UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

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

IPR2022-00578
Patent No. 8,580,264

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

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I. INTRODUCTION

Celltrion, Inc. ("Petitioner") hereby requests review of claims 1-12 of United States Patent No. 8,580,264 to Zhang et al. ("the '264 patent," EX1001), assigned to Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc., and Hoffman-La Roche, Inc. (collectively, "Patent Owner").

The challenged claims, directed generally to a method for treating rheumatoid arthritis (RA) in a patient comprising administering 162 mg of tocilizumab subcutaneously every week or every two weeks, are anticipated by or obvious from Patent Owner's own prior art disclosures. NCT00965653 ("*NCT '653*") (EX1004), a clinical trial protocol sponsored by Patent Owner, disclosed the very same method. WO2009/084659 (*"Morichika"*) (EX1110), a patent application assigned to Patent Owner, disclosed concentrated, stable formulations of tocilizumab especially suitable for subcutaneous administration in protocols like that of *NCT '653*.

While *NCT '653* did not disclose the results of the clinical trial, the claims contain no limitation directed to efficacy. Even if they did, that limitation would not make the claimed method of treatment patentable over the method in *NCT '653*. They are the same. Nor can the efficacy of this method be disputed. Patent Owner has obtained approval of the method by the U.S. Food & Drug Administration ("FDA") as an effective treatment for RA.

A person of ordinary skill in the art ("POSA") would have also had a reasonable expectation that the protocol in *NCT '653* would be at least somewhat effective in at least some patients, which is all that could be required under even the most favorable construction for Patent Owner. The prior art disclosed a wealth of information establishing the efficacy of the intravenous product across a broad range of dosages. A POSA would have also understood that the subcutaneous dosages in *NCT '653* were similar to, or higher than, IV dosages known to be effective. The pharmacokinetic properties of tocilizumab had also been published, and routine modeling using prior-art, open-source software programs would have confirmed that the 162 mg dose in *NCT '653*, when administered once-weekly or every other week, will produce mean blood plasma levels of tocilizumab that were known to be efficacious.

In light of this anticipating and obviating prior art, Petitioner respectfully submits it has demonstrated at least a reasonable likelihood that the claims are unpatentable, and thus requests institution of *inter partes* review.

A. Brief Overview of the '264 Patent

The '264 patent, entitled "Subcutaneously Administered Anti-IL-6 Receptor Antibody," issued on November 12, 2013. The earliest possible effective filing date is November 8, 2010.

The ’264 patent is drawn to methods of treating an IL-6 mediated disorder, such as RA, by subcutaneously administering an antibody that binds the IL-6 receptor (“IL-6R”), *e.g.*, tocilizumab, wherein the antibody is administered at a fixed dose of 162 mg/dose. EX1001, 1:13-23, 4:36-37. The 162 mg dose may be administered once a week (“QW”) or once every two weeks (“Q2W”). *Id.*, 4:42-46.

Independent claim 1 is representative and recites (indents added):

1. A method of treating rheumatoid arthritis (RA) in a patient comprising subcutaneously administering an anti-IL-6 receptor (IL-6R) antibody to the patient,

wherein the anti-IL-6R antibody is administered as a fixed [dose][1] of 162 mg per dose every week or every [two][2] weeks, and

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[1] Original claim 1 included the word “dose”; however, the Certificate of Correction that issued on August 17, 2021 omits the word “dose” from claim 1. EX1001.

[2] Original claim 1 included the word “two”; however, the Certificate of Correction that issued on August 17, 2021 omits the word “two” from claim 1. EX1001.

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

B. Brief Overview of the Scope and Content of the Prior Art

1. Background

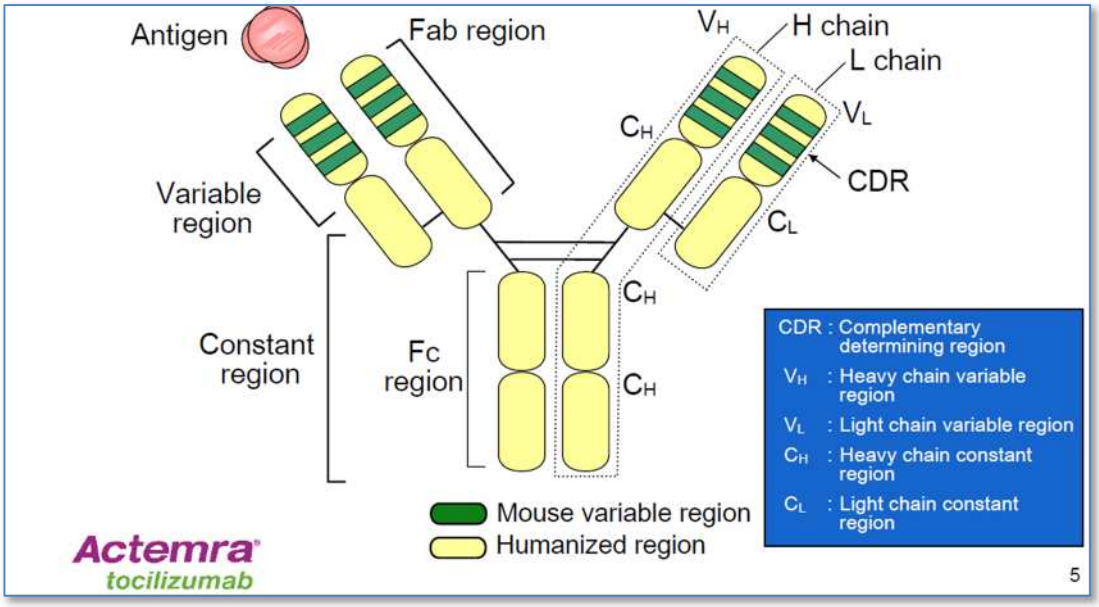
As explained in the corresponding Declarations of Drs. Maarten Boers (EX1034), Dhaval Shah (EX1032), and Paul Dalby (EX1036), the method of treating RA using subcutaneous administration of an anti-IL-6R antibody, such as tocilizumab, as described in claims 1-12, is not novel or non-obvious. As of November 8, 2009, one year before the earliest-possible priority date of the claims, tocilizumab had been approved as a treatment for RA, including for patients who had failed to respond to TNF inhibitors and MTX (or other disease-modifying anti-rheumatic drugs ("DMARDs")), and was known to inhibit the joint damage caused by the inflammation associated with RA. The particular fixed-dose regimen of the claims—162 mg of tocilizumab administered subcutaneously every week or every two weeks—had been published, as had a formulation for subcutaneous ("SC") administration. Moreover, the pharmacokinetic properties of tocilizumab, including the threshold mean blood plasma concentration needed for efficacy, were also publicly available. Tocilizumab's known pharmacokinetic properties, when plugged into pharmacokinetic software models that were routinely used for drug

development in 2009, would have given a POSA a reasonable expectation that the published 162 mg SC regimen will produce efficacious mean blood plasma levels.

a. Tocilizumab Was Already An Approved, Effective Treatment For RA

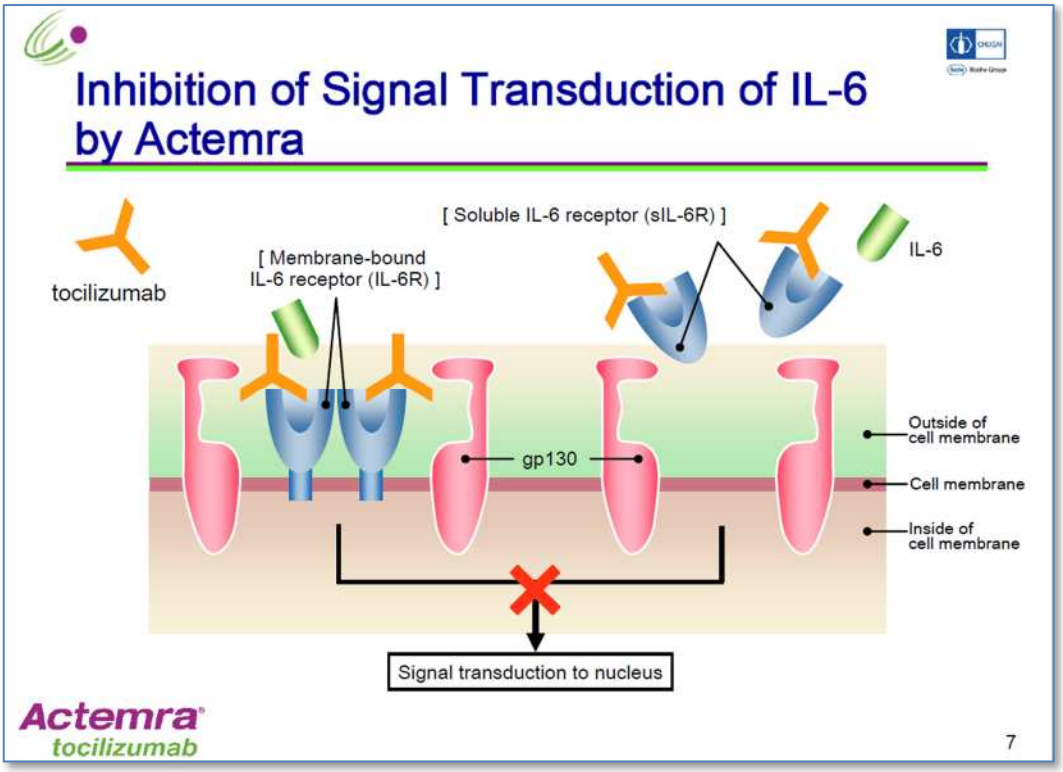
RA is a chronic, immune-mediated, systemic disease characterized by inflammation that causes pain, swelling and progressive destruction of the joints of the hands and feet. EX1034 ¶50. By the mid-1990s, methotrexate ("MTX") had become the most commonly-used DMARD for treating RA, yet many patients did not adequately respond to MTX alone. *Id.* ¶51; EX1037, 88; EX1038, 36.

Tocilizumab, also known as MRA, is a humanized mAb of the IgG1 *kappa* subclass that binds to the IL-6 receptor. EX1040, 3; EX1032 ¶130; EX1034 ¶52. It has two heavy chains (of the IgG1 subtype) and two light chains (of the *kappa* subtype) forming two antigen-binding sites. EX1032 ¶¶130-31; EX1034 ¶52. As shown below, the light and heavy chains both include a constant region (shown as C_H and C_L), and variable regions (shown as V_H and V_L):



EX1041, 5.

Chronic overproduction of IL-6, a "cytokine" signaling protein, and its interaction with its receptor, IL- 6R, which is expressed on cells of the immune system, causes the chronic inflammation associated with RA. EX1034 ¶53. Originally intended as a treatment for multiple myeloma, Chugai repurposed tocilizumab for the treatment of RA based on its ability to block the action of IL-6, which was known to be involved in the pathogenesis of RA. *Id.*; EX1042, 42-43. IL-6 binds to both soluble and membrane-bound IL-6 receptors. EX1041, 8. Tocilizumab works by binding to the IL-6 receptors, which blocks the receptors from binding IL-6 and issuing the signal that initiates the damaging inflammation associated with RA:



Id., 8; EX1034 ¶53.

By November 8, 2009, several clinical trials had been completed that confirmed that tocilizumab was a safe and effective treatment for RA. EX1034 ¶¶54-58. *Maini 2006* demonstrated that tocilizumab was safe and effective for treating RA when administered intravenously at a dose of either 4 mg/kg or 8 mg/kg every four weeks in patients who had discontinued MTX. EX1040, 2817-18, 2825-26. The SAMURAI study, published in 2007, showed that 8 mg/kg intravenous "tocilizumab monotherapy in patients with active RA significantly inhibited the progression of structural joint damage compared with conventional DMARDs therapy." EX1026, 1166. The LITHE study, published in 2008, demonstrated that both 4 mg/kg and 8 mg/kg tocilizumab administered

intravenously every four weeks resulted in "significantly less" progression of structural joint damage." EX1029, 516; EX1028, 1. The RADIATE study, published in 2008, showed that both 8 mg/kg and 4 mg/kg tocilizumab every four weeks, in combination with MTX, was effective in RA in patients who had inadequately responded to TNF antagonists. EX1034 ¶56; EX1043, 1518-19.

The published clinical data also disclosed that the minimum effective mean blood plasma concentration ("MEC") of tocilizumab was 1 μg/ml. EX1034 ¶59. RA patients with active disease have elevated levels of C-reactive protein ("CRP") compared to normal patients. *See, e.g.,* EX1008, 3961-3. Roche scientists had reported the utility of CRP as a biomarker of efficacy for RA and explained that tocilizumab caused CRP levels in RA patients to return to normal as long as it was detectable in serum, *i.e.,* the mean blood plasma level was greater than 1 μg/mL:

> Tocilizumab normalized the CRP level in patients with RA…as long as the free tocilizumab, which is capable of binding IL-6R and of inhibiting IL-6 actions, remained above 1 μg/ml in serum….This shows that tocilizumab effectively inhibits IL-6 signaling when it is detectable in serum….Since CRP is mainly produced by hepatocytes which express cell-surface IL-6R, membrane-bound IL-6R would be also fully occupied by tocilizumab. CRP is thus a useful surrogate

marker for tocilizumab levels that are high enough to inhibit the effects of IL-6 in patients.

EX1008, 3961-63; *see also* EX1024, 22-24.

The published clinical data confirmed that both 4 mg/kg and 8 mg/kg dosages of tocilizumab given intravenously ("IV") every 4 weeks were effective, *i.e.,* they achieved plasma concentrations above the MEC. EX1034 ¶60; EX1006[3], 75; EX1027, 1761-62. Both the 4 mg/kg and 8 mg/kg dosage regimens produced significant improvements in the DAS28 (Modified Disease Activity Score on 28 joint counts) score over placebo. EX1024, 40-41.

b. Antibody Therapies Like Tocilizumab Were Routinely Administered Subcutaneously Because of the Known Advantages of This Route of Administration

It was also well known that SC administration provides significant benefits over IV administration. SC administration, which a patient can self-administer at home, is generally faster, more convenient and less expensive than IV administration, which must be performed in a hospital or clinic by trained medical professionals. EX1034 ¶¶62-64; EX1048, 787-88; EX1049, 265-66. SC therapies are especially important to patients with poor venous access or who suffer from a

[3] Citations to this exhibit are to the stamped page numbers.

chronic disease like RA and must travel to a clinic to receive repeated infusions for the rest of their lives. *See* EX1034 ¶62; EX1049, 265; *see also* EX1048, 779.

SC administration of antibodies in particular was also well known by 2009. SC administration of antibodies offered "several advantages [over IV dosing] that promote adherence to therapy":

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

EX1050, 110.

It was also known that administering an equivalent amount of an antibody as a smaller, more frequent SC dose, rather than a larger, less-frequent IV dose, was preferable because it reduces fluctuation in mean plasma concentration, *i.e.,* it prevents mean peak concentrations from spiking and producing side effects, and mean trough concentrations from dropping below the threshold of efficacy. EX1051, 814; EX1034 ¶62. A fixed SC dose was also generally considered preferable for antibodies over "mg/kg" dosing that had to be adjusted for each

patient based on body weight, since fixed dosing provides "better compliance, less risk of medical errors, and cost-effectiveness." EX1052, 1012, 1023; EX1034 ¶64. Because of the myriad advantages of SC dosing, there were a number of biologics approved by FDA for SC administration with a fixed dose as of 2009. EX1034 ¶¶65-67.

Patent Owner published and claimed a formulation of tocilizumab for SC use. EX1034 ¶68. *Morichika* disclosed a liquid formulation containing MRA antibodies (i.e., tocilizumab) at high concentration. Patent Owner represented that this formulation was "especially suited for subcutaneous injection," (EX1110, [0053]; *see also* EX1115, 308, [0053]) and that this was an "important medical breakthrough." (EX1115, 96); *see also id.*, 91 (noting that the antibody used in the examples was MRA). In US 8,568,720, which is a 35 U.S.C. § 371 application claiming priority to the PCT, Patent Owner specifically claimed a formulation of MRA at 180 mg/ml suitable for subcutaneous administration. EX1112.

c. It Was Routine to Use Modeling to Predict Mean Plasma Concentration and Efficacy of IV and Subcutaneous Dosage Regimens

As of 2009, a variety of public-domain software programs were commonly used to model the pharmacokinetics and pharmacodynamics of antibodies. EX1032 ¶30. "Pharmacokinetics" ("PK") is the study of how a drug or biologic is absorbed, distributed, metabolized, and excreted within the bodies of patients.

"Pharmacodynamics" ("PD") refers to the physiologic effect a drug or biologic exerts on a patient. *Id.* ¶¶28-29. The programs, including ADAPT and NONMEM, had greatly simplified the construction and use of software-based PK/PD models. By 2009, such models had become routine in the pharmaceutical industry, and their reliability was well established. *Id.* ¶4.

Scientists were routinely using software-based models to predict the mean plasma concentrations of antibody over time when administered via a specific IV or SC dosage regimens. *Id.* ¶¶4, 30-31, 35. This included IgG1 *kappa*-subtype antibodies with very similar structures to tocilizumab. *See, e.g.,* EX1007 (ADAPT II software PK/PD model of IV and SC efalizumab, a humanized IgG1-*kappa* antibody).

As was typical, Roche used the NONMEM software program to create a PK/PD model of tocilizumab in human patients, regarding the results generated by the model as sufficiently reliable to be submitted to FDA in support of Actemra's approval. EX1010, 110-124[4]. Roche also published the specific PK parameter values for tocilizumab needed to duplicate this model for IV dosage regimens:

[4] Citations to this exhibit are to the stamped page numbers.

Table 3. NONMEM parameter values for final PK model (Source: Table 14, Page 32 from 1027775.pdf)

Parameter	Unit	Estimate	RSE (%) (*)
Fixed Effects			
CL	L/d (mL/h)	0.3 (12.5)	4.1
V1	L	3.5	1.8
Q	L/d (mL/h)	0.21 (8.75)	8.1
V2	L	2.9	5.0
VM	mg/d (mg/h)	7.5 (0.31)	5.8
KM	µg/mL	2.7	9.6

Id., 109, Table 3; EX1032 ¶¶77-79, Table 1. Even if a POSA did not have access to Roche's table of PK parameters, the POSA would have been able to extract the necessary parameters from other prior art published by Roche and Chugai. EX1032 ¶¶87-88.

To use the model for SC dosage regimens, a POSA would have needed to plug in two additional PK parameters. EX1032 ¶43. The first, "relative bioavailability," denoted by the letter "F," is the relative fraction of tocilizumab that makes it into the systemic bloodstream when administered subcutaneously. EX1032 ¶44. The second, "rate of absorption," denoted by the symbol "K_a," is the rate at which tocilizumab is absorbed into the bloodstream when administered subcutaneously. *Id.* ¶45. The actual values of F and K_a for tocilizumab were not disclosed in the prior art. But F was published for a number of IgG1 *kappa*-subtype antibodies that are similar in structure to tocilizumab, including adalimumab, canakinumab, efalizumab, golimumab, and omalizumab. Similarly, K_a was published for efalizumab, omalizumab, ustekinumab, and golimumab. A

POSA would have been able to estimate reasonable mean values for F and K_a from these published data. EX.1032 ¶¶92-98; *see* Table in section VII.F.2 below.

As Dr. Shah has demonstrated in his declaration, when prior-art ADAPT software is provisioned with the above prior-art PK parameters, the model predicts that 162 mg of tocilizumab, when administered SC QW or Q2W as disclosed in *NCT '653*, will produce mean plasma concentrations at or above the MEC of 1 µg/mL. EX1032 ¶¶115-123.

2. Prior Art Relied Upon

The prior art Petitioner relies upon to challenge the claims is briefly described below.

a. *NCT '653 (EX1004)*

NCT '653 is a clinical trial protocol, entitled "A Study of Subcutaneously Administered Tocilizumab in Patients With Rheumatoid Arthritis." It was publicly available on ClinicalTrials.gov in August 2009 and thus is prior art under pre-AIA § 102(b). EX1035 ¶¶12-33, 50. *NCT '653* was cited on an IDS but was not cited or relied upon by the examiner.

The "Brief Summary" section of *NCT '653* describes the clinical trial as follows:

> This open-label randomized 2 arm study will investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of

subcutaneously administered tocilizumab in patients with rheumatoid arthritis who have shown an inadequate response to methotrexate. Patients will be randomized to receive tocilizumab 162 mg sc either weekly or every other week, in combination with methotrexate, for 12 weeks. Assessments will be made at regular intervals during treatment and on the 3 weeks of follow-up. Target sample size is <50 individuals.

Id., 6.

The "Arms and Interventions" section of *NCT '653* (*id.*, 7) describes the 162 mg SC QW and Q2W dosage regimens as follows:

▼ **Arms and Interventions**

Arms	Assigned Interventions
Experimental: 1	Drug: tocilizumab 162 mg sc weekly (QW)for 12 weeks Drug: methotrexate 7.5 - 25 mg weekly (oral or parenteral) Drug: folic acid >/= 5 mg po weekly
Active Comparator: 2	Drug: tocilizumab 162 mg sc every other week (Q2W) for 11 weeks Drug: methotrexate 7.5 - 25 mg weekly (oral or parenteral) Drug: folic acid >/= 5 mg po weekly

b. *Morichika (EX1110)*

WO2009/084659 ("*Morichika*") was published on July 9, 2009, and is thus prior art under 35 U.S.C. §102(b). *Morichika* was not before the examiner, nor did

Fresenius cite it in either of IPR2021-01288 (the '1288 IPR) or IPR2021-01542 ("the '1542 IPR"), both challenging the '264 patent.

Morichika discloses a high-concentration formulation of tocilizumab (referred to as "MRA" in the reference). EX1110. *Morichika* explains that "the formulation according to the present invention is especially suited for subcutaneous injection," (EX1110, [0053]; *see also* EX1115[5] 308, [0053]), and that the formulation most preferably contains the following ingredients:

a. "150 to 200 mg/mL" antibody (EX1110, [0015]; EX1115, 287, [0015]

b. "the arginine concentration is 100 to 300 mM, and the amount of methionine is 10 to 50 mM" (EX1110, [0035]; EX1115, 304, [0035])

[5] EX1115 is a copy of portions of the prosecution history for U.S. Application No. 12/810,938, the U.S. national-phase counterpart to the *Morichika* application. Applicants submitted an English-language translation as the specification to the U.S. Patent & Trademark Office. EX1115, 285-321. Petitioner has included citations to both Petitioner's certified translation of the original *Morichika* reference and the specification provided by Patent Owner. These translations include minor differences in word choice.

c. "[a] histidine buffer is particularly preferred" and most preferably at a concentration of "10-20 mM" (EX1110, [0036] , EX1115, 304-305, [0036])

d. "most preferred" surfactants are polysorbates 20 and 80, and Pluronic F-68 (Poloxamer 188) and most preferably at a concentration of "0.005-3%." (EX1110, [0040]-[0041]; EX1115, 306, [0040]-[0041]).

The specification discloses examples of formulations of tocilizumab that were tested for stability. Formulation A8 in Table 1-1, which also appears as A26 in Table 3-1, was shown to be among the most stable (EX1110, Table 1-3 and [0062]-[0070]; *see also* EX1115, 309-312, Table 1-3 and [0062]-[0070]), indicating low percentages of dimer ("Dimer (%")) and low-molecular weight degradation products (LMW (%)) after accelerated (40º C) and room-temperature (25º C) storage; *see also* EX1110, [0068], [0086]; EX1115, 311 [0068], 318 [0086]. Formulation A8/A26 contains essentially the same ingredients as Patent Owner's clinical trial formulations in Table 2 of the '677 patent specification:

180 mg/mL tocilizumab

100 mM arginine

30 mM methionine

0.5 mg/mL Polysorbate 80

20 mM histidine buffer

pH 6.0

This formulation differs from the Table 2 formulation only in that it contains a slightly higher amount of Polysorbate 80: 0.5 mg/mL versus 0.2 mg/mL.

The U.S. national-phase counterpart to *Morichika* issued as U.S. Patent 8,568,720 (EX1112; "the '720 patent"). In this patent, Chugai and Roche claimed a "stable" formulation of tocilizumab ("MRA") containing the same ingredients as formulation A8/26.

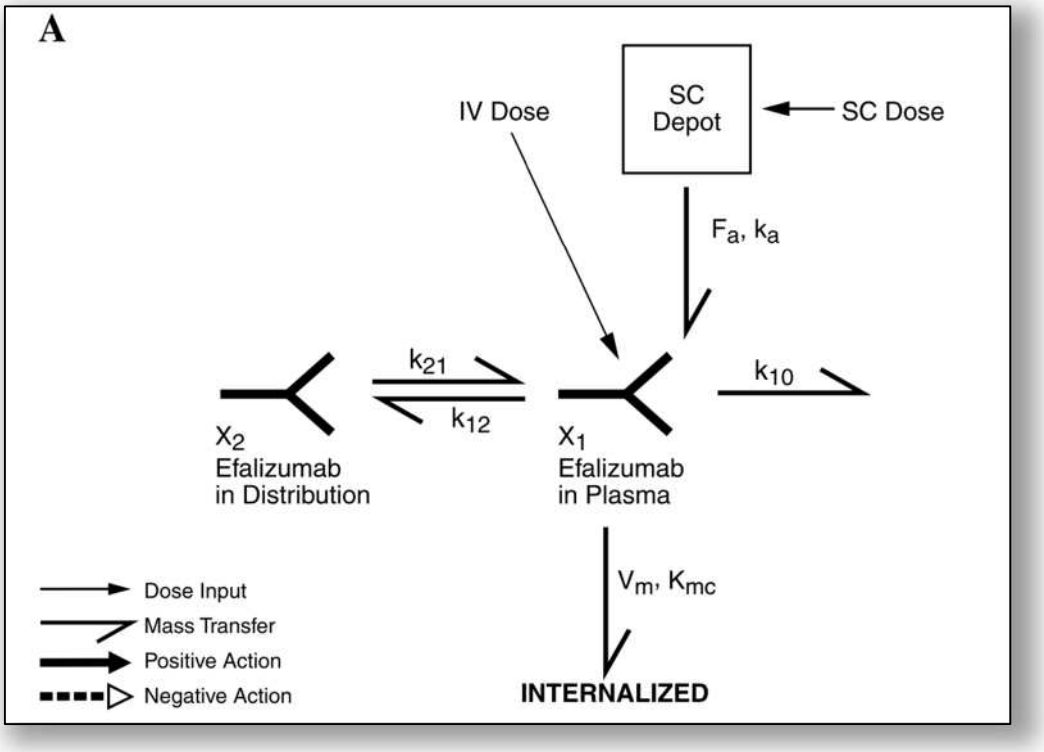
c. *Ng 2005 (EX1007)*

Ng 2005 was available as of July 2005, and thus is prior art under pre-AIA § 102(b). *Ng 2005* was not before the examiner, nor was it cited by Fresenius in the related '1288 and '1542 IPRs.

Ng 2005 reports the design and results of a PK/PD modeling analysis in which the ADAPT software program is used to model the pharmacokinetic parameters of intravenously- and subcutaneously-dosed efalizumab, a humanized monoclonal IgG1-*kappa* antibody that is structurally similar to tocilizumab. *See generally* EX1007.

Ng 2005 reported that efalizumab displayed dose-dependent, non-linear pharmacokinetics in psoriasis patients. *Id.*, 1088. *Ng 2005* used a two-compartment model that accounted for both linear and non-linear pharmacokinetics

to describe the plasma concentration of efalizumab over time after SC administration. *Id.*, 1091-92, Fig. 1A (reproduced below):

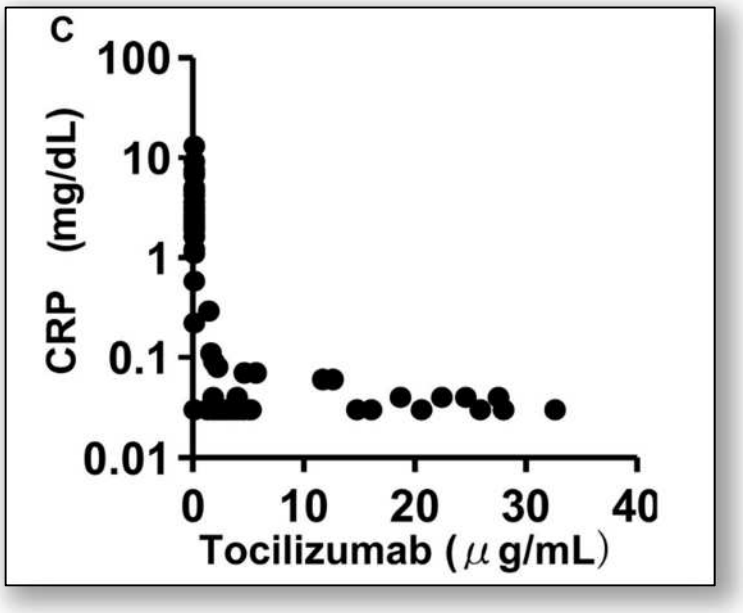


The model uses a central compartment X1 and a peripheral compartment X2 to represent the distribution of efalizumab in a patient. *Id.*, 1091. Absorption into the bloodstream and elimination from the body takes place in the central compartment, while the second compartment represents poorly-perfused tissues in the body. EX1032 ¶47. To model the subcutaneous dose, a subcutaneous "depot" was used, which factored in the bioavailability and rate of absorption ("F_a" and "K_a" in the figure, respectively) of the subcutaneous dose as it enters the central compartment. EX1007, 1091.

d. *Nishimoto 2008 (EX1008)*

Nishimoto 2008 was published as of September, 2008, and thus is prior art under pre-AIA § 102(b). *Nishimoto 2008* was not before the examiner.

Nishimoto 2008 describes the role of IL-6 in immune-inflammatory diseases such as RA and Castleman's disease. EX1008. *Nishimoto 2008* disclosed that after administration of tocilizumab, more than 95% of the sIL-6R molecules were bound in a sIL-6R/tocilizumab immune complex as long as the free tocilizumab concentration remained detectable in serum (at least 1 μg/mL). *Id.*, 3961. *Nishimoto 2008* additionally disclosed that C-reactive protein (CRP) was a useful surrogate marker for tocilizumab levels that are high enough to inhibit the effects of IL-6 in patients. *Id.*, 3961-63. Change in CRP levels correlated with severity of inflammation. *Id.*, 3961. *Nishimoto 2008* disclosed that tocilizumab normalized the CRP level in patients with RA as long as the free tocilizumab remained above the 1 μg/mL level in serum, illustrating the importance of maintaining this threshold level of serum concentration. *Id.*, 3962, Fig. 2C (reproduced below).



e. *Kremer 2009 (EX1029)*

Kremer 2009 was published as of October 2009, and thus is prior art under pre-AIA § 102(b). *Kremer 2009* was not before the examiner. *Kremer 2009* disclosed results from a double-blind, phase III clinical trial in which 688 patients who were inadequate responders to methotrexate received methotrexate weekly plus either 4 mg/kg or 8 mg/kg tocilizumab every four weeks for 24 months. EX1029, 516.

The results established that patients treated with tocilizumab had "significantly less" progression of structural joint damage." *Id.*, 516. The percentage of patients showing no progression of joint erosion, joint space narrowing or progression in Genat-modified total Sharp score (GnTSS) were

essentially the same for the 4 mg/kg group (75% showing no GmTSS progression) and the 8 mg/kg group (83% showing no GmTSS progression). EX1029, Table A.

f. *Emery (EX1043)*

Emery was published as of 2008 and thus is prior art under pre-AIA § 102(b). *Emery* was cited in an IDS but was not cited or relied upon by the examiner.

Emery discloses results of the Phase III RADIATE clinical study, in which the investigators concluded that "[i]n patients with moderate to severe active RA responding inadequately or who are intolerant to TNF antagonists, changing to tocilizumab plus methotrexate is effective, and the safety profile is manageable." *Id.*, 1522. "Participants were randomly assigned to tocilizumab 8 mg/kg or 4 mg/kg intravenously every 4 weeks or placebo intravenously every 4 weeks (controls)." *Id.*, 1517. "Both the 8 mg/kg (50.0%) and 4 mg/kg (30.4%) groups exhibited superior ACR20 responses compared with control (10.1%; less than $p<0.001$)." *Id.*, 1518.

g. *Maini 2006 (EX1040)*

Maini 2006 (EX1040) was published as of 2006 and thus is prior art under pre-AIA § 102(b). *Maini 2006* was not before the examiner.

Maini 2006 discloses results of the CHARISMA (Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody) study, a double blind

randomized clinical trial of tocilizumab in combination with methotrexate in treatment of RA in patients who had an incomplete response to methotrexate alone. *Id.*, 2818. "Three groups of patients received intravenous infusions of tocilizumab (2 mg/kg, 4 mg/kg, and 8 mg/kg, respectively) every 4 weeks, plus MTX placebo once weekly." *Id.* "The primary endpoint of the study, an ACR20 response at week 16, was achieved by 61% and 63% of the patients receiving monotherapy with 4 mg/kg and 8 mg/kg of tocilizumab, respectively, compared with 41% of patients receiving placebo plus MTX ($P < 0.05$)." *Id.*, 2821. Maini 2006 discloses that the results of the study "clearly show that infusions of tocilizumab every 4 weeks, with or without background MTX therapy, can produce marked and dose-related improvement in RA disease activity as measured by ACR20, ACR50, and ACR70 responses and clinically meaningful changes in the DAS28 (Modified Disease Activity Score on 28 Joint Counts)." *Id.*, 2826.

h. FDA Review (EX1010)

The Clinical Pharmacology and Biopharmaceutics Review for BLA 125276, ACTEMRA® (Tocilizumab) Liquid Concentration for Solution for IV Infusion ("*FDA Review*") was publicly available no later than March 9, 2010 and is prior art under pre-AIA § 102(a). EX1035 ¶¶40-49, 51. *FDA Review* was not before the examiner, nor was it cited by Fresenius in the related '1288 and '1542 IPRs.

FDA Review provides a wealth of data regarding the Actemra IV tocilizumab product. EX1010. It discloses that Roche used the NONMEM modeling software program to create a two-compartment model of the pharmacokinetics for tocilizumab in human patients, viewing the data generated by the model as being reliable enough to submit to FDA in support of Actemra's safety and efficacy. *See, e.g., id.*, 110-124.[6] This would have indicated to a POSA that the pharmacokinetics of tocilizumab could be reliably modeled using software programs like NONMEM. The document discloses the parameters used in Roche's two-compartment PK model in Table 3.

i. EMA Report (EX1006)

EMA Report was published online as of July 2009 and is prior art under pre-AIA § 102(b). *EMA Report* was not before the examiner.

EMA Report provided information on the pharmacokinetic behavior of IV tocilizumab. *EMA Report* disclosed that the pharmacokinetics of tocilizumab is non-linear, *i.e.*, tocilizumab tends to be cleared from in the bloodstream at a greater rate at lower concentrations than at higher concentrations. EX1006, 41.

[6] Citations to this exhibit are to the stamped page numbers.

EMA Report disclosed that Roche had used a two-compartment model with parallel linear and nonlinear clearance to model the pharmacokinetics of tocilizumab:

> The observed concentration-dependency of the tocilizumab CL could be best described by a population PK model rather than by non-compartmental analysis. A two-compartment disposition model with parallel first-order (linear CL) and Michaelis-Menten elimination (nonlinear or concentration-dependent CL) kinetics was obtained which could explain convincingly the dose proportionality of Cmax, the over-proportional increase in AUC and Cmin and the apparent increase of half-life with dose observed in single and multiple dose ascending studies.

Id., 41.

To a POSA, the fact that Roche had submitted data generated by this model to a regulatory agency would have confirmed that the pharmacokinetics of tocilizumab could be reliably modeled using a two-compartment model that accounted for linear and nonlinear clearance.

EMA Report discloses some of the pharmacokinetic parameters associated with tocilizumab, describing their non-linear and linear behavior, depending on serum concentration, including CL (clearance), KM (Michaelis constant) and Vss, from which V1 and V2 can be calculated: "The total CL [clearance] of tocilizumab

is concentration-dependent and is the sum of linear CL and nonlinear CL. The portion of the nonlinear CL is reflecting a zero-order process which is saturated at very low concentrations (estimated KM: 2.7 μg/ml). This is believed to reflect the target-mediated CL via binding to IL-6R. At higher tocilizumab concentrations, total CL is mainly determined by linear CL which was calculated to be 12.5 mL/h.…Estimated volume of distribution during steady state (Vss) was small (6.4 L). This corresponds to 1-2 times the plasma volume which is in accordance with values obtained for other monoclonal antibodies." *Id.*, 41-42; EX1032 ¶60.

j. *Chernajovsky 2008 (EX1009)*

Chernajovsky & Nissim, "Therapeutic Antibodies" (2008), was published as of 2008 and is prior art under pre-AIA § 102(b). Chernajovsky & Nissim contains a chapter authored by N. Nishimoto and T. Kishimoto, entitled "Humanized Antihuman IL-6 Receptor Antibody, Tocilizumab", ("*Chernajovsky 2008*") (EX1009). This chapter discusses the structure, immunopharmacological characteristics, and clinical utility of tocilizumab. EX1009. *Chernajovsky 2008* was not before the examiner, nor was it cited by Fresenius in the related '1288 and '1542 IPRs.

Chernajovsky 2008 provides pharmacokinetic plots of tocilizumab, showing tocilizumab concentration (μg/mL) versus time, after doses of 2, 4, and 8 mg/kg,

Q2W. *Chernajovsky 2008* additionally provides area under the curve (AUC) and half-life data for the doses of tocilizumab. *Id.*, 155, Fig. 3.

Chernajovsky 2008 reported that tocilizumab was known to have nonlinear pharmacokinetics in the 2-8 mg/kg dose range, and that the half-life of tocilizumab was known to be dose-dependent and prolonged as dosage increased from 2 to 8 mg/kg when the number of repeat doses are increased. *Id.*, 154-55, Fig. 3. The pharmacokinetic parameters Q and VM can be extracted from the pharmacokinetic profile of tocilizumab published in Figure 3. *Id.*; EX1032 ¶¶88-89.

C. Brief Overview of the Level of Skill in the Art

A POSA that would have typically developed subcutaneous dosage protocols and means for administering them would in fact have been a team of individuals possessing the different skill sets typically employed on such a project. That team would have included individuals skilled in the relevant area(s) of clinical medicine (e.g., rheumatologists), pharmacokineticists, formulators and project leads. These diversely-qualified individuals would have worked together as needed during development. EX1034 ¶48; EX1032 ¶27; EX1036 ¶25-26. Even if a different definition of POSA is adopted, that POSA would have had access to individuals skilled in clinical medicine, pharmacokinetics and formulation. EX1034 ¶49; EX1032 ¶27; EX1036 ¶27.

II. THE BOARD SHOULD DECLINE TO EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. The Board Should Not Exercise Its Discretion Under Section 325(d) to Deny Institution

Paten Owner may urge the Board to deny institution because "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. §325(d). As described below, this petition presents new arguments and art not before the Office, either during prosecution of the '264 patent or in the '1288 and '1542 petitions filed by Fresenius.

In determining whether to exercise its discretion to deny institution under §325(d), the Board applies a two-part framework. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8 (Feb. 13, 2020) (precedential). The first part assesses "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.*, 8. "[I]f either condition of [the] first part of the framework is satisfied," the second part assesses "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Id. Advanced Bionics* provides factors that help inform whether the first part of the framework is satisfied. *Id.*, 9-10; *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential).

This petition presents art and arguments that are materially different than those presented to the Office during prosecution of the '264 patent and by Fresenius the '1288 and '1542 petitions. The first part of the Board's two-part framework is not satisfied, and the second part need not be reached. The Board should decline to exercise its discretion under §325(d).

During prosecution, the examiner cited *Ohta 2010* (EX1066) against the claim. EX1065, 1004-1009. In response, applicant filed a declaration under 37 C.F.R. §131 to remove *Ohta 2010* as prior art. *Id.*, 1021-1028. The examiner found that the declaration was sufficient to remove *Ohta 2010* as a reference, and issued a notice of allowability. *Id.*, 1057-1059. The examiner did not use *NCT '653* substantively or cite it during prosecution.

Factors (a), (b), and (c) favor institution. Except for *NCT '653* and *Emery*, none of the references relied upon in this petition were before the examiner. And while *NCT '653* and *Emery* were cited in an IDS, they were never cited by the examiner or used to reject the claims. EX1065, 904-911. Moreover, the excerpt of *NCT '653* provided by applicant omitted the first posted date of August 25, 2009, failing to indicate it was prior art. *Id.*, 676-678.

Factors (d) and (f) also favor institution, as there is no overlap between the arguments made during prosecution and this petition. And while the '1288 petition relies on *NCT '653*, it relies on a different version than is relied upon in this

petition. This petition is accompanied by the expert declarations of Drs. Shah, Boers, and Dalby, and Mr. Lassman. The declaration of Dr. Shah presents PK/PD modeling analyses that were not presented during either prosecution or in the '1288 and '1542 petitions. As this petition presents new art, declarations, and argument that were not before the examiner, and as the examiner failed to substantively apply *NCT '653*, factor (e) also supports institution.

B. The Board Should Not Exercise Its Discretion under Section 314(a) to Deny Institution[7]

Patent Owner may also urge the Board to exercise its discretion under §314(a) to deny institution because this is the second petition filed requesting IPR of claims 1-12 of the '264 patent. When evaluating whether to deny institution of a "follow-on" petition, the Board generally looks at seven factors provided in *Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 9-

[7] To the extent Patent Owner argues that the Board should exercise its discretion under *Fintiv* given future parallel district court proceedings, the *Fintiv* factors relate to whether a co-pending district court proceeding will finish before or close to the date the PTAB issues its final written decision. *Apple v. Fintiv*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential). *Fintiv* is thus not applicable here.

10 (Sept. 6, 2017) (precedential). The *General Plastic* factors weigh heavily in favor of institution of the petition.

Factors (1) and (2) favor institution. This is the first petition filed by Celltrion against the '264 patent, and Celltrion was not a real-party-in-interest in either of the '1288 or '1542 petitions. And although the '1288 and '1542 petitions and the instant petition rely on *NCT '653*, this petition relies on a different version of the reference, and adds the declarations of Drs. Shah, Boer, and Dalby, and Mr. Lassman. *Morichika*, which was not cited by Fresenius in its '1288 or '1542 petitions, discloses tocilizumab formulations for subcutaneous administration, and the declaration of Dr. Shah presents pharmacokinetic modeling that was not presented in the '1288 or '1542 petitions.

Factor (3), (4), and (5) also favor institution. Celltrion had no say in the timing of the filing of the '1288 and '1542 petitions. And although this petition was filed after the POPR, the differences in the evidence and arguments, such as the Shah declaration, for which much of the data was generated before patent owner filed its POPR, demonstrates that the POPRs in the '1288 and '1542 IPRs were not used as a roadmap. *See* EX1032 ¶188, Appendix B. This petition is also being filed before the issuance of an institution decision in the '1288 and '1542 IPRs.

Finally, factors (6) and (7) favor institution. Given the differences between the '1288 and '1542 petitions and the instant petition, the Board will not be using its resources to consider duplicative arguments. And there is no reason that Celltrion is aware of that would prevent the Board from meeting its one year statutory requirement to issue a final written decision after institution.

III. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '264 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '264 patent on the grounds identified.

IV. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): Petitioner identifies the following real parties-in-interest: Celltrion, Inc.; Celltrion Healthcare Co. Ltd.; and Celltrion Healthcare U.S.A., Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)):

Petitioner notes that it also filed IPR2022-00579 against related U.S. Patent 10,874,677 on the same day as the filing of this petition. Petitioner also notes that petitioners Fresenius Kabi USA, LLC and Fresenius Kabi Swissbiosim GmbH ("Fresenius"), filed IPR2021-01288 challenging the '264 patent on August 18, 2021, and IPR2021-01542 challenging claims 4, 5, and 12 of the '264 patent on September 24, 2021. Fresenius also filed IPR2021-01336 against related U.S.

Patent 10,874,677 on September 24, 2021.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

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Petitioner hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition.

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V. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

Petitioner requests review of claims 1-12 of the '264 patent under 35 U.S.C.

§ 311 and AIA § 6. Claims 1-12 of the ’264 patent are unpatentable as follows:

Ground	Claims	Description
1	1-3, 6-12	Anticipated by *NCT ’653* (EX1004)
2	1-3, 6-11	Obvious over the combination of *NCT ’653* and *Morichika* (EX1110)
3	4	Obvious over the combination of *NCT ’653* and *Morichika* as further combined with *Emery* (EX1043)
4	5	Obvious over the combination of *NCT ’653* and *Morichika* as further combined with *Maini 2006* (EX1040)
5	12	Obvious over the combination of *NCT ’653* and *Morichika* as further combined with *Kremer 2009* (EX1029)
6	1-11	Obvious over the combination of *NCT ’653, Morichika* and *Ng 2005* (EX1007) (claims 1-11), *Emery* (claim 4 only), and *Maini 2006* (claim 5 only), in view of *Nishimoto 2008* (EX1008) and *FDA Review* (EX1010) and the *SC PK Prior Art* (EXS1007, 1012-1016, 1018-1022; *see infra* section VII.F.2)
7	1-11	Obvious over the combination of *NCT ’653*,

		Morichika and *Ng 2005* (claims 1-11), *Emery* (claim 4 only), and *Maini 2006* (claim 5 only), in view of *Nishimoto 2008*, *EMA Report* (EX1006), *Chernajovsky 2008* (EX1009) and the *SC PK Prior Art*
8	12	Obvious over the combination of *NCT '653, Morichika*, *Ng 2005* and *Kremer 2009* (EX1029) in view of *Nishimoto 2008, FDA Review* and the *SC PK Prior Art*
9	12	Obvious over the combination of *NCT '653, Morichika*, *Ng 2005* and *Kremer 2009* in view of *Nishimoto 2008, EMA Report*, *Chernajovsky 2008* and the *SC PK Prior Art*

VI. CLAIM CONSTRUCTION

Claim terms are generally given their ordinary and customary meaning as would be understood by a POSA. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*); s*ee also* 37 C.F.R. § 42.100(b)[8]. Below are some terms

[8] Without taking a position on whether the claims are sufficiently definite, even when the metes and bounds of a claim are indefinite, the Board nevertheless can determine whether embodiments plainly within the scope of the claim would have

that warrant discussion.

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

Independent claims 1 and 10 both recite a "method of treating rheumatoid arthritis in a patient" in the preamble of the claim. The preamble should not be construed as limiting because it does not alter how the actual steps of the method are to be performed. *See* EX1034 ¶118; *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1375-76 (Fed. Cir. 2001). *see also In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018).

The preamble in claims 1 and 10 is not limiting because it does not—and cannot—alter the active steps of the claims, which are to "subcutaneously administer" the fixed dose QW or Q2W.

Even if the preamble was limiting, that limitation would merely require administering the dose with an intent to treat RA without any particular degree of efficacy. EX1034 ¶¶121-22. The plain meaning of "treating" is to give a treatment and is not limited by whether that treatment ultimately ends up being

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been obvious. *Ex parte Tanksley*, 26 U.S.P.Q.2d (BNA) 1384, 1387 (B.P.A.I. 1991) (embodiment within scope despite indefiniteness); *Ex parte Sussman*, 8 U.S.P.Q.2d (BNA) 1443, 1445 n.a1 (B.P.A.I. 1988) (affirming obviousness despite indefinite claim format).

effective. EX1034 ¶119-21; *see also* EX1061 (*Webster's*), 2434-35 (defining "treat" as to "give a medical treatment to"; "to seek cure or relief of (as a disease)"); EX1062 (*AHM Dictionary*), 838.

This plain meaning is consistent with the way "treatment" is used in the '264 patent, where it is repeatedly used to refer to both the effective and ineffective administration of drugs or biologics.[9] EX1034 ¶119. For example, the specification defines a "DMARD inadequate responder" as "one who has experienced an ***inadequate response*** to previous or current ***treatment*** with one or more DMARDs (including one or more TNF inhibitors) because of toxicity or inadequate efficacy." EX1001, 14:46-50; *see also id.*, 14:51-57, 14:58-63.

The examples in the specification are consistent with a definition of "treatment" that does not require efficacy. EX1034 ¶120. Example 2 states that some of the patients in the Phase 3 clinical trial had "failed previous anti-TNF-α ***treatment***." EX1001, 32:10-27. Similarly, Example 6 states that 85% of the

[9] The specification states that "'[t]reatment' of a subject herein refers to both therapeutic treatment and prophylactic or preventative measures." EX1001, 15:1-2. This does not define what a "treatment" is, but merely explains that the term is not limited to therapeutic embodiments, but also prophylactic or preventative ones.

"treated" patients in the clinical trial met the efficacy endpoint, meaning that the treatment was not efficacious in at least some of the patients. *Id.*, 47:35-52.

To the extent that the claims are construed to require that the method be effective against RA, that efficacy is not limited to any particular threshold or degree. It would encompass some efficacy in at least some patients. *Id.* The claims recite no efficacy threshold for the "treatment," and the intrinsic description of the invention contains no clear and unambiguous threshold that would warrant importing such a limitation into the claims. *Acceleration Bay, LLC v. Activision Blizzard Inc.*, 908 F.3d 765, 771 (Fed. Cir. 2018); *Cadence Pharms. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1369 (Fed. Cir. 2015).

B. "DMARD inadequate responder" (claim 3)

A "DMARD inadequate responder" is defined in the specification as "one who has experienced an inadequate response to previous or current treatment with one or more DMARDs (including one or more TNF inhibitors) because of toxicity or inadequate efficacy." EX1001, 14:46-50. MTX is an example of a DMARD. *Id*., 14:22-32.

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

A "TNF-inhibitor-inadequate responder" is defined in the specification as "one who has experienced an inadequate response to previous or current treatment with one or more TNF inhibitors because of toxicity or inadequate efficacy." *Id.*,

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

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

The term "treats the rheumatoid arthritis," as used in claims 6 and 11, should be construed the same as "treating rheumatoid arthritis" in the preamble. It does not require any specific level of efficacy. EX1034 ¶125.

E. "inhibiting" and "inhibited" (claim 12)

Claim 12 describes a "method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient" and requires that "structural joint damage at week 24 or week 48 is found to be inhibited." The claim does not recite a particular degree of inhibition, and the plain meaning of "inhibiting" and "inhibited" to a POSA would include any amount of inhibition. EX1034 ¶126. The specification does not alter this plain meaning. It describes "inhibiting progression of structural joint damage in a RA patient" as "preventing or slowing structural joint damage caused by RA, for example based on eroded joint count and/or joint damage score," and explains that "[m]ethods for measuring

progression of structural joint damage are known to the skilled person, and include, without limitation Genant modified Total Sharp Score (TSS), erosion score (ES), and/or joint space narrowing (JSN) score." EX1001, 15:14-21. This description does not place any limits on the degree of "slowing" that would qualify as "inhibiting." Indeed, the specification does not contain any actual clinical data quantifying the degree of inhibition achieved at weeks 24 and 48 by the claimed method, but merely a qualitative prediction that the claimed regimen "can inhibit progression of structural joint damage at Week 24 and Week 48". EX1001, 38:23-24; EX1034 ¶¶144-45. Thus, the claims embrace *any* degree of inhibition.

VII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Ground 1: Claims 1-3 and 6-12 are Anticipated By *NCT '653* (EX1004).

1. *NCT '653* Was Publicly Available Prior to November 2009

NCT '653 is a printed publication that was available on ClinicalTrials.gov prior to November 2009, which makes it prior art under § 102(b). EX1035 ¶¶12-33, 50; EX1034 ¶¶73-77.

To the extent that patent owner attempts to argue it is not prior art under 35 U.S.C. §312, petitioner notes that the very purpose of ClinicalTrials.gov is to make such trials as widely and promptly available to the public as possible. *See* EX1035

¶¶13-19, 23. The FDA Modernization Act of 1997 required that the National Institutes of Health ("NIH") establish a database of information on clinical trials conducted in the United States on drugs for serious or life-threatening diseases and conditions, and the NIH's National Library of Medicine launched ClinicalTrials.gov in February 2000 to give the public better access to information on clinical studies. *Id.* ¶13, 14. The database was intended to provide "patients, families and members of the public ***easy access to information***." EX1079, 1. The FDA Amendments Act of 2007 later expanded the database by requiring sponsors of clinical trials to disclose additional information, enabling electronic searching, and imposing a fine for failure to submit information within 21 days of first patient enrollment. EX1035 ¶¶15-16.

The ClinicalTrials.gov database provides key publication dates for each study submitted. The NIH has represented that the "First Posted" date is "[t]he date on which the study record was first available on ClinicalTrials.gov." EX1064, 8. The study record for *NCT '653* was "First Posted" on August 25, 2009. EX1004, 1. That is sufficient to demonstrate that the posting was publicly available by August 2009. EX1035 ¶32; *see also Grunenthal GmbH v. Antecip Bioventures II, LLC.*, PGR 2019-00003, Paper 22, 17-18 (PTAB May 5, 2020).

2. *NCT '653* Discloses Every Element of Claims 1 and 10 As Arranged in the Claims

a. "[a] method of treating rheumatoid arthritis (RA) in a patient comprising subcutaneously administering ["an anti-IL-6 receptor (IL-6R) antibody" (claim 1)] ["tocilizumab" (claim 10)] to the patient"

NCT '653 discloses a study of subcutaneously administered tocilizumab, in which patients will be "randomized to receive tocilizumab 162mg sc either weekly or every other week, in combination with methotrexate, for 12 weeks." EX1004, 6. One of the outcomes measured by the study is efficacy. *Id.*, 8. A POSA would have understood that tocilizumab is "an anti-IL-6R antibody." EX1034 ¶¶52, 129; EX1032 ¶187.

As explained above, the preamble should not be construed as being limiting. *See supra* section VI.A. *NCT '653* and independent claims 1 and 10 are directed to the *same* protocol requiring the *same* active steps. As *NCT '653* discloses every active step required by the challenged claims, it anticipates the claim.

Even if the preamble is construed as limiting, it should be construed as requiring only that a patient be administered the claimed fixed dose with the intent to treat RA. *NCT '653* describes an "open label randomized 2 arm study" to "investigate the pharmacokinetics, pharmacodynamics, efficacy and safety of subcutaneously administered tocilizumab ***in patients with rheumatoid arthritis*** who have shown an inadequate response to methotrexate." EX1004, 6. Further,

"assessments will be made at regular intervals during ***treatment*** and on the 3 weeks of follow-up." *Id.* The patients of *NCT '653* were thus administered tocilizumab with the intent to treat their RA, and to assess the efficacy of that treatment at regular intervals. EX1034 ¶127.

If the preamble were construed to require efficacy, this does not distinguish the claimed method from *NCT* '653. As discussed above in section VI.A, the claims should not be construed as requiring any particular degree or threshold of efficacy. It cannot reasonably be disputed that the efficacy produced by carrying out the method of *NCT '653* is any different than what would result from carrying out the claimed method. They are the same. To the extent one produces at least some efficacy in some patients, so must the other. *See, e.g.*, *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable."); *In re Papesch*, 315 F.2d 381, 391 (1963) ("a compound and all of its properties are inseparable; they are one and the same thing."); *King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010) (to anticipate, the prior art need only meet the claimed limitation to the extent the patented method does.). The efficacy of this common method also cannot be reasonably disputed. Patent Owners have obtained FDA approval of the method—162 mg of tocilizumab

administered subcutaneously every week or every other week—as a safe and effective treatment for RA. EX1034 ¶¶4, 128; EX1116, 1, 45-65.

b. "wherein ["the anti-IL-6R antibody" (claim 1)] ["tocilizumab" (claim 10)] is administered as a fixed dose of 162 mg per dose every week or every two weeks"

Patients in *NCT '653* received a fixed dose of 162 mg, regardless of body weight or body surface area, *i.e.,* it was not administered as either a mg/kg or mg/m^2 dose. *Id. NCT '653* thus discloses this limitation. EX1034 ¶130.

SC formulations of tocilizumab, such as that required by *NCT '653*, would have been known to the skilled artisan. As explained in section I.B.2.b *supra*, *Morichika* disclosed more than a year before the earliest possible filing date of the '264 patent a recipe for a high-concentration formulation of tocilizumab that a POSA could have used to practice the method of *NCT '653*. This recipe is disclosed as formulation A8 (Table 1-1) and A26 (Table 3-1). *See* Section I.B.2.b.

As Dr. Dalby explains in his declaration, this is effectively[10] the same formulation Patent Owner used in its clinical trials for SC tocilizumab as described in Table 2 of the '264 patent. EX1036 ¶¶29-32; EX1034 ¶131. A POSA could easily have followed this recipe and other guidance in *Morichika* to make a

[10] The A8/A26 formulation contains 0.5 mg/mL Polysorbate 80, while "SC Actemra" contained 0.2 mg/mL. This is not a material difference. EX1036 ¶32.

suitable subcutaneous 162 mg dose of tocilizumab to use in the *NCT '653* protocol. *Id.* ¶¶31-37. It is thus clear from *Morichika* that *NCT '653* is enabled. *Id.* ¶37; *see In re Samour*, 571 F.2d 559, 562-63 (CCPA 1978); *In re Donohue*, 766 F.2d 531, 533-34 (Fed. Cir. 1985).

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

NCT '653 discloses the administration of tocilizumab, an anti-IL-6R antibody that comprises the light chain and heavy chain amino acid sequences of SEQ ID. Nos. 1 and 2, respectively. It is clear from the following evidence—including Chugai's and the '264 patent inventors' own admissions—that tocilizumab has the claimed amino acid sequences:

- The '264 patent specification confirms that tocilizumab comprises 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." EX1001, 6:60-62.
- The Examiner understood that tocilizumab comprises the claimed sequences, rejecting claims directed to SEQ ID Nos. 1 and 2 as anticipated by *Ohta 2010* (EX1066), which discloses tocilizumab, stating that the "amino acid sequence characteristics would be inherent in the antibody of

the prior art." EX1065 ('264 Patent File History), 1004; *see also* EX1115, 91.

- The named inventors of the '264 patent confirmed that tocilizumab comprises the claimed sequences. The inventors submitted an inventor declaration to the Examiner to antedate *Ohta 2010*, admitting therein 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." EX1065, 1025-1027.[11]
- Chugai further confirmed in a Request for Patent Extension that tocilizumab has the claimed amino acid sequences. EX1067, 2; EX1032 ¶¶175-182.
- As explained by Dr. Shah, tocilizumab inherently has the claimed amino acid sequences for the heavy and light chains. EX1032 ¶¶151-86.

[11] The named inventors made the same admission during prosecution of U.S. Patent No. 10,874,677, which shares the same specification as the '264 patent. EX1068, 257-258.

Thus, the tocilizumab administered in *NCT '653* 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." EX1034 ¶¶132-37.

Because all limitations of claims 1 and 10 of the '264 patent are disclosed in *NCT '653,* arranged as in the claims, it anticipates those claims. EX1034 ¶138.

3. Claims 2 and 9 Are Anticipated By *NCT '653*

Dependent claims 2 and 9 contain the additional limitations "wherein the fixed dose is administered every week," and "wherein the fixed dose is administered every two weeks," respectively. *NCT '653* discloses administration of tocilizumab at a fixed dose every week or every two weeks. *See supra* sections I.B.2.a and VII.A.2.a. For this reason and the reasons explained for claims 1 and 10, claims 2 and 9 are anticipated by *NCT '653*. EX1034 ¶139.

4. Claim 3 Is Anticipated By *NCT '653*

Dependent claim 3 contains the additional limitation "wherein the RA patient is a DMARD inadequate responder." To be included in *NCT '653*, the patients must have demonstrated "inadequate response to at least 12 weeks of methotrexate." EX1004, 9. Methotrexate is a DMARD. EX1001, 14:22-33. For this reason and the reasons explained for claims 1 and 10, claim 3 is also anticipated. EX1034 ¶140.

5. Claims 6-8 and 11 Are Anticipated by *NCT '653*

Dependent claims 6-8 and 11 further require the administration of an additional drug to the patient.

NCT '653 discloses the treatment of patients with RA with a combination of tocilizumab and MTX, which is a DMARD. EX1004, 6-7; EX1001, 14:22-33. Both arms of the trial (experimental and active comparator) included treatment with this combination. EX1004, 7. For this reason and the reasons explained for claims 1 and 10, *NCT '653* anticipates claims 6-8 and 11. EX1034 ¶¶141-42.

6. Claim 12 Is Anticipated by *NCT '653*

The preamble of claim 12 refers to a "method of inhibiting progression of structural joint damage in a rheumatoid arthritis patient." The body of the claim contains the limitation "wherein structural joint damage at week 24 or week 48 is found to be inhibited."

Structural joint damage was a known consequence of RA and known to be at least partially caused by IL-6. EX1034 ¶¶144, 190; *see also* EX1004, 9. A POSA would have understood that tocilizumab, which strongly reduces disease activity in RA, would reduce all consequences of RA, including structural joint damage. EX1034 ¶¶144, 190; EX1001, 38:23-24. The artisan also would have regarded an intent to treat RA as being the same as an intent to inhibit all consequences of RA, including structural joint damage. EX1034, ¶144. This is clear from the

specification which, as explained above, does not disclose clinical results showing the degree of inhibition at weeks 24 and 48, but merely relies on an assumption of from the clinical results showing efficacy against RA. *Id*.

Thus, a skilled artisan would have recognized that the method of treating RA in *NCT '653* encompasses treating the symptoms of RA, including structural joint damage. *Id. NCT '653* anticipates claim 12.

Similar to claims 1 and 10, if claim 12 requires efficacy against structural joint damage, then there can be no dispute that the method of *NCT '653* has the same efficacy as the method of claim 12, since their operative steps are the same. The patent merely assumes, without supporting data, this method will inhibit structural joint damage, so Patent Owners cannot reasonably dispute its efficacy in that regard. *Id.* ¶145; *see also* EX1001, 33:49-38:24 (Example 3).

To the extent that Patent Owners argue that claim 12 requires the additional operative step of a doctor actually "finding" inhibition, that cannot render the claim separately patentable. Firstly, *NCT '653* expressly discloses the step of examining patients at regular intervals to determine efficacy. *See* EX1004, 6 ("assessments will be made at regular intervals during ***treatment*** and on the 3 weeks of follow-up."). While *NCT '653* does not expressly identify structural joint damage as a symptom to be measured as a "secondary outcome," the protocol does mention that plasma levels of tocilizumab, CRP, and free IL-6/IL-6R levels will be assessed, as

will ACR and DAS-EULAR scores. EX1004, 8. To a POSA, levels of tocilizumab above the MEC, normalized CRP and low IL-6/IL-6R levels, and positive ACR/DAS-EULAR scores, would have indicated inhibition of joint damage. EX1034 ¶146.

Secondly, as explained, an intent to treat RA in *NCT '653* is the same as an intent to treat, *e.g.,* joint damage caused by RA. Merely "finding" that a prior art method works for its intended purpose cannot render the old method newly patentable. *Bristol–Myers Squibb Co. v. Ben Venue Laboratories, Inc.,* 246 F.3d 1368 at 1376 (Fed. Cir. 2001).

For this reason and the reasons explained for claims 1 and 10, claim 12 is also anticipated. EX1034 ¶147.

B. [Ground 2] Claims 1-3 and 6-11 are Obvious over the Combination of *NCT '653* and *Morichika*

To the extent that *NCT '653* does not anticipate claims 1-3 and 6-12, then they would have been obvious from the combination of *NCT '653* and *Morichika*.

As explained above in section VII.A *supra*, *NCT '653* teaches all of the steps of the methods of claim 1-3 and 6-12. A POSA would have been interested in the method of subcutaneous administration in *NCT '653* because of all of the well-known advantages of that route of administration over the IV route. EX1034 ¶¶62-65; 149; *see also* EX1050, 110, 113-14; EX1048, 787-88; EX1049, 266. A POSA would have combined *NCT '653* with *Morichika* because it disclosed a

subcutaneous formulation of tocilizumab that would be suitable for use in a protocol like *NCT '653*. EX1034 ¶149. Further motivation would have come from the fact that *Morichika* touted the formulation as being "especially suited for subcutaneous injection." *Id.*; EX1110, [0053]; EX1115, 308, [0053].

The POSA also would have had a reasonable expectation of success with this combination. Using the *Morichika* formulation to execute the protocol in *NCT '653* would have involved only routine skill. EX1034 ¶150; EX1036 ¶37.

While the claims should not be construed to require efficacy, the skilled practitioner nevertheless would have expected the combination to have at least some efficacy, including inhibiting the progression of structural joint damage, in at least some patients. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). *Morichika*, and its teaching that Patent Owner's high-concentration formulation for tocilizumab "is especially suited for subcutaneous injection," would have given the POSA an expectation that Patent Owner's formulation would have at least some efficacy when administered subcutaneously. EX1034 ¶151-52. This expectation would have been bolstered by the fact that Roche had sponsored *NCT '653*, had announced that subcutaneous Actemra was "in development," (EX1071, 4; EX1072 slide 12), and had expressed the view that the "preferred" form of administering tocilizumab was "thought to be subcutaneous formulation." (EX1030, 4). A POSA would have assumed that

Roche would not have made these statements, nor risked the investment in *NCT '653* or the wellbeing of the participating patients, unless it believed the protocol would produce at least some efficacy. EX1034 ¶¶69, 154-57.

A POSA would have expected that in at least some patients, 162 mg of tocilizumab administered SC QW or Q2W would produce roughly similar antibody exposure as the 4 mg/kg monthly (Q4W) dose that was known to be effective. EX1034 ¶153. A 4 mg/kg monthly dose for patients who weigh, *e.g.,* 50-60 kg[12] would be 200-240 mg. *Id.* The total monthly dose of tocilizumab administered in *NCT '653* (approximately 650 mg QW or 325 mg Q2W) is *higher* than this known-effective dose. *Id.* ¶153. Even accounting for less than 100% bioavailability associated with subcutaneous administration, a POSA would have expected at least some patients to receive dosages of tocilizumab that were at least roughly equivalent to the known effective dose. *Id.*

For all of these reasons, a POSA would have had a reasonable expectation that the method in *NCT '653,* when practiced with the recipe in *Morichika*, would have at least some efficacy in at least some patients. *Id.* ¶¶69, 154-57.

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[12] RA patients will have a range of body weights that vary by age, ethnicity, sex, and a variety of other factors. A significant fraction weigh in the 50-60 kg range. EX1034 ¶153 (citing EX1021, Table 1).

C. [Ground 3] Claim 4 Is Obvious over the Combination of *NCT '653* and *Morichika* as Further Combined with *Emery* (EX1043)

Claim 4 depends from claim 1 and requires that the patient be a "TNF-inhibitor-inadequate responder," *i.e.,* they "experienced an inadequate response to previous or current treatment with one or more TNF inhibitors because of toxicity or inadequate efficacy."

RA patients treated in *NCT '653* with tocilizumab and methotrexate had had an "inadequate response to at least 12 weeks of methotrexate," which is not a TNF inhibitor. EX1004, 6. But a POSA would have found it obvious to also apply the treatment in *NCT '653* to RA patients who had had an inadequate response to TNF inhibitors. The prior art expressly disclosed that a combination of tocilizumab and MTX—the same treatment in *NCT '653*— was effective in patients who did not respond to TNF antagonists. *Emery* discloses results of the phase III RADIATE study, which studied patients who had previously not responded to treatment with adalimumab, etanercept, or infliximab (all of which are "TNF inhibitors" as that term is defined in the '264 patent).[13] EX1043, 1519. *Emery* reported that the combination of tocilizumab and MTX was effective in treating RA in the TNF-

[13] *Emery* disclosed that "[n]inety-five per cent of [the] previous TNF antagonist failures [in the patient study group] were due to inadequate efficacy." EX1043, 1519; EX1034 ¶159.

non-responders, noting that the patients "exhibited superior ACR20 responses compared with control (10.1%; less than p = 0.001)." EX1043, 1518. *Emery* concludes that, "[i]n patients with moderate to severe active RA responding inadequately or who are intolerant to TNF antagonists, changing to tocilizumab plus methotrexate is effective, and the safety profile is manageable, regardless of the number of previous failed agents." *Id.*, 1522. EX1034 ¶¶61, 159-60.

The published efficacy of tocilizumab and MTX in TNF inhibitor-inadequate-responders, as well as the commercial approval of this use, *see* EX1006, 55, would have motivated a POSA to treat such patients with the fixed-dose SC regimen in *NCT '653*. EX1034 ¶161. Further motivation would have come from the well-known advantages of SC formulations over IV formulations. *Id.* A POSA would reasonably have expected success in administering the *NCT '653* treatment to TNF-inadequate-responders, since such administration presents no greater difficulty than to the RA patients treated in *NCT '653*. EX1034 ¶162.

To the extent that the Board construes the claims as requiring efficacy, a POSA would have had a reasonable expectation that the *NCT '653* treatment would have at least some efficacy against RA in at least some TNF-inadequate-responders, given tocilizumab's known efficacy in such patients and for the reasons given for claims 1-3 and 6-12. EX1034 ¶¶163-64.

D. [Ground 4] Claim 5 Is Obvious Over the Combination of *NCT '653* and *Morichika* as Further Combined with *Maini 2006* (EX1040)

Claim 5 depends from claim 1 and requires that the patient be MTX-naïve or has discontinued MTX. The prior art disclosed the use of tocilizumab alone or in combination with MTX to treat such patients. *Maini 2006* discloses results from a clinical trial in which "[t]ocilizumab was used either as a monotherapy (by discontinuation of MTX) or concomitantly with MTX therapy" to RA patients who had inadequately responded to methotrexate. EX1040, 2818. *Maini 2006* reports that both treatments were safe and efficacious. *Id.*, 2821; *see also id.*, 2827-28; EX1034 ¶¶61, 166; EX1006, 55. In light of this known efficacy, and as explained for claim 4, claim 5 would have been obvious. *Id.* ¶¶166-67.

E. [Ground 5] Claim 12 Is Obvious Over the Combination of *NCT '653* and *Morichika* as Further Combined with *Kremer 2009* (EX1029)

Claim 12 describes the intended result of the claimed method as "inhibiting progression of structural joint damage in a rheumatoid arthritis patient," limiting the claim to administering the fixed dose of tocilizumab "wherein structural joint damage at week 24 or week 48 is found to be inhibited." The prior art disclosed that tocilizumab was effective in inhibiting structural joint damage. EX1034 ¶169-170. *Kremer 2009* (EX1029) disclosed results from a double-blind phase III clinical trial in which 688 patients who were inadequate responders to

methotrexate received methotrexate weekly plus either 4 mg/k or 8 mg/kg tocilizumab every four weeks for 12 months. These results confirmed that the patients receiving 4 mg/kg had almost the same inhibition of structural joint damage (75% showing no GmTSS progression) as the 8mg/kg patients (83% showing no GmTSS progression). *Id.*, Table A; *see also Kremer 2008* (EX1028). In light of this known efficacy, and for all of the reasons explained with respect to claims 1-11, claim 12 also would have been obvious. EX1034 ¶171-72, 190.

F. [Ground 6] Claims 1-11 Are Obvious over the Combination of *NCT '653*, *Morichika*, and *Ng 2005* (EX1007) (claims 1-11), *Emery* (claim 4 only), and *Maini 2006* (claim 5 only), in View Of *Nishimoto 2008*, *FDA Review* and *SC PK Prior Art*

As explained, *Morichika* and tocilizumab's IV efficacy would have given a POSA a reasonable expectation that a 162mg SC fixed dose of tocilizumab, whether administered once- or twice-weekly, would have efficacy against RA. Other prior art would have bolstered this expectation of efficacy. EX1034, ¶173; EX1032 ¶5-6, 80.

1. The Prior Art Disclosed That the Minimum Effective Concentration of Tocilizumab Is 1 µg/mL

The lowest blood plasma concentration of tocilizumab that would have been expected to be effective against RA is known as the "minimum effective concentration" ("MEC"). The prior art disclosed that 1 µg/mL was a reliable value to use for MEC. EX1032 ¶¶105-07; EX1034 ¶¶175-78. It was known that RA

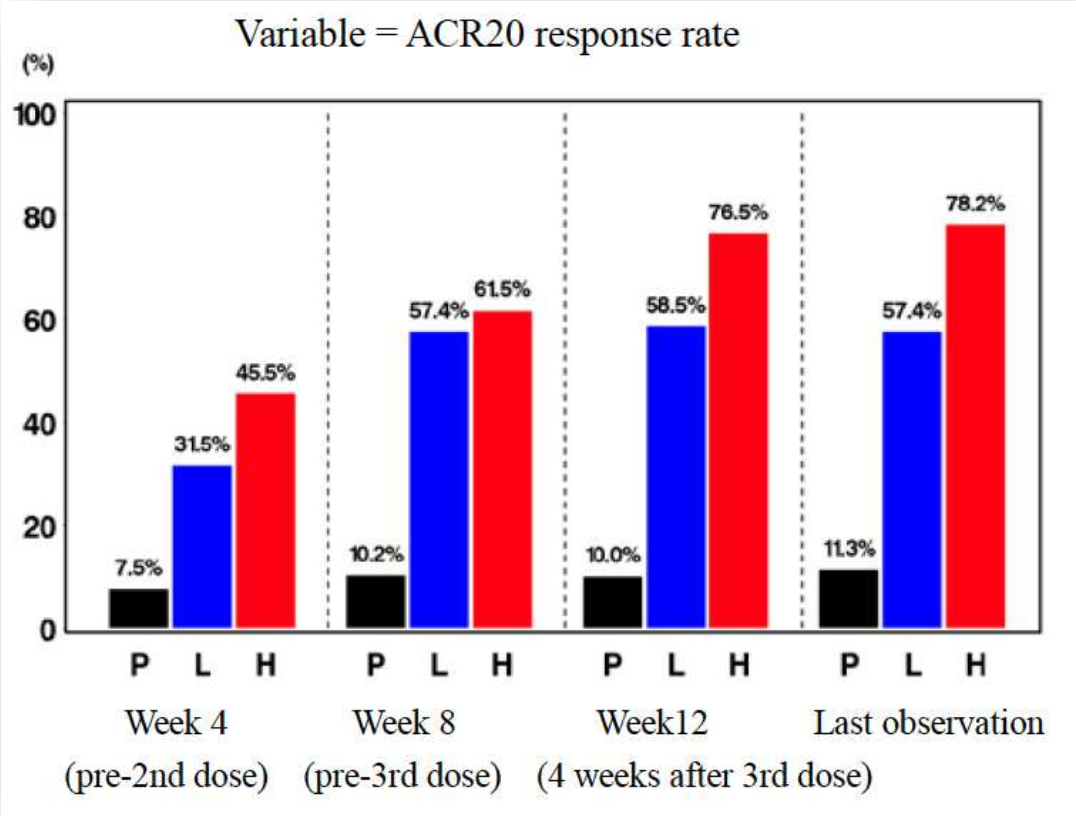
patients with active disease have elevated CRP levels compared to normal patients, and normalization of CRP indicates that the action of IL-6, which causes RA, has been blocked. EX1032 ¶105; EX1034 ¶¶175-76. *Nishimoto 2008* (EX1008) reported the utility of CRP as a biomarker of efficacy for RA. It explained that 1 μg/mL was the MEC at which tocilizumab would effectively block the activity of IL-6, since this is the MEC at which tocilizumab would normalize CRP:

> Tocilizumab normalized the CRP level in patients with RA…as long as the free tocilizumab, which is capable of binding IL-6R and of inhibiting IL-6 actions, remained above 1 μg/ml in serum….This shows that tocilizumab effectively inhibits IL-6 signaling when it is detectable in serum….Since CRP is mainly produced by hepatocytes which express cell-surface IL-6R, membrane-bound IL-6R would be also fully occupied by tocilizumab. CRP is thus a useful surrogate marker for tocilizumab levels that are high enough to inhibit the effects of IL-6 in patients.

EX1008, 3961-63; *see also* EX1024, 22-24.

The reliability of 1 μg/mL as the MEC is supported by the fact that 4 mg/kg and 8 mg/kg of tocilizumab given intravenously every 4 weeks were reported in the prior art as producing plasma concentrations that were generally above 1 μg/mL and as being effective for the treatment of RA. EX1032 ¶107; EX1034

¶178. *Oldfield* reported that that "[a]mong patients who received tocilizumab 4 or 8 mg/kg every 4 weeks for 24 weeks in the OPTION study, normalized CRP levels were maintained in patients with serum tocilizumab concentrations of >1 μg/mL." EX1005, 613; *see also* EX1001, 2:20-23. The *EMA Report* and *Actemra PDMA Report* disclosed that various clinical trials had established that both the 4 mg/kg and 8 mg/kg dosage regimens were effective at treating RA. EX1006, 75. As can be seen from the plot below, both 4 mg/kg (Group L) and 8 mg/kg (Group H) dosed every 4 weeks produced ACR20 response rates that were markedly better than placebo (Group P):



EX1024, 39-40. Both the 4 mg/kg and 8 mg/kg dosage regimens also produced significant improvements in the DAS28 (Modified Disease Activity Score on 28 Joint Counts) score over placebo. *Id.*, 40-41.

2. Prior-Art Pharmacokinetic Data, When Plugged Into Routine Prior-Art Pharmacokinetic Models, Would Have Confirmed that the Dosage Regimen of *NCT '653* Will Produce Mean Blood Plasma Concentrations of Tocilizumab In Excess of 1 µg/ml

At the time of its publication, a POSA who wanted to analyze whether the SC dosage regimen of *NCT '653* would be effective would have simply plugged the regimen and known PK parameters of tocilizumab into a suitable PK/PD model

and then observed whether the regimen would produce efficacious mean blood plasma levels of antibody. EX1032 ¶5; EX1034 ¶¶179-83. By 2009, PK/PD models had become an essential and routine part of drug product development, being in wide use for precisely this sort of analysis. EX1032 ¶¶4, 30; EX1034 ¶179.

The POSA would have chosen a two-compartment PK model for tocilizumab, guided in part by the two-compartment model in *Ng 2005* for efalizumab, which is an IgG1-*kappa* subtype antibody structurally similar to tocilizumab, and the two-compartment model for tocilizumab that Roche included in the *FDA Review*, which it submitted to the FDA in support of the regulatory approval of Actemra. EX1032 ¶¶47, 80-81, 84-85.

Constructing this model would have been greatly simplified by the fact that there were many "plug and play" software programs available in the prior art that allowed a POSA to create a two-compartment model by simply plugging in a handful of pharmacokinetic parameters for the antibody of interest. *Id.* ¶86. *Ng 2005* used the ADAPT software program and Roche used NONMEM, but there were many others in common use as of 2009. *Id.*; EX1007, 1088; EX1010, 105-119.

A POSA would have searched the prior art for the pharmacokinetic parameters required by the software to model tocilizumab. EX1032 ¶87. All of

those parameters are set forth in Table 3 of the *FDA Review* which, as explained, disclosed Roche's two-compartment NONMEM model for tocilizumab. EX1010, 114.

It would have been routine for the POSA to create the same standard, two-compartment model Roche used using NONMEM, ADAPT or similar prior-art software. EX1032 ¶¶4-5, 84-86. A POSA would have had confidence in the results of this two-compartment model given that Roche had deemed it accurate enough for the results to be submitted in support of regulatory approval. *Id.* ¶78.

Roche's two-compartment model simulated the PK and PD of tocilizumab administered via IV. To model SC administration, two additional pharmacokinetic parameters are required. These are bioavailability (F), which is the fraction of the subcutaneous dose that reaches the bloodstream, and the rate of absorption (K_a), which refers to how quickly the dose migrates through the subcutaneous tissue and into the bloodstream.[14] EX1032 ¶¶43-47. The prior art discussed herein does not report these parameters. However, the prior art is replete with F and K_a values for other IgG1-*kappa*-subtype antibodies which, because they are structurally similar to tocilizumab, a POSA would have expected to have roughly similar PK

[14] Since 100% of an IV dose reaches the bloodstream very quickly, F and K_a normally are not relevant to IV administration. EX1032 ¶ 44.

properties. *Id.* ¶¶92-98. At least six such antibodies had been formulated into subcutaneous therapeutics, and F and K_a values for them had been published in the prior art. *Id.* ¶97, Table 4 (collectively, "*SC PK Prior Art*"):

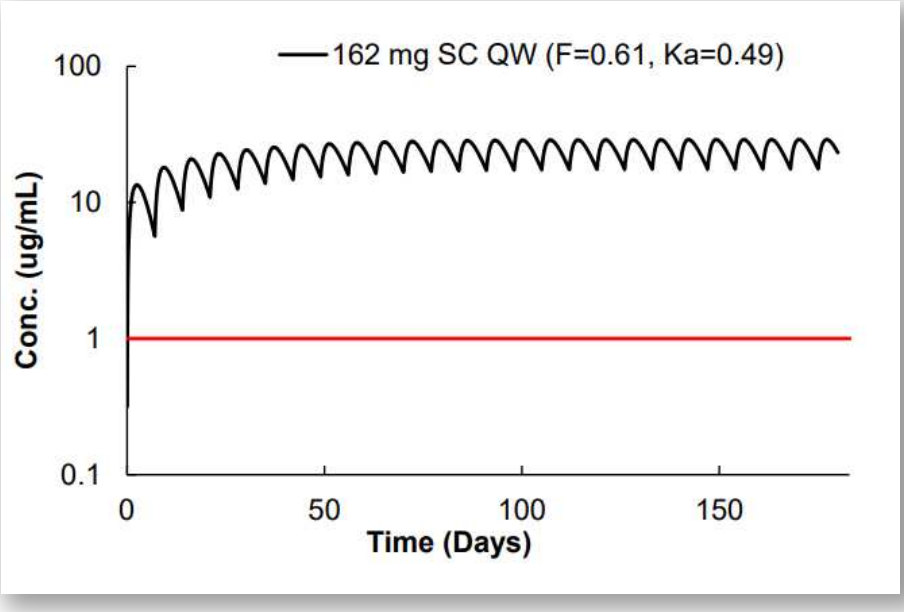
Compound	**F**	**Ka (d^{-1})**	**Source**
Efalizumab	0.56		*Ng 2005* (EX1007)
Omalizumab	0.62		*PDR 2007 Excerpt – Xolair* (EX1016)
Adalimumab	0.64		*Humira 2008 Label* (EX1012) *Vena 2007* (EX1013) *Awni 2004* (EX1022)
Canakinumab	0.70		*Ilaris 2009 Label* (EX1014)
Golimumab	0.53		*Simponi 2009 Label* (EX1015)
Efalizumab		0.22	*Ng 2005* (EX1007) *Sun 2005* (EX1019)
Omalizumab		0.48	*Hayashi 2006* (EX1021)
Ustekinumab		0.35	*Zhu 2009* (EX1020)
Golimumab		0.91	*Xu 2009* (EX1018)
Average	**0.61**	**0.49**	

A POSA would have known that for these similar IgG1-*kappa* antibodies, F ranged from about 0.53 (that is, about 53% of the subcutaneously administered drug will make its way into the bloodstream/central compartment), to about 0.70

(about 70%). The average was 0.61 (61%). K_a ranged from about 0.22 d^{-1} to about 0.91 d^{-1}. The average was 0.49 d^{-1}. *Id.* ¶¶95-96.

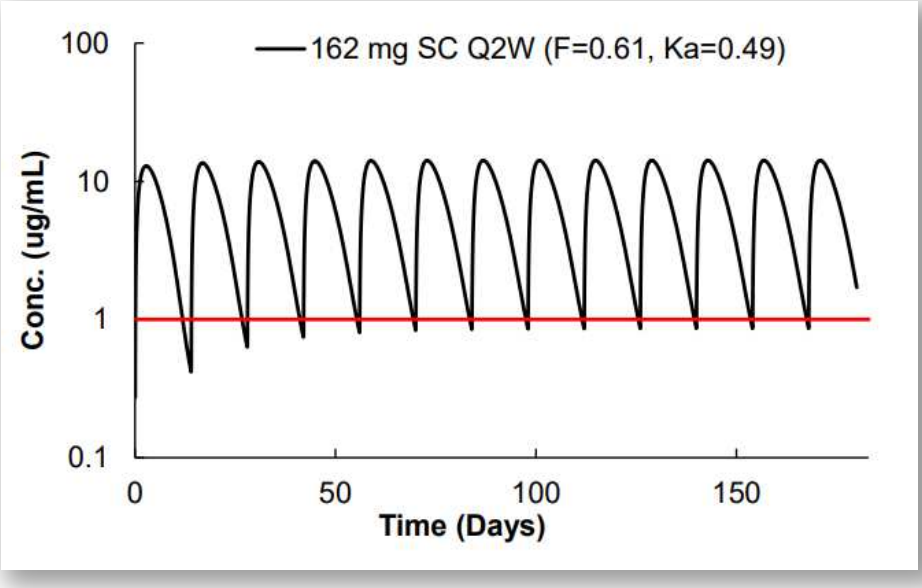
As Dr. Shah demonstrates in his declaration, plugging the above pharmacokinetic parameters from the *FDA Review* and the *SC PK Prior Art* into the prior-art ADAPT software program to create a two-compartment PK/PD model of tocilizumab, like the ones published in each of *Ng 2005* and *FDA Review*, would have allowed a POSA to predict the steady-state[15] mean blood plasma concentration resulting from a 162 mg fixed dose of tocilizumab administered according to the once-weekly dosage regimen of *NCT '653*. EX1032 ¶¶104-114. The concentration-versus-time profile shows that mean plasma concentration is well above the 1 μg/ml MEC for tocilizumab at steady state:

[15] A "steady state" serum concentration profile is the pattern of peaks and troughs that stabilize and become constant over time as tocilizumab continues to be administered. EX1032 ¶108.

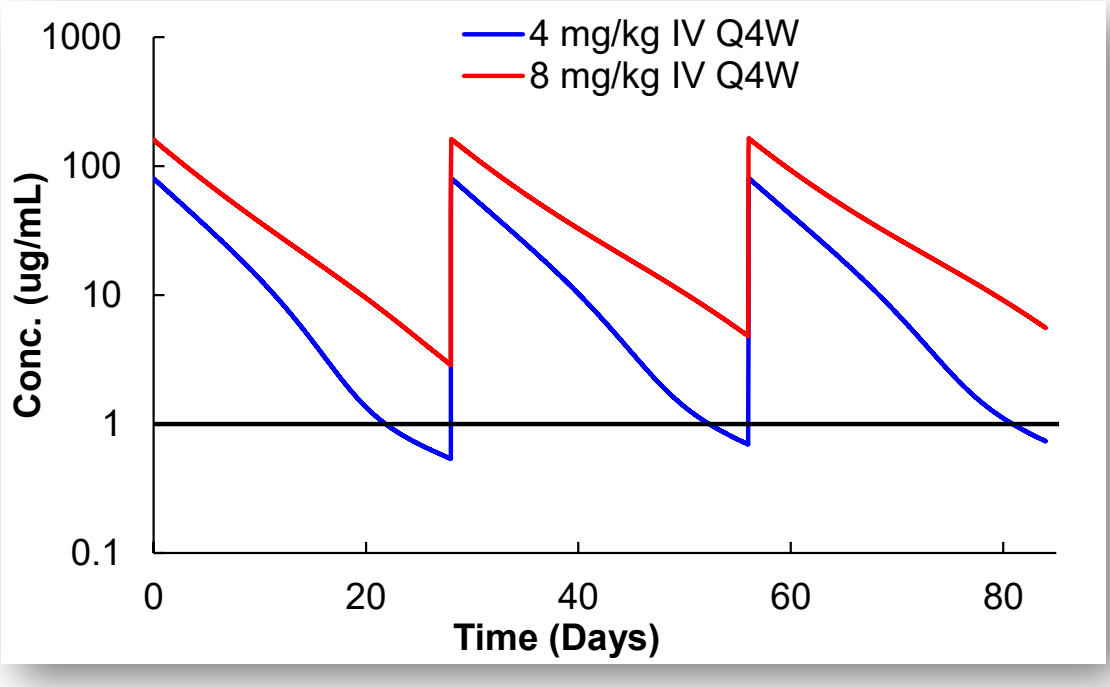


Id. ¶117, Fig 14. The plasma concentration is well above the 1 µg/ml MEC at steady state even at the extremes of F and K_a reported in the prior art for IgG1-*kappa* antibodies. *Id.* ¶117. This is true for the "worst case" values, *i.e.,* the least-bioavailable F value of 0.53, and the fastest-absorbing K_a of 0.91 d^{-1}, as well as for the "best case" values, *i.e.,* the most-bioavailable F value of 0.70 and the slowest-absorbing K_a of 0.22 d^{-1}. *Id.* ¶118 and Fig. 15.

The mean plasma concentration is also at or above the 1 µg/ml MEC when the 162 mg dose is administered once every two weeks:



Id. ¶122, Fig 18. Again, for the "best case" values of F and K_a, *i.e.,* the most-bioavailable F value of 0.70 and the slowest-absorbing K_a of 0.22 d^{-1}, the mean plasma concentration is well above the MEC at steady state. *Id.* ¶122, Fig. 19. For the "worst case" values, *i.e.,* the least-bioavailable F value of 0.53, and the fastest-absorbing K_a of 0.91 d^{-1}, mean plasma concentration dips briefly below the MEC just before the next dose. *Id.* This is similar to the plasma concentration of tocilizumab predicted by the model for 4 mg/kg tocilizumab administered via IV every 4 weeks, which clinical trials have established is effective:



Id. ¶108, Fig 10.

From these modeling results, a POSA would have had at least a reasonable expectation that both the once-weekly and once-every-two-week dosage regimens of *NCT '653* would have at least some efficacy in at least some patients. Indeed, the results would have given a POSA a reasonable expectation that the *NCT '653* regimens would have substantial efficacy. *Id.* ¶¶6, 82, 120-123; EX1034 ¶179-83.

Moreover, the POSA would have assumed from the fact that Patent Owners had sponsored *NCT '653*, had publicly announced that subcutaneous Actemra was "in development," (EX1071, 4; EX1072 slide 12), and had published PK/PD modeling results for tocilizumab (EX1006, 41; EX1010, 111; EX1032 ¶84), that Patent Owners had engaged in similar modeling to design the human clinical trial

of *NCT '653*. This would have added to the reasonable expectation of success. EX1034 ¶¶69, 155, 183; *see also* EX1110, [0053]; EX1115, 308, [0053].

For the same reasons provided with respect to Ground 2, a POSA would have been able to make and administer a 162mg dose of tocilizumab subcutaneously to a RA patient every week or every other week using nothing more than routine skill. EX1034 ¶150; EX1036 ¶37.

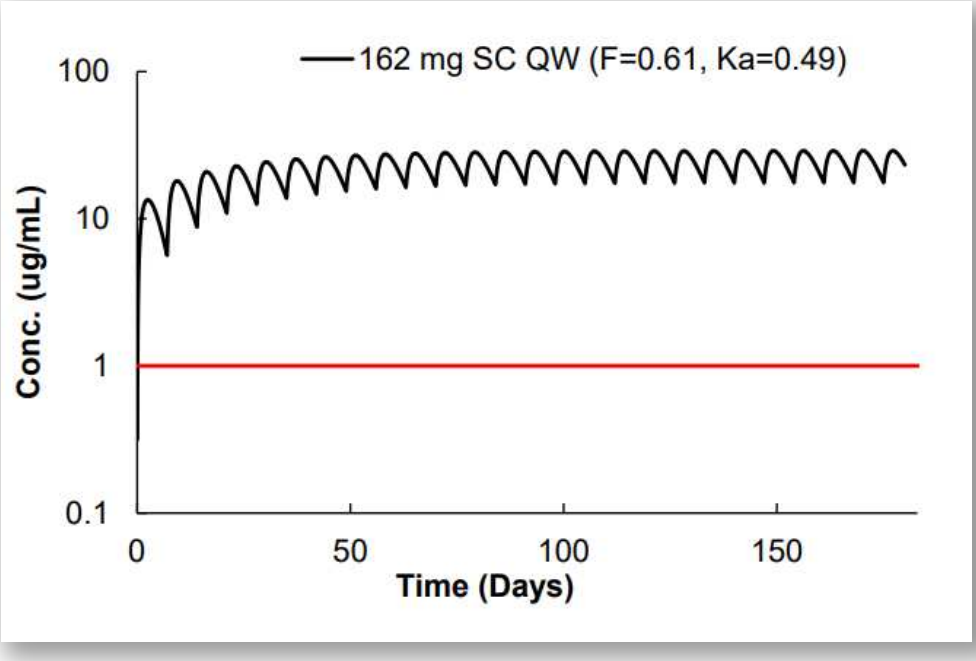
For the foregoing reasons, claims 1-11 are obvious over the cited prior art. EX1034 ¶184.

G. [Ground 7] Claims 1-11 Are Obvious Over the Combination of *NCT '653*, *Morichika* and *Ng 2005* (claims 1-11), *Emery* (claim 4 only), and *Maini 2006* (claim 5 only), In View of *Nishimoto 2008*, *EMA Report*, *Chernajovsky 2008* and the SC PK Prior Art

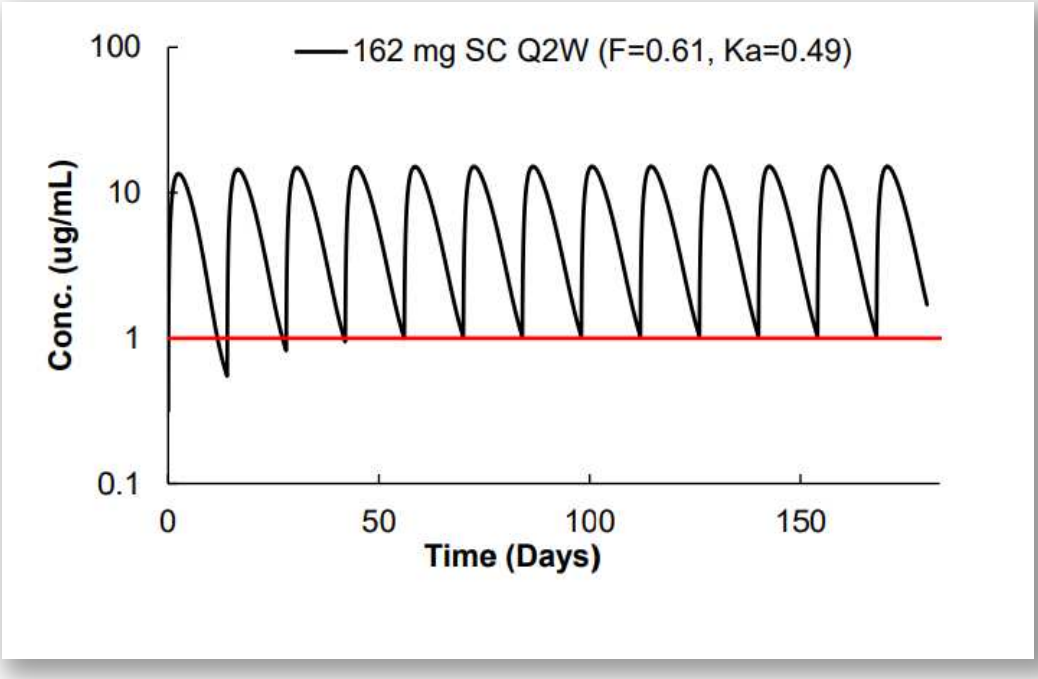
As explained, Roche had published its two-compartment PK/PD model of IV tocilizumab in the *FDA Review*, along with a chart of the pharmacokinetic parameters used to generate the model. EX1010, 110-124. The *FDA Review* was published in March 2010 and thus is prior art under pre-AIA section 102(a). But as Dr. Shah explains, a POSA would have found the necessary PK parameters elsewhere in the prior art, as essentially the same parameters were disclosed in *EMA Report* and *Chernajovsky 2008*, or derivable from the data published

therein.[16] EX1032 ¶87, 90. Specifically, CL and KM were disclosed in *EMA Report*, V1 and V2 can be estimated from the *EMA Report*, and Q and VM can be estimated from *Chernajovsky 2008*. *Id.* ¶¶87-89. Roche also revealed in the *EMA Report* that it had relied on its two-compartment PK/PD model of tocilizumab for approval in Europe. *Id.* ¶84; EX1006, 41. *EMA Report* was published in July 2009 and *Chernajovsky 2008* was published in 2008, thus both qualify as prior art under pre-AIA section 102(b). As can be seen from the below graph, even using the parameters obtained and derived from *EMA Report* and *Chernajovsky 2008*, mean plasma concentration is well above the 1 μg/ml MEC for tocilizumab at steady state for the QW dose:

[16] Although the values of the parameters published in the *FDA Review* are slightly different than those obtained from the *EMA Report* and *Chernajovsky 2008*, those differences do not materially alter the output of the model. EX1032 ¶¶ 91, 102, 103, 115, 117, 120, 122.



EX1032 ¶115 and Fig. 12. The same is true for the Q2W dose, as seen below:



EX1032 ¶120, Fig. 16. As explained in Ground 6, even with the "worst case scenario," the values for the Q2W dose are still well above the MEC. *Id.* ¶116, Fig. 13. Similar to Ground 6, while for the "worst case" values, mean plasma concentration dips briefly below the MEC just before the next dose, this is similar to the plasma concentration of tocilizumab predicted by the model for 4 mg/kg tocilizumab administered via IV every 4 weeks. *Id.* ¶121 and Fig. 17.

Thus, for the reasons given in Grounds 6 and 7, claims 1-11 would have been obvious regardless of whether the *FDA Review* qualifies as prior art. EX1034 ¶¶185-88.

H. [Ground 8] Claim 12 is Obvious Over the Combination of *NCT '653*, *Morichika*, *Ng 2005* and *Kremer 2009* (EX1029), In View of *Nishimoto 2008*, *FDA Review* and the *SC PK Prior Art*

Claim 12 would have been obvious from *NCT '653* and *Morichika* because a POSA would have had at least a reasonable expectation that a 162 mg SC fixed dose of tocilizumab, whether administered once- or twice-weekly, alone or in combination with MTX, would inhibit structural joint damage after 24 or 48 weeks of administration. As with claims 1-11, other prior art would have bolstered this expectation of efficacy.

As explained in Ground 6, a POSA would have had at least a reasonable expectation that the regimens of *NCT '653* would produce steady-state mean blood plasma levels of tocilizumab at or above the MEC of 1 μg/ml. As explained in

section VII.F *supra*, administering sufficient tocilizumab to meet or exceed this MEC strongly reduces disease activity in RA by blocking the action of IL-6. A POSA would thus have reasonably expected that the regimens of *NCT '653* would inhibit structural joint damage, as well as the other consequences of RA. EX1034 ¶190.

To the extent a POSA would have had any uncertainty about the effectiveness of tocilizumab in combination with MTX in inhibiting structural joint damage, the prior art disclosed the results of a clinical trial that confirmed this efficacy. EX1034 ¶191. *Kremer 2009* disclosed results from a double-blind, phase III clinical trial in which 688 patients who were inadequate responders to MTX received MTX weekly plus either 4 mg/k or 8 mg/kg IV tocilizumab every four weeks for 24 months. EX1029, 516. The results showed that tocilizumab significantly inhibited the progression of structural joint damage in both the 4 mg/kg and 8 mg/kg treatment groups, and that the percentage of patients showing no progression of joint erosion, joint space narrowing or progression in Genant-modified total Sharp score (GnTSS) were essentially the same for both groups. *Kremer 2009* reported that the patients receiving 4mg/kg had almost the same inhibition of structural joint damage (75% showing no GmTSS progression) as the 8 mg/kg patients (83% showing no GmTSS progression). EX1029, Table A; s*ee also* EX1028, Table.

A POSA also would have understood that both the 4 mg/kg and 8 mg/kg dosage regimens maintained mean plasma concentrations of tocilizumab at or above the 1 μg/ml MEC. EX1034, ¶192. It would have been routine for a POSA to recreate the NONMEM model Roche described in the *FDA Review* for IV tocilizumab, using only the pharmacokinetic parameters Roche published in that document. As Dr. Shah confirmed, when the 4 mg/kg and 8 mg/kg IV dosage regimens tested in *Kremer 2009* are plugged into the model, they produce concentration levels that generally fall above the MEC (black horizontal line), although the 4 mg/kg trough concentrations briefly fall below it immediately prior to the next dose. EX1032 ¶108, Fig. 10; *see also* figure at section VII.F.2, *supra*.

A POSA would have viewed the 4 mg/kg data, which effectively inhibited structural joint damage even though mean plasma concentrations transiently dipped below the MEC, as confirming the expectation that the dosage regimens *NCT '653* would effectively inhibit structural joint damage. EX1034 ¶193.

For the same reasons provided with respect to Ground 1, a POSA would have been able to make and administer a 162 mg dose of tocilizumab subcutaneously to a RA patient every week or every other week using nothing more than routine skill. EX1036 ¶37.

For the foregoing reasons, claim 12 is obvious over the cited prior art. EX1034 ¶194.

I. [Ground 9] Claim 12 is Obvious Over the Combination of *NCT '653*, *Morichika*, *Ng 2005* and *Kremer 2009*, In View of *Nishimoto 2008, EMA Report*, *Chernajovsky 2008* and the *SC PK Prior Art*

As explained, the PK parameters needed to construct a PK/PD model for tocilizumab were disclosed in the *EMA Report* and *Chernajovsky 2008* (or derivable from the data published therein), as well as the *SC PK Prior Art*. EX1032 ¶¶87, 93-97. Thus, for the reasons given in Grounds 7 and 8, claim 12 would have been obvious regardless of whether the *FDA Review* qualifies as prior art or not. EX1034 ¶195.

VIII. SECONDARY CONSIDERATIONS

Petitioner is not aware of any relevant secondary considerations that have a nexus to, or are commensurate in scope, with any of the challenged claims. EX1034, ¶196. Moreover, to the extent the claims are anticipated by *NCT '653*, "secondary considerations are not an element of a claim of anticipation." *Cohesive Techs. Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008).

IX. CONCLUSION

For the reasons set forth above, claims 1-12 of the ’264 patent are unpatentable. Petitioner therefore requests that an *inter partes* review of these claims be instituted.

Respectfully submitted,

Dated: February 21, 2022

/Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

X. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,501 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: February 21, 2022

/Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

XI. REG. NO. 43,541 PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,580,264 ("the '264 Patent")
1002	Curriculum Vitae of Dhaval K. Shah B. Pharm., M.S., Ph.D.
1003	Excerpts from Milo Gibaldi and Donald Perrier, Pharmacokinetics, 2d Ed. (2007) ("*Gibaldi 2007*")
1004	U.S. National Library of Medicine, ClinicalTrials.gov, NCT00965653, "A Study of Subcutaneously Administered Tocilizumab in Patients with Rheumatoid Arthritis" (August 21, 2009), available at https://clinicaltrials.gov/ct2/history/NCT00965653?V_1 ("*NCT '653*")
1005	Vicki Oldfield, et al., "Tocilizumab, A Review of its Use in the Management of Rheumatoid Arthritis", *Drugs* 2009: 69(5): 609-632 ("*Oldfield*")
1006	Affidavit of Duncan Hall (Internet Archive), containing *About Clinicaltrials.gov* (p.5), *About the ClinicalTrials.gov Results Database* (p.7), *ClinicalTrials.gov Protocol Data Element Definitions* (p.10), *FAQ: ClinicalTrials.gov – Submission and Review of Information* (p.19), *FDA Talk Paper* (p.21), *Assessment Report for RoActemra* (p.24) ("*EMA Report*"), *ClinicalTrials.gov Fact Sheet* (p.80), *Registering Clinical Trials With ClinicalTrials.gov* (p. 86) ("*Duncan Hall Aff.*")
1007	Chee M. Ng et al., "Pharmacokinetic-Pharmacodynamic-Efficacy Analysis of Efalizumab in Patients with Moderate to Severe Psoriasis", *Pharmaceutical Research* 22(7): 1088-1100 (July 2005) ("*Ng 2005*")
1008	Norihiro Nishimoto et al., "Mechanisms and pathological 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* 112:3959-64 (2008) ("*Nishimoto 2008*")
1009	Excerpt from Y. Chernajovsky and A. Nissim, Handbook of Experimental Pharmacology 181, "Humanized Antihuman IL-6

	Receptor Antibody, Tocilizumab" 151-60 (2008) ("*Chernajovsky 2008*")
1010	Clinical Pharmacology and Biopharmaceutics Review(s) for IV Actemra, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000ClinPharmR.pdf ("*FDA Review*")
1011	Nicolas Frey et al., "Population Pharmacokinetic Analysis of Tocilizumab in Patients With Rheumatoid Arthritis", *J. Clin. Pharmacol.* 2010;50:754-766 "(*Frey 2010*")
1012	Package Insert for HUMIRA (adalimumab), Revised January 2008, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125057s0110lbl.pdf ("*Humira 2008 Label*")
1013	Gino Vena et al., "Drug focus: adalimumab in the treatment of moderate to severe psoriasis", *Biologics: Targets & Therapy* 2007:1(2) 93-103 ("*Vena 2007*")
1014	Package Insert for ILARIS (canakinumab), Revised June 2009, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125319s000lbl.pdf ("*Ilaris 2009 Label*")
1015	Package Insert for SIMPONI (golimumab), Revised April 2009, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s000lbl.pdf ("*Simponi 2009 Label*")
1016	Excerpt of Physicians' Desk Reference, 61st Edition (2000) for Xolair® (omalizumab) ("*PDR 2007 Excerpt – Xolair*")
1017	Intentionally left blank
1018	Zhenhua Xu et al., "Population Pharmacokinetics of Golimumab, an Anti-Tumor Necrosis Factor-α Human Monoclonal Antibody, in Patients With Psoriatic Arthritis", *J. Clin. Pharmacol.* 2009;49:1056-1070 ("*Xu 2009*")
1019	Yu-Nien Sun et al., "Population Pharmacokinetics of Efalizumab (Humanized Monoclonal Anti-CD11a Antibody Following Long-Term Subcutaneous Weekly Dosing in Psoriasis Subjects", *J. Clin. Pharmacol.* 2005;45:468-476 ("*Sun 2005*")
1020	Yaowei Zhu et al., "Population Pharmacokinetic Modeling of Usketinumab, a Human Monoclonal Antibody Targeting IL-12/23p40, in Patients With Moderate to Severe Plaque Psoriasis" *J. Clin. Pharmacol.* 2009;49:162-175 ("*Zhu 2009*")

1021	Naoto Hayashi et al., "A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab", *Br. J. Clin. Pharmacol.* 63(5):548-561 (2006) ("*Hayashi 2006*")
1022	WM Awni et al., "Steady-state Adalimumab (HUMIRA) Pharmacokinetics (PK) Following Every Other Week (eow) Dosing of 40mg Subcutaneous (s.c.) Injection, in Rheumatoid Arthritis (RA) Patients Treated With and Without Concomitant Methotrexate (MTX)" (2004) ("*Awni 2004*")
1023	David Z. D'Argenio et al., ADAPT V User's Guide (July 2009) ("*ADAPT V User's Guide*")
1024	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 ("*Actemra PDMA Report*")
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1026	Norihiro Nishimoto et al., "Study of Active Controlled Monotherapy Used For Rheumatoid Arthritis, an IL-6 Inhibitor (SAMURAI): Evidence of Clinical Radiographic Benefit From an X-Ray Reader-Blinded Randomised Controlled Trial of Tocilizumab", *Ann. Rheum. Dis.* 2007;66:1162-1167 ("*Nishimoto 2007*")
1027	Norihiro Nishimoto et al., "Treatment of Rheumatoid Arthritis With Humanized Anti-Interleukin-6 Receptor Antibody", *Arthritis & Rheumatism* 50(6), 1761-1769 (June 2004) ("*Nishimoto 2004*")
1028	J.M. Kremer et al., "Tocilizumab Inhibits Joint Structural Damage in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate: The LITHE Study," Arthritis & Rheumatism, Vol. 58, No. 12 (December 2008) ("*Kremer 2008*")
1029	J. Kremer et al., "LITHE: Tocilizumab Inhibits Radiographic Progression and Improves Physical Function in Rheumatoid Arthritis (RA) Patients (Pts) at 2Yrs with Increasing Clinical Efficacy Over Time", American College of Rheumatology Abstract Supplement (October 16-21, 2009) ("*Kremer 2009*")
1030	Certificate of Translation (pg. 1), Translation (pgs. 2-183) & Original (pgs. 184-364):

	PCT International Publication No. WO2009/041621 A1 ("*WO '621*")
1031	Sequence Listing for WO2009/041621 A1, available at available at https://patentscope.wipo.int/search/docs2/pct/WO2009041621/file/PphyAKMJApl6qJur_mQDG7n2NOAu9YwcdqjMGsyXX6b_bnMLPWCn_59rPesoMSl4mjvztdpx7fiDIHCOKJVdgz8J9eGByoDOWNx1v2cz1uuUeFKSU_AVoVegLcdK2DoO5KC3fpHz4mBZZBfs PdRfhg?docId=id00000007993190 ("*Sequence Listing*")
1032	Declaration of Dhaval K. Shah, B. Pharm., M.S., Ph.D. ("Shah Decl.")
1033	Intentionally Left Blank
1034	Declaration of Maarten Boers, M.D., M.Sc., Ph.D. ("Boers Decl.")
1035	Declaration of Prescott M. Lassman, Esq. ("Lassman Decl.")
1036	Declaration of Paul A. Dalby, Ph.D. ("Dalby Decl.")
1037	G. Jones et al., "Comparison of Tocilizumab Monotherapy Versus Methotrexate Monotherapy in Patients with Moderate to Severe Rheumatoid Arthritis: The AMBITION Study," *Annals of the Rheumatic Diseases* 69:88–96 (2010) ("*Jones*")
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1039	Eric L. Matteson, "Concise Review for Clinicians, Current Treatment Strategies for Rheumatoid Arthritis," *Mayo Clinic Proceedings* 75:69–74 (2000) ("*Matteson*")
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1044	Pharmaceuticals and Medicals Devices Agency of Japan, Annual Report FY 2008, available at https://www.pmda.go.jp/files/000232775.pdf ("*PMDA FY 2018 Report*")
1045	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 125276 Approval Letter*")
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1047	David Macht, The History of Intravenous and Subcutaneous Administration of Drugs, *J. of Am. Med. Ass'n,* Vol. LXVI, No. 12 (March 18, 1916) ("*Macht*")
1048	Melvin Berger, "Subcutaneous Administration of IgG," *Immunology and Allergy Clinics of North America* 28:779–802 (2008) ("*Berger*")
1049	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 ("*Ochs*")
1050	Alan Kivitz and Oscar G. Segurado, "HUMIRA® Pen: a novel autoinjection device for subcutaneous injection of the fully human monoclonal antibody adalimumab," *Expert Rev. Med. Devices* 4(2):109–16 (2007) ("*Kivitz*")

1051	Francisco A. Bonilla, "Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes," *Immunology and Allergy Clinics of North America* 28:803–19 (2008) ("*Bonilla*")
1052	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 (September 2009) ("*Wang*")
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1055	Package Insert for HUMIRA (Adalimumab), Revised (December 2002) ("*2002 Humira FDA Label*")
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1058	"TNF Blocker Wins Approvals," *Internal Medicine News*, Vol. 42, No. 11 (2009) ("*TNF Blocker Wins Approvals*")
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1065	Prosecution File History of U.S. Patent No. 8,580,264 ("'264 File History")
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1067	Application for Patent Term Extension Under 35 U.S.C. § 156 to the PTO for U.S. Patent. No. 5,795,965 ("*Application for Patent Term Extension*")
1068	Prosecution File History of U.S. Patent No. 10,874,677 ("'677 File History")
1069	Josef S. Smolen et al., "Effect of Interleukin-6 Receptor Inhibition with Tocilizumab in Patients with Rheumatoid Arthritis (OPTION Study): A Double-Blind, Placebo-Controlled, Randomised Trial," *Lancet* 371:987–97 (2008) ("*Smolen*")
1070	Mark C. Genovese, "Interleukin-6 Receptor Inhibition with Tocilizumab Reduces Disease Activity in Rheumatoid Arthritis with Inadequate Response to Disease-Modifying Antirheumatic Drugs," *Arthritis & Rheumatism* 58(10):2968–80 (2008) ("*Genovese*")
1071	"Overview of Development Pipeline," Chugai Pharmaceutical Co., Ltd., Tatsuro Kosaka, February 4/5, 2009, available at https://www.chugai-harm.co.jp/cont_file_dl.php?f=FILE_2_63.pdf&src=[%0],[%1]&rep=139,63 ("*Chugai 2009 Report*")
1072	Roche, "Investor Event at EULAR 2009," June 12, 2009, available at https://www.roche.com/dam/jcr:aa643d56-6ea3-47b0-9109-5f027b1c1fef/en/irp090612_eular.pdf ("*Roche 2009 Report*")
1073	Curriculum Vitae of Maarten Boers, M.D., M.Sc., Ph.D.
1074	Mike A. van Leeuwen et al., "Individual Relationship Between Progression of Radiological Damage and the Acute Phase Response in Early Rheumatoid Arthritis. Toward Development

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1077	Curriculum Vitae of Scott M. Lassman, Esq.
1078	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *History, Policies, and Laws*, https://clinicaltrials.gov/ct2/about-site/history ("*ClinicalTrials.gov*, *History, Policies, and Laws*")
1079	Intentionally Left Blank
1080	Affidavit of Nathaniel E Frank-White (Internet Archive), including *ClinicalTrials.Gov, Basic Search* (p.5); *ClinicalTrials.Gov, Advanced Search* (p. 7); *ClinicalTrials.Gov, Help For Searching ClinicalTrials.Gov* (p.9) ("*Nathaniel E Frank White Aff.*")
1081	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, *How to Edit Your Study Record*, https://clinicaltrials.gov/ct2/manage-recs/how-edit ("*ClinicalTrials.gov, How to Edit Your Study Record*")
1082	Deborah A. Zarin et al., "Reporting 'Basic Results' in ClinicalTrials.gov", *CHEST* 136(1), 295-303 (July 2009) ("*Zarin*")
1083	U.S. National Library of Medicine, National Institutes of Health, *ClinicalTrials.gov, ClinicalTrials.gov Background*, https://www.clinicaltrials.gov/ct2/about-site/background ("*ClinicalTrials.gov Background*")
1084	Food & Drug Administration, *Drugs@FDA Homepage*, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm ("*Drugs@FDA Homepage*")
1085	Food & Drug Administration, *Drugs@FDA FAQ*, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=faq.page ("*Drugs@FDA FAQ*")

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1087	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *History of Changes for Study: NCT00965653*, https://clinicaltrials.gov/ct2/history/NCT00965653 ("*History of Changes*")
1088	U.S. National Library of Medicine, U.S. National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 21, 2009 (v1) – November 1, 2016 (v69)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=1&B=69&C=merged#StudyPageTop ("*Comparison of August 21, 2009 Record and November 1, 2016 Record*")
1089	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 21, 2009 (v1) – August 26, 2009 (v2)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=1&B=2&C=merged#StudyPageTop ("*Comparison of August 21, 2009 Record and August 26, 2009 Record*")
1090	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, August 26, 2009 (v2) – September 15, 2009 (v3)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=2&B=3&C=merged#StudyPageTop ("*Comparison of August 26, 2009 Record and September 15, 2009 Record*")
1091	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov archive, *Changes (Merged) for Study: NCT00965653, September 15, 2009 (v3) – October 15, 2009 (v4)*, https://clinicaltrials.gov/ct2/history/ NCT00965653?A=3&B=4&C=merged#StudyPageTop ("*Comparison of September 15, 2009 Record and October 15, 2009 Record*")
1092	Food & Drug Administration, *Drugs@FDA, BLA 125276 Homepage*, https://www.accessdata.fda.gov/scripts/cder /daf/index.cfm?event=overview.process&ApplNo=125276

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1095	Food & Drug Administration, *Drugs@FDA, BLA 125276 Approval Package*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000TOC.cfm ("*BLA 125276 Approval Package*")
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1101	World Intellectual Property Office, WO2009041621, available at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009041621&tab=PCTDOCUMENTS ("*WIPO*")
1102	Lawrence W. Dick et al., "Determination of the origin of the N-terminal pyro-glutamate variation in monoclonal antibodies using model peptides," *Biotechnology & Bioengineering* 97(3):544–53 (November 10, 2006) ("*Dick*")
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1104	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*")
1105	William E. Werner et al., "The removal of pyroglutamic acid from monoclonal antibodies without denaturation of the protein chains," *Anal. Biochem.* 342:120–25 (2005) ("*Werner*")
1106	Certificate of Translation (pg. 1), Translation (pgs. 2–27), & Original (pg. 28–52): PCT International Publication No. WO2005/090405 A1 ("*WO '405*")
1107	U.S. Patent No. 5,795,965 ("The '965 patent")
1108	NCATS description of tocilizumab, https://gsrs.ncats.nih.gov/ginas/app/substance/fff5a4c0-d59d-4327-b2e7-7e36e4e676e1 ("*NCATS – Tocilizumab*")
1109	Curriculum Vitae of Paul A. Dalby, Ph.D.
1110	Certificate of Translation (pg. 1-2), Translation (pgs. 3-32), & Original (pg. 33–64): PCT International Publication No. WO 2009084659A1 ("*Morichika"*)
1111	Package Insert for CIMZIA (certolizumab pegol), Revised May 2009 ("*CIMZIA 2009 Label*")
1112	U.S. Patent No. 8,568,720 ("The '720 patent")
1113	U.S. Patent No. 6,267,958 ("The '958 patent")
1114	September 17, 2013 PTO Notice of Final Determination and Requirement for Election for U.S. Pat. No. 5,795,965 ("*September 17, 2013 PTO Notice of Final Determination and Requirement for Election*")
1115	Prosecution File History of U.S. Patent No. 8,568,720 ("'720 File History")
1116	Package Insert for ACTEMRA (tocilizumab), Revised March 2021, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf ("*Actemra March 2021 Label*")
1117	Declaration of Yahn Lin Chu, Esq. ("Chu Decl.")

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter *Partes* Review (and accompanying Exhibits 1001-1117) by overnight courier (Federal Express or UPS), on this 21st day of February 2022, on the Patent Owner at the correspondence address of the Patent Owner as follows:

Genentech
1 DNA Way
South San Francisco, CA 94080

Respectfully submitted,

Dated: February 21, 2022

/Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541