed dosage and administration frequency such that a POSA would be able to practice the claims. Ex. 1002 ¶115; *see Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003) ("An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more."). Moreover, the '981 patent discloses a formulation for subcutaneous administration of tocilizumab that includes the exact same ingredients as the prior art intravenous formulation. *Compare id.* at 39:Table 2 (disclosing a subcutaneous formulation consisting of tocilizumab, phosphate, polysorbate 80, sucrose, and water) *with* Ex. 1019 at 15 (disclosing an intravenous formulation consisting of tocilizumab, phosphate, polysorbate 80, sucrose, and water). Accordingly, there is no legitimate question that a POSA would have been able to practice the claimed invention based on the disclosures in NCT02165345.

C. Ground 3: Claims 1-14 Are Obvious in View of NCT02165345

As set forth above for Ground 2, claims 1-14 are anticipated by NCT02165345, which discloses treatment regimens for JIA patients using a

subcutaneous fixed dose of 162 mg of tocilizumab. These regimens meet each and every limitation of claims 1-14, as discussed above. The claims are also unpatentable as obvious over NCT02165345 because a POSA would have been motivated to administer the disclosed regimens and would have had a reasonable expectation of success in so doing, particularly because of the wide therapeutic window provided by tocilizumab. Ex. 1002 ¶¶131-140.

A POSA would have been motivated to carry out the claimed methods for treating pcJIA and sJIA, for at least the following reasons. First, NCT02165345 itself discloses subcutaneous administration of a fixed dose of 162 mg of tocilizumab for treatment of pcJIA and sJIA at the claimed frequencies. *Supra* § X.B.1. Second, while Actemra® (tocilizumab) had been approved by FDA for treatment of pcJIA and sJIA intravenously, the prior art taught that tocilizumab was preferably administered subcutaneously. Ex. 1002 ¶127; Ex. 1029 at 4 (tocilizumab's "preferred form of administration is thought to be subcutaneous formulation in chronic autoimmune diseases"). Indeed, in 2013, FDA approved Actemra® (tocilizumab) as a subcutaneous formulation for treatment of RA. Ex. 1059. As stated by Chugai in a press release in May 2013:

> This new subcutaneous formulation of Actemra®, in addition to the already launched intravenous infusion, will offer treatment options that suit patients' life style or meet the needs of health care providers,

> contributing to improved convenience of Actemra® therapy.
>
> Subcutaneous formulation requires short time of administration and will reduce the burden on patients of visits to medical institutions as it can be administrated at home by self-injection. For health care providers, it has additional benefit as it does not require preparation procedures prior to injection.

Id. at 1.

Chugai's statements in 2013 were consistent with the general knowledge that subcutaneous administration of antibodies is preferable as compared to intravenous administration because it allows for more constant serum levels and improved convenience for patients. Ex. 1002 ¶134. Subcutaneous treatment was known to provide significant improvement in quality of life and treatment, for example, due to increased independence and scheduling flexibility associated with self-administered subcutaneous therapy. *Id.*; Ex. 1070 at 2. Thus, a POSA would have been motivated to administer the claimed regimens to treat pcJIA and sJIA.

A POSA would have reasonably expected that the regimens disclosed by NCT02165345 would have been successful. Ex. 1002 ¶135. The prior art makes clear that an intravenously-administered antibody would be at least as safe and effective if instead administered at an equivalent amount subcutaneously. *Id.* For example, Bonilla discloses that antibodies may be administered subcutaneously

less frequently than intravenously in an amount that "over time is generally equivalent." Ex. 1061 at 15. Such less frequent subcutaneous administration provides the same mean serum levels along with fluctuations that are "much smaller" and therefore trough levels are higher and peak levels are lower than with intravenous administration. *Id.* And, for tocilizumab, it was known that the efficacy of tocilizumab depends upon maintaining adequate serum trough levels throughout treatment. Ex. 1033 at 9. Therefore, a POSA would have reasonably expected that safety and efficacy would be maintained when using a subcutaneous dose equivalent to the known IV dose. Ex. 1002 ¶135.

A POSA would have also known that FDA had approved Actemra® (tocilizumab) for treating pcJIA patients intravenously at 10 mg/kg (for patients < 30 kg) and 8 mg/kg (for patients > 30 kg), every four weeks; and, for treating sJIA patients intravenously at 12 mg/kg (for patients < 30 kg) and 8 mg/kg (for patients ≥ 30 kg) every two weeks. Ex. 1023 at 1. A POSA would have reasonably expected that the subcutaneous dosing regimens disclosed in NCT0216535 would be at least as safe and effective as the foregoing intravenous treatment regimen that had already been approved by FDA given wide therapeutic window provided by tocilizumab. Ex. 1002 ¶136. NCT02165345 discloses treating pcJIA patients with 162 mg subcutaneously every two weeks (for patients at least 30 kg) or every three weeks (for patients under 30 kg); and, sJIA patients

every week (for patients at least 30 kg) or every two weeks (for patients under 30 kg). This equates to a total dosage of 324 mg or 216 mg per four weeks for pcJIA patients heavier than 30 kg and lighter than 30 kg, respectively, and 648 mg or 324 mg every four weeks for sJIA patients heavier than 30 kg and lighter than 30 kg, respectively. Ex. 1002 ¶137. These amounts are approximately equivalent to the amount of tocilizumab administered in the FDA-approved intravenous regimen. *Id.* For example, a pcJIA patient weighing 40 kg would have an IV dosage amount of 320 mg per four weeks (vs. 324 mg for SC). *Id.* at ¶137 n.44. A pcJIA patient weighing 22.5 kg would have an IV dosage amount of 225 mg per four weeks (vs. 216 mg for SC). *Id.* at ¶137. And, an sJIA patient weighing 40 kg would have an IV dosage amount of 640 mg per four weeks (vs. 648 mg for SC), while an sJIA patient weighing 13 kg would have an IV dosage amount of 312 mg per four weeks (vs. 324 mg for SC). *Id.* at ¶138 n.45. Therefore, a POSA would have been motivated to carry out the subcutaneous methods disclosed in NCT02165345 for treating pcJIA, and would have reasonably expected those methods to be at least as safe and effective as the known IV regimens. Ex. 1002 ¶139.

A POSA would have further expected that the same dose could be successfully administered to JIA patients as a fixed dose rather than on a mg/kg basis. Ex. 1002 ¶140. The prior art taught that, for tocilizumab, large differences in AUC "did not affect efficacy or safety in a clinically relevant manner." Ex.

1019 (EMA Assessment Report) at 24. For drugs with such a large therapeutic window, fixed dosing was in fact considered preferable. Ex. 1027 at 7, 17. Accordingly, a POSA would have reasonably expected that this tocilizumab fixed dose would retain its safety and efficacy despite weight-based differences in tocilizumab clearance rate. Ex. 1002 ¶140.

D. Ground 4: Claims 1-14 Are Obvious In View of Herlin and Ohta 2010

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

Herlin is an article titled "Tocilizumab: The evidence for its place in the treatment of juvenile idiopathic arthritis," published in the Dove Press Journal on August 6, 2009. Ex. 1011. Herlin is prior art under AIA § 102(a)(1).[15]

[15] Claims 1-14 have an effective priority date of August 3, 2017 (*supra* § VIII), and therefore the '981 patent is subject to AIA § 102. Leahy-Smith America Invents Act ("AIA"). Pub. L. No. 112-29, § 3(n)(1), 125 Stat. 284, 293 (2011). Herlin is prior art to all claims of the '981 patent under AIA § 102(a)(1) and does not qualify under the one-year exception in § 102(b)(1). Furthermore, even if all of the claims of the '981 patent were entitled to a priority date of Oct. 3, 2011 (based on the filing date of the second provisional application), Herlin would nonetheless be prior art under pre-AIA § 102(b).

Herlin discloses successful clinical trials in which intravenous tocilizumab was shown to be effective in treating sJIA and pcJIA patients. Ex. 1011 at 1, 4-6. Herlin teaches that tocilizumab is used in the "targeted therapy of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA)," and "blocks the activity of the proinflammatory cytokine, IL-6, which exerts a central role in both diseases." *Id.* at 2. Herlin states that "[t]wo phase II studies of the blockade of IL-6 signaling using the anti-IL-6 receptor antibody (MRA, tocilizumab) for systemic JIA suggested that it was a highly effective treatment." *Id.* at 4.

Herlin further reports that a dosage of 8 mg/kg of intravenous tocilizumab every two weeks was effective in treating sJIA, and that "sustained and high response rates of clinical improvement have been achieved with American College of Rheumatology Pediatric criteria (ACRPed) 30, 50, and 70 observed in 98%, 94%, and 90% of patients, respectively, after 48 weeks." *Id.* at 1. And with respect to pcJIA, Herlin discloses successful results of an open-label, multicenter study in which children were treated with 8 mg/kg tocilizumab every four weeks, resulting in a "significant decrease in all core set parameters with an ACRPed30 of 94.1% after 12 weeks." *Id.* at 6.

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. During prosecution of the '677 patent,[16] the applicant represented that the "Ohta et al. abstract was first published [on] September 28, 2010 on the ACR website." Ex. 1007 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."[17] *Id.* at 289-90. Ohta 2010 is therefore prior art to the '981 patent under AIA § 102(a)(1) and not subject to an exception under section 102(b)(1) because it was publicly available more than one year

[16] The '677 patent shares the same specification as the '981 patent, and also claims priority to the '015 Application and '615 Application.

[17] 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 ¶89 n.39.

before August 3, 2017 priority date.[18]

Ohta 2010 discloses an open-label, multi-center clinical study "[t]o evaluate the safety, pharmacokinetics and efficacy of tocilizumab subcutaneous injection." Ex. 1039 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*. RA patients received a fixed dose of 162 mg tocilizumab subcutaneously either weekly or every other week. *Id.* at 2-3. Ohta 2010 reports that both regimens were "well tolerated" and "associated with good clinical response." *Id.* at 3.

2. A POSA Would Have Been Motivated to Combine Herlin and Ohta 2010

[18] Even if all of the claims were entitled to a priority date of October 3, 2011 (the filing date of the second provisional application), Ohta 2010 would be prior art under pre-AIA § 102(b).

A POSA would have been motivated to combine Herlin's disclosure that JIA can be treated with tocilizumab at 8 mg/kg (every two weeks for sJIA, and every four weeks for pcJIA) with Ohta 2010's disclosed 162 mg subcutaneous fixed dose, and would have arrived at the claimed methods. Ex. 1002 ¶¶146-155.

While tocilizumab had been used to successfully treat JIA at the intravenous dose and known to be useful for treating RA (8 mg/kg), by the time of the alleged invention of the '981 patent, the art had progressed such that it could instead 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. 1039 at 3. In fact, Ohta 2010 demonstrated that tocilizumab administered subcutaneously at a dose of 162 mg every week or every other week was well-tolerated and resulted in at least comparable improvement in disease indicators in RA patients to that observed when administered in comparable amounts in intravenous clinical studies. Ex. 1002 ¶147; Ex. 1039 at 2-3; Ex. 1021 at 3-5; Ex. 1022 at 2-3. For example, C-reactive protein (CRP) levels decreased, "indicating that tocilizumab concentration … was sufficient to inhibit IL-6 signal" and AC20/50/70 scores were in fact higher for both 162 subcutaneous regimens than had been reported for the

intravenous regimen.[19] *Id.*

In view of: (a) the general preference for subcutaneous administration of antibodies (*supra* § V.B), (b) the knowledge that intravenous tocilizumab regimens had been successful for treating both JIA and RA, and (c) the observed comparable efficacy for treating RA with the Ohta 2010 subcutaneous regimens as compared to intravenous administration of a similar total amount of tocilizumab over time, a POSA would have been motivated to administer the 162 mg subcutaneous dose disclosed by Ohta 2010 at a frequency that would provide an equivalent dosage over time to the IV regimens disclosed by Herlin in order to treat JIA. *See In Re Copaxone Consolidated Cases*, 906 F.3d 1013, 1025-28 (Fed. Cir. 2018) (finding method of treatment claims obvious where "a POSITA had only a limited number

[19] CRP is a protein found in blood, with elevated levels found in patients with RA and JIA. Ex. 1002 ¶147 n.46. ACR20/50/70 were standard criteria for evaluating clinical response to RA treatment. Ex. 1066 at 6; Ex. 1002 ¶147 n.46. An ACR20 response requires a 20% improvement in tender and swollen joint counts, as well as a 20% improvement in three of the following five criteria: patient and physician global assessment, pain, disability, and an acute phase reactant. Ex. 1066 at 3 n.2. ACR70 is analogous to ACR20, except it requires a 70% improvement rather than a 20% improvement. Ex. 1066 at 3; Ex. 1002 ¶147 n.46.

of permutations of dose and frequency to explore that were not already disclosed in the prior art"); *Hoffman-La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014) (finding claims obvious where directed to a monthly oral dosing regimen where a POSA "looking to scale to a monthly dose of oral ibandronate from a known-effective daily dose was thus faced with a very limited set of possibilities").

Notwithstanding the advantages of a fixed dose, a POSA would have further recognized that smaller JIA patients may require a different fixed dose regimen than larger patients. Indeed, Herlin disclosed that JIA patient dosing may be different for patients weighing less than 30 kg and those weighing more than 30 kg. Ex. 1011 at 186. Accordingly, a POSA would have sought to identify the appropriate frequency with which to administer the subcutaneous 162 mg fixed dose disclosed by Ohta to patients weighing more than 30 kg and patients weighing less than 30 kg. Ex. 1002 ¶149.

a) A POSA Would Have Been Motivated to Treat sJIA Patients Every Week or Every Other Week, Depending on a Patient's Weight

Herlin disclosed that an 8 mg/kg IV tocilizumab dose administered every other week was safe and effective for treating sJIA patients. Ex. 1011 at 1, 4-6. JIA affects children under age 16 and as young as 3. Ex. 1011 at 2. The median weight for children in this age bracket ranges from about 15 kg to about 60 kg. Ex.

1067 at 27-28. Thus, a POSA would have understood that a range of approximately 120 to 240 mg tocilizumab dose every two weeks would be effective in sJIA patients weighing less than 30 kilograms, and 240 to 480 mg every two weeks for sJIA patients weighing more than 30 kilograms. Ex. 1002 ¶151.

For patients weighing less than 30 kg, a POSA would have been motivated to use the fixed 162 mg subcutaneous dose (disclosed in Ohta 2010) every two weeks as it would fall within the range of dosages (120-240 mg) found to be effective in treating these sJIA patients. Ex. 1002 ¶152. And for patients weighing more than 30 kg, a POSA would have been motivated to use the fixed 162 mg dose every week (324 mg every two weeks) as it would fall within in the range of dosages (240-480 mg) found to be effective in treating these sJIA patients. *Id.* Accordingly, it would have been obvious to administer the 162 mg subcutaneous tocilizumab weekly dose disclosed by Ohta 2010 to patients weighing more than 30 kg to treat sJIA; and, it would have been obvious to administer the 162 mg subcutaneous tocilizumab every other week dose disclosed by Ohta 2010 to patients weighing less than 30 kg to treat sJIA. *Id.*

b) A POSA Would Have Been Motivated to Treat pcJIA Patients Every Two Weeks or Every Three Weeks, Depending on a Patient's Weight

Herlin also disclosed that an 8 mg/kg IV dose administered every four weeks was safe and effective for treating pcJIA patients. Ex. 1011 at 6. As explained

above, the average weight of JIA patients ranged from about 15 kg to about 60 kg. Thus, a POSA would have known that a range of approximately 120 to 240 mg every four weeks would be effective in sJIA patients weighing less than 30 kilograms, and 240 to 480 kilograms every four weeks for patients weighing more than 30 kilograms. Ex. 1002 ¶153. For patients weighing less than 30 kg, a POSA would have been motivated to use the fixed 162 mg dose every three weeks (amounting to 216 mg every four weeks) as it would fall within the range of dosages found to be effective in treating these pcJIA patients. *Id.* And for patients weighing more than 30 kg, a POSA would have been motivated to use the fixed 162 mg dose every two weeks (324 mg every four weeks) as it would also fall within the range of dosages found to be effective in treating these sJIA patients. *Id.* Accordingly, it would have been obvious to administer the 162 mg subcutaneous tocilizumab dose disclosed by Ohta 2010 every two weeks to patients weighing more than 30 kg to treat pcJIA; and, it would have been obvious to administer the 162 mg subcutaneous tocilizumab dose disclosed by Ohta 2010 every three weeks to patients weighing less than 30 kg to treat pcJIA. *Id.*

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

As set forth above, a POSA would have been motivated to combine Herlin and Ohta 2010 to administer a fixed 162 mg subcutaneous tocilizumab dosage at

the claimed dosage frequencies. A POSA would also have reasonably expected administering these subcutaneous dosing regimens to be successful for treating sJIA and pcJIA patients. Ex. 1002 ¶154.

As explained above, a subcutaneous fixed dose regimen was known to be safe and effective when administered at an equivalent amount over time to the known intravenous regimen for treating RA, another IL-6 mediated disease. *See, e.g.*, *supra* § X.C; Ex. 1002 ¶154. A POSA would have reasonably expected that the same would also be true for treating JIA patients, for whom tocilizumab had already been shown to be safe and effective when administered intravenously. Ex. 1002 ¶154. Indeed, Herlin itself states that "the significant effect on adult RA may indicate that tocilizumab could also have a promising role for polyarticular JIA." Ex. 1011 at 7. Furthermore, the prior art made clear that antibodies may be administered subcutaneously at shorter intervals instead of intravenously every four weeks in an amount that "over time is generally equivalent." Ex. 1002 ¶154. And, as discussed above, equivalent IV dosing regimens to the claimed subcutaneous JIA regimens had been shown to be both safe and effective. *See, e.g.*, *supra* § X.C. Thus, a POSA would have reasonably expected that the claimed subcutaneous treatment regimens using a 162 mg fixed dose of tocilizumab would have been safe and effective in treating JIA. *Hoffman-La Roche*, 748 F.3d at 1331 ("Conclusive proof of efficacy is not necessary to show obviousness.").

Notably, the '981 inventors themselves anticipated success with the claimed treatment regimens before they had any clinical data. The '981 patent specification does not contain any clinical results for the treatment of either sJIA or pcJIA using the claimed subcutaneous treatment regimens. And yet, the named inventors stated in the specification that they expected the results to be successful:

> It is ***anticipated that the anti-IL-6R antibody (TCZ) will be effective in sJIA patients*** with body weight ≥ 30 kg when administered as a fixed dose of 162 mg every week (QA) by subcutaneous administration, e.g., for up to 14 weeks. It is further ***anticipated that the anti-IL-6R antibody (TCZ) will be effectiv*****e*** ***in sJIA patients*** with body weight < 30 kg when administered as a fixed dose of 162 mg every 10+/-1 days (Q10D) by SQ administration, e.g., for up to 14 weeks. Alternative dosing regimens include 162 mg every week (QW) or every two weeks (Q2W).
>
> . . .
>
> It is ***anticipated that the anti-IL-6R antibody (TCZ) will be effective in pcJIA patients*** when administered as 162 mg dose every 2 weeks (Q2W) by SQ administration, e.g., for up to 12 weeks.

Ex. 1001 at 52:51-60, 55:25-30. Therefore, Patent Owners cannot plausibly 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).

4. Application to the Claims

a) Claims 1 and 8

By combining Herlin and Ohta 2010, a POSA would have arrived at a method of treating JIA in a patient comprising administering tocilizumab (an anti-IL-6R antibody) subcutaneously as a fixed dose of 162 mg every week, every other week, or every three weeks, as recited in claims 1 and 8. Ex. 1002 ¶156. As explained above, a POSA would have been motivated to combine Herlin and Ohta 2010 in this manner, and would have had a reasonable expectation that the treatment regimen would have been successful in treating JIA. *Supra* § X.D.2.

b) Claims 2-4 and 9-11 Are Obvious

Claims 2-4 and 9-11 are all directed to methods of treating sJIA. Specifically, claims 2 and 9 depend from claims 1 and 8, respectively, and further recite that "JIA

is systemic JIA (sJIA)." Claims 3 and 10 depend from claims 2 and 9, respectively, and further recite "wherein the fixed dose is administered every week if the patient's weight is ≥ 30 kilograms." Claims 4 and 11 depend from claims 2 and 9, respectively, and further recite "wherein the fixed dose is administered every two weeks if the patient's weight is <30 kilograms."

By combining Herlin and Ohta 2010, a POSA would have arrived at a method of treating sJIA in a patient comprising administering tocilizumab subcutaneously as a fixed dose of 162 mg every week (for patients ≥ 30 kilograms) and every two weeks (for patients < 30 kilograms). As explained above, a POSA would have been motivated to combine Herlin and Ohta 2010 in this manner, and would have had a reasonable expectation that the treatment regimen would have been successful in treating sJIA. *Supra* § X.D.2; Ex. 1002 ¶158.

c) Claims 5-7 and 12-14 Are Obvious

Claims 5-7 and 12-14 are all directed to methods of treating pcJIA. Specifically, claims 5 and 12 depend from claims 1 and 8, respectively, and further recite that the "JIA is polyarticular course juvenile idiopathic arthritic (pcJIA)." Claims 6 and 13 depend from claims 5 and 12, respectively, and further recite "wherein the fixed dose is administered every two weeks if the patient's weight is ≥ 30 kilograms." Claims 7 and 14 depend from claims 5 and 12, respectively, and further recite "wherein the fixed dose is administered every three weeks if the

patient's weight is <30 kilograms."

By combining Herlin and Ohta 2010, a POSA would have arrived at a method of treating pcJIA in a patient comprising administering tocilizumab subcutaneously as a fixed dose of 162 mg every two weeks (for patients ≥ 30 kilograms) and every three weeks (for patients < 30 kilograms). As explained above, a POSA would have been motivated to combine Herlin and Ohta 2010 in this manner, and would have had a reasonable expectation that the treatment regimen would have been successful in treating pcJIA. *Supra* § X.D.2; Ex. 1002 ¶160.

E. 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.

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 (P.T.A.B. 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 (P.T.A.B. Dec. 15, 2017) (precedential).

For Grounds 1-3 Petitioners assert that claims 1-14 of the ’981 patent are not entitled to a priority date of any priority application, and are thereby anticipated or obvious in view of the ’264 patent or NCT02165345. During prosecution, the Examiner did not issue a single rejection. There is no evidence that the Examiner considered whether the claims were entitled to the priority date of any priority application, and to the extent the Examiner did so, she plainly erred. For that reason alone, institution is warranted. *Nrg Energy, Inc. v. Midwest Energy Emissions Corp.*, No. IPR2020-00832, 2020 WL 6277239, at *6 (P.T.A.B. Oct. 26, 2020) (declining to deny institution under § 325 where Examiner failed to consider during prosecution whether priority applications provided written description support for the claims). Indeed, because the same or substantially the same arguments regarding priority were not presented to the Examiner during prosecution, the Board need not consider the remaining factors. *Id.* (“We need not necessarily analyze the second part of the *Advanced Bionics* framework,” in view of Examiner’s failure to consider the priority issues).

In any case, as yet another reason why institution is warranted, Petitioners rely on references that were not before the Examiner. For Grounds 2-3, Petitioners rely on NCT02165345, and for Ground 6, Petitioners rely on Herlin. These

references were not the basis for any rejection, nor were they cited on an IDS during prosecution. Indeed, the Examiner did not issue any formal written rejections during prosecution of the '981 patent. The Examiner had a single telephone conference with the applicant to convey expected rejections for scope of enablement and written description. Ex. 1006 at 699.[20] For all of these additional reasons, institution is plainly warranted. *See Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR2017-01884, Paper 14 at 12-13 (P.T.A.B. 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 Owners here have argued that the Board

[20] The Examiner's error is particularly clear in view of an earlier-filed application, No. 14/061,989, that was later abandoned by the same applicant. During prosecution of that application, the Examiner rejected nearly identical claims as obvious in view of the prior art. Ex. 1045 at 3-8. The Examiner properly rejected the claims as obvious in view of prior art that taught a method of treating JIA by administering 8 mg/kg intravenous tocilizumab. *Id.* at 8-9. On July 19, 2016, the applicant abandoned that application, and about a year later, filed the application that issued as the '981 patent. In short, the Examiner should have at least issued the same rejection for the '981 patent claims.

should decline to institute under *NHK Spring* and *Fintiv* because there is potential for future district court litigation between the parties. IPR2021-01024, Paper 8 at 39-41 (Oct. 12, 2021); IPR2021-01025, Paper 8 at 54-57 (Oct. 12, 2021). The Board has already rejected this argument. In its institution decisions, the Board stated that the "discretionary analysis, as set forth in *NHK Spring/Fintiv* pertains to matters before us that involve a parallel proceeding—typically an ongoing lawsuit in court." IPR2021-01024, Paper 23 at 34 (Jan. 6, 2022); *see also* IPR2021-01025, Paper 23 at 18 (Jan. 6, 2022). Further, the Board stated that "[b]ecause Patent Owner has not identified an existing parallel proceeding to consider, we decline Patent Owner's invitation for us to consider discretionary denial of the institution under *Fintiv*." IPR2021-01024, Paper 23 at 34 (Jan. 6, 2022); *see also* IPR2021-01025, Paper 23 at 18 (Jan. 6, 2022). The same reasoning applies here—there is no parallel proceeding to consider, and therefore the Board should reject any argument from Patent Owner that discretionary denial is warranted.

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: June 7, 2022

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the *Petition for Inter Partes Review of U.S. Patent No. 10,231,981* contains 13,916 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: June 7, 2022

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: *Petition for Inter Partes Review of U.S. Patent No. 10,231,981* and the exhibits cited therein has been caused to be served on the Patent Owners via Federal Express Standard Overnight Delivery on this day, June 7, 2022, at the correspondence address of record for the subject patent as follows:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

Dated: June 7, 2022

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