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Paper 23
Date: June 3, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and
FRESENIUS KABI SWISSBIOSIM GmbH,
Petitioner,

v.

CHUGAI SEIYAKU KABUSHIKI KAISHA and
HOFFMAN-LA ROCHE INC.,
Patent Owner.

IPR2022-00201
Patent 9,750,752 B2

Before ERICA A. FRANKLIN, JOHN G. NEW, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH (collectively, "Petitioner") filed a Petition (Paper 3 ("Pet.")), seeking an *inter partes* review of claims 1–16 of U.S. Patent No. 9,750,752 B2 (Ex. 1001, "the '752 patent"). Chugai Seiyaku Kabushiki Kaisha ("Chugai") and Hoffmann-La Roche Inc. (collectively, "Patent Owner") represent that they "have elected to waive their right to a preliminary response and to defend the challenged claims in this proceeding on the merits, should the Board choose to institute a trial." Paper 11, 1.

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). The Federal Circuit has interpreted the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition." *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018).

For the reasons provided below, we determine Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. Thus, we institute an *inter partes* review of claims 1–16 of the '752 patent on all grounds.

A. Related Matters

According to Petitioner, the '752 patent is not currently the subject of any litigation or post-grant proceedings. Pet. 4.

Petitioner explains that the '752 patent claims priority to Application No. 13/390,266, which issued as U.S. Patent No. 8,580,264 ("the '264

patent"). *Id.* Petitioner previously filed IPR2021-01288 and IPR2021-01542, seeking *inter partes review* of the claims of the '264 patent. *Id.* Petitioner also filed IPR2021-01336, seeking an *inter partes* review of the claims of U.S. Patent No. 10,874,677, which is in the same family as the '264 patent. *Id.* We instituted trial in each of those cases.

B. The '752 Patent and Related Background

The '752 patent "relates to identification of a fixed dose of [anti-interleukin-6 receptor] anti IL 6R antibody, e.g. tocilizumab ["TCZ"], which is safe and effective for subcutaneous administration in patients with [interleukin-6] IL 6 mediated disorders," including giant cell arteritis ("GCA"). Ex. 1001, 1:13–23.

IL-6 is a proinflammatory cytokine. *Id.* at 1:53–54. Elevated IL-6 levels had been reported in patients with rheumatoid arthritis ("RA"). *Id.* at 2:4–5; *see also id.* at 2:8–10 ("IL 6 levels correlate with disease activity in RA . . . and clinical efficacy is accompanied by a reduction in serum IL 6 levels.").

IL-6 binds to its soluble and membrane-bound receptors. *Id.* at 2:1–3. TCZ is a recombinant humanized monoclonal antibody that binds to human IL-6R. *Id.* at 2:12–14. In the '752 patent, the amino acid sequences of TCZ light chain and heavy chain comprise SEQ ID NOs. 1 and 2, respectively. *Id.* at 7:1–3; FIGs. 7A, 7B.

Before the '752 patent,

> TCZ 8 mg/kg IV ha[d] been approved in over 70 countries for use in RA, including Japan and Europe. In the United States, TCZ IV (4 mg/kg and 8 mg/kg) has been approved in RA patients who have had an inadequate response to anti-TNF

> agents. Additionally, TCZ was approved for use in Castleman's disease in India and Japan.

Id. at 2:19–24.

GCA is a primary vasculitis involving large and medium sized arteries. *Id.* at 3:32–33. It is an immune-mediated disease and typically affects those over fifty years old. Ex. 1012, 1.[1,2] Takayasu's arteritis ("TA"), a rare variant of GCA, mainly affects young females. *Id.* In addition, polymyalgia rheumatica ("PMR") is closely related to GCA. Ex. 1015,[3] 1. Population-based studies showed that 16–21% of patients with PMR have GCA, and PMR is present in 40–60% of patients with GCA. *Id.* at 2. The clinical connections between PMR and GCA "suggested that they are different manifestations of the same disease process." *Id.*

Prior-art evidence suggests that IL-6 "has a major role in sustaining disease activity" in GCA and PMR. Ex. 1015, 9; *see also* Ex. 1012, 2 ("IL-6 plays an important role in the pathogenesis of GCA. IL-6 levels are elevated in active disease."). In addition, "serum IL-6 levels have been reported to be elevated in patients with TA and to correlate with disease activity." Ex. 1012, 2.

According to the '752 patent, at the time of its priority date, high dose corticosteroids ("CS") were the then-current standard of care for GCA.

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[1] Seitz et al., *Rapid Induction of Remission in Large Vessel Vasculitis by IL-6 Blockade*, 141 Swiss Medical Weekly w13156 (2011) (Ex. 1012, "Seitz"). Seitz is one of the prior-art references asserted by Petitioner.
[2] Unless otherwise noted, we cite to the page numbers provided by the parties.
[3] Salvarini et al., *Polymyalgia Rheumatica and Giant-Cell Arteritis*, 372 Lancet 234–45 (2008) (Ex. 1015).

Ex. 1001, 3:39–40; *see also* Ex. 1012, 1 ("Glucocorticoids (GCs) remain the treatment of choice."); Ex. 1015, 1 (stating GCs were "the cornerstone of treatment" of both PMR and GCA). The '752 patent states, however, "more durable remissions [we]re needed (50% of patients relapse), and steroid sparing treatment options are needed in view of steroid-related complications[]." Ex. 1001, 3:40–43; *see also* Ex. 1015, 1 ("Adverse events of glucocorticosteroids affect more than 50% of patients.").

The '752 patent states that "GCA is an unmet medical need." Ex. 1001, 3:38–39. Acknowledging that prior art, including Seitz, teaches using TCZ to treat GCA, the '752 patent nonetheless points out that in those studies, TCZ was administered intravenously. *Id.* at 3:43–48. According to the '752 patent, its purported invention relates to a method of treating GCA in a patient comprising subcutaneously administering an anti-IL-6R antibody to the patient in an amount effective to treat the GCA. *Id.* at 5:66–6:2.

C. Illustrative Claims

Among the challenged claims, claims 1 and 8 are independent. Claim 1 is illustrative and is reproduced below:

> 1. A method of treating giant cell arteritis (GCA) in a patient comprising administering an anti-IL-6 receptor (IL-6R) antibody to the patient in an amount effective to treat the GCA, wherein the anti-IL-6R antibody is administered subcutaneously as a fixed dose of 162 mg per dose every week or every two weeks, and wherein the anti-IL-6R antibody comprises the light chain and heavy chain amino acid sequences of SEQ ID NOs. 1 and 2, respectively.

Ex. 1001, 63:8–15.

Claim 8 is similar to claim 1, except that, instead of the SEQ ID NOs., it recites TCZ by name. *Id.* at 64:7–11.

D. Asserted Challenge to Patentability

Petitioner asserts the following challenge to patentability:

Claims Challenged	35 U.S.C. §[4]	Reference(s)
1–16	103(a)	Seitz, Ohta 2010[5]
1–16	103(a)	Hagihara,[6] Ohta 2010

Petitioner relies on the Declarations of Thomas M. Zizic, M.D. (Ex. 1002) and Howard L. Levine, Ph.D. (Ex. 1003).

II. ANALYSIS

A. Level of Ordinary Skills

Petitioner argues that an ordinarily skilled artisan "would have been an individual with an M.D. specializing in the treatment of autoimmune and inflammatory disorders and having several years of experience treating patients with such disorders, including GCA and RA, or having several years of experience researching treatments for autoimmune and inflammatory disorders, including GCA and RA." Pet. 16–17 (citing Ex. 1002 ¶ 30). For purposes of this Decision, we adopt Petitioner's definition as it is consistent with the disclosures of the '752 patent and the prior art of record.

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[4] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the '752 patent has an effective filing date before March 16, 2013, the pre-AIA version of § 103 applies.

[5] Ohta et al., *Optimal Dose Prediction by Pharmacokinetic and Biomarker Response of Subcutaneous Tocilizumab Treatment – A Phase I/II Study Evaluating the Safety, Pharmacokinetics and Clinical Response in Patients with Rheumatoid Arthritis*, 62(10) Arthritis & Rheumatism S467–68 (2010) (Ex. 1011, "Ohta 2010").

[6] Hagihara et al., *Tocilizumab Ameliorates Clinical Symptoms in Polymyalgia Rheumatica*, 37 J. of Rheumatol. 1075–76 (2010) (Ex. 1010, "Hagihara").

B. Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b) (2020). Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we find no claim term needs express construction.

C. Alleged Obviousness over Seitz and Ohta 2010

Petitioner asserts that claims 1–16 of the '752 patent would have been obvious over the combination of Seitz and Ohta 2010. Pet. 26–44. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion. We focus our analysis on independent claim 1.

1. Prior-Art Status of Seitz

The '752 patent claims priority to provisional application No. 61/542,615 ("the '615 application"), filed on October 3, 2011, and provisional application No. 61/411,015 ("the '015 application"), filed on November 8, 2010. Ex. 1001, code (60).

According to Petitioner, although the '015 application lists a number of IL-6 mediated disorders that may be treated with TCZ, it does not mention GCA anywhere. Pet. 17–18. Thus, Petitioner argues there is no written description support for the challenged claims in the '015 application, and the claims are not entitled to priority to November 8, 2010, the filing date of the '015 application. *Id.* at 18. Instead, Petitioner contends that the challenged claims are entitled to a priority date no earlier than October 3, 2011, when the applicant, in the '615 application, added GCA to the list of IL-6 mediated disorders that may be treated with TCZ. *Id.* at 19. Based on the current record, we find Petitioner's argument persuasive.

As a result, we agree with Petitioner that Seitz, published on January 17, 2011, qualifies as prior art under 35 U.S.C. § 102(a). *See* Pet. 22.

2. Prior Art Disclosures

a. Seitz

Seitz teaches a study in which five patients with GCA and two with TA were treated with TCZ infusions at 8 mg/kg. Ex. 1012, 1. In Seitz, TCZ was given every other week for the first month and once monthly thereafter. *Id.* All patients in the Seitz study "achieved a rapid and complete clinical response and normalization of the acute phase proteins" and "[n]o relapse and no drug-related side effects were noted." *Id.* Seitz concludes "the data suggest that IL-6 blockade using tocilizumab qualifies as a therapeutic option to induce rapid remission in large vessel vasculitides." *Id.* According to Seitz, "the fact that all patients responded to this IL-6 targeting strategy argues for interesting therapeutic potential, not only for patients with newly

diagnosed GCA but also for patients with relapse of the disease at moderate to high doses of GCs." *Id.* at 3.

b. Ohta 2010

Ohta 2010 teaches an open-label, multicenter clinical study. Ex. 1011, 2. Ohta 2010 states that "[i]t has been shown IL-6 inhibition therapy by tocilizumab is effective in RA, JIA and Castleman's disease." *Id.* Ohta 2010 points out that in those studies, TCZ was administered "by one hour infusion." *Id.* Ohta 2010 "evaluated the safety, pharmacokinetics, biomarker response and clinical response in patients with rheumatoid arthritis using a tocilizumab new formulation for subcutaneous injection" for its "ease of use." *Id.*

Patients received a fixed dose of 162 mg tocilizumab subcutaneously either weekly or every other week for the treatment of RA. *Id.* at 2–3. Ohta 2010 reports that both regimens were "well tolerated" and "associated with good clinical response." *Id.* at 3.

3. Analysis

Petitioner contends that the combination of Seitz and Ohta 2010 teaches each limitation of claim 1. Pet. 36–39. Based on the current record, we agree with Petitioner and adopt Petitioner's analysis as our own. We focus our discussion on the reason to combine the teachings of the prior art and the reasonable expectation of success.

a. Reason to Combine

Petitioner argues "[t]he only difference between the '752 patent claims and the treatment regimen disclosed in Seitz is that the claims are directed to a 162 mg subcutaneous dose every week or every other week to

treat GCA, whereas Seitz reports treating GCA with an intravenous dose of 8 mg/kg once per month." Pet. 24. Petitioner relies on Ohta 2010 for teaching the subcutaneous dosing regimens "as safe and effective for treating RA (i.e., a fixed dose of 162 mg administered subcutaneously weekly or every two weeks)." *Id.* at 25. According to Petitioner, an ordinarily skilled artisan would have been motivated to combine the teachings of Seitz and Ohta 2010 to arrive at the claimed methods for treating GCA. *Id.* at 26–30.

Petitioner argues "subcutaneous administration is generally preferred over intravenous administration," because it "offers significant improvement in quality of life and treatment." *Id.* at 28 (citing Ex. 1002 ¶ 45; Ex. 1016, 11–13; Ex. 1070, 2). Petitioner points out that before the priority date of the '752 patent, Patent Owner Chugai disclosed that subcutaneous was the "preferred" form of TCZ. *Id.* at 29 (citing Ex. 1034,[7] 4). In addition, Petitioner relies on prior art's teaching that "more frequent administration of an equivalent amount of an immunoglobulin by subcutaneous injection instead of by IV advantageously provides more stable serum concentration levels." *Id.* (citing Ex. 1021,[8] 15).

Furthermore, according to Petitioner, the prior art teaches that "a fixed subcutaneous dose was considered preferable to a weight-based dose for monoclonal antibodies in the absence of a specific reason to the contrary, as

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[7] WO2009/041621 A1, published April 2, 2009 (Ex. 1034).
[8] Bonilla, *Pharmacokinetics of Immunoglobulin Administered via Intravenous or Subcutaneous Routes*, 28 Immun. and Allergy Clinics of N. America 803–19 (2008) (Ex. 1021, "Bonilla").

the former provides better compliance, less risk of medical errors, and cost effectiveness." *Id.* (citing Ex. 1002 ¶ 127; Ex. 1022,[9] 7, 18) (quotation marks omitted).

As evidence, Petitioner points to several biologics, including antibodies and other proteins such as etanercept, adalimumab, certolizumab, and golimumab, that were approved for subcutaneous administration using a fixed dose. *Id.* at 10–11, 29.

Based on the current record, we find Petitioner's arguments persuasive. Seitz teaches treating GCA with TCZ at an intravenous dose approved for treating RA. Ex. 1012, 1. In view of the prior art's teaching that subcutaneous injection of TCZ is the preferred route of administration (Ex. 1034, 4), an ordinarily skilled artisan would have had a reason to combine the teachings of Seitz with those of Ohta 2010, which shows subcutaneous injection of TCZ at a fixed dose of 162 mg every week or every two weeks is safe and effective for treating RA (Ex. 1011, 2–3).

In sum, based on this record, we determine that Petitioner has shown sufficiently, for purposes of institution, that an ordinarily skilled artisan would have been motivated to administer TCZ subcutaneously at a fixed dose of 162 mg every week or every two weeks to treat GCA.

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[9] Wang et al., *Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials*, 49 J. of Clin. Pharm. 1012–24 (2009) (Ex. 1022, "Wang").

b. Reasonable Expectation of Success

Petitioner argues that an ordinarily skilled artisan would have reasonably expected the claimed subcutaneous TCZ regimen to successfully treat GCA. Pet. 31.

Petitioner first points to the prior success of the intravenous TCZ regimen treating various other IL-6 mediated disorders, including RA, Castleman's disease, polyarticular-course juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. *Id.* (citing Ex. 1002 ¶¶ 131–137; Ex. 1013, 4; Ex. 1028, 13; Ex. 1041, 1; Ex. 1058, 5; Ex. 1063, 12; Ex. 1066, 1, 4–5).

Petitioner next relies on prior art, including Seitz, for teaching that 8 mg/kg intravenous dose of TCZ, a dose useful for treating RA and other IL-6 mediated disorders, also successfully treated GCA. *Id.* at 31–33 (citing Ex. 1002 ¶ 132; Ex. 1012, 1; Ex. 1037, 2; Ex. 1042, 1). According to Petitioner, "[f]or an average patient weighing 70 kg, an intravenous dosage of 8 mg/kg every month of tocilizumab corresponds to approximately 560 mg/every four weeks, or 140 mg/week." *Id.* at 34. In view of Ohta 2010's teaching that a fixed subcutaneous dose at 162 mg every week was "well tolerated" and "associated with good clinical response" (Ex. 1011, 3), Petitioner argues that "a POSA would have reasonably expected that a 162 mg fixed subcutaneous dosage of tocilizumab every week would successfully treat GCA." *Id.* at 35 (citing Ex. 1002 ¶ 135).

In addition, Petitioner points out that TCZ was approved for treating RA at an intravenous dose of 4 mg/kg every four weeks. *Id.* at 35 (citing Exs. 1041, 1063). According to Petitioner, the prior art also teaches that

when treating GCA, the dose "could be reduced [from 8 mg/kg] to 4 mg/kg every four weeks once clinical symptoms were under control, and that the patient remained in remission after treatment at the lower dose." *Id.* (citing Ex. 1037, 2). "For an average patient weighing 70 kg," Petitioner continues, "a 4 mg/kg every four week dosage of tocilizumab corresponds to a dose of 280 mg/every four weeks, or 140 mg every other week." *Id.* Thus, Petitioner concludes "a POSA would have reasonably expected that a fixed 162 mg subcutaneous dosage of tocilizumab every other week would also successfully treat GCA." *Id.* (citing Ex. 1002 ¶ 137).

Based on the current record and for purposes of this Decision, we find Petitioner's arguments persuasive. The prior art teaches that TCZ regimens that were approved to treat RA would also successfully treat GCA. Because Ohta 2010 teaches TCZ at a 162 mg fixed dose administered subcutaneously weekly or every other week safely and effectively treated RA, an ordinarily skilled artisan would have reasonably expected that the same subcutaneous regimens would also successfully treat GCA.

In sum, for purposes of institution, Petitioner has made a sufficient showing of reasonable expectation of success.

c. Summary

Based on this record, Petitioner has shown a reasonable likelihood that it would prevail on its obviousness challenge of claim 1 over the combination of Seitz and Ohta 2010. Thus, we institute an *inter partes* review as to all challenges raised in the Petition. *See* Patent Trial and Appeal

Board Consolidated Trial Practice Guide ("CTPG") 64 (Nov. 2019)[10] ("The Board will not institute on fewer than all claims or all challenges in a petition.").

D. Alleged Obviousness over Hagihara and Ohta 2010

Petitioner also asserts that the combination of Ohta 2010 and Hagihara renders the challenged claims obvious. *Id.* at 45–54. As discussed above, we institute trial because Petitioner has met its burden in its challenge based on Seitz and Ohta 2010. Thus, we do not address this ground. We, however, encourage the parties to further address the relevant issues of all challenges to fully develop the record during trial.

III. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. We, thus, institute an *inter partes* review of all challenged claims on all asserted grounds.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing could change upon further development of the record during trial.

[10] Available at https://www.uspto.gov/sites/default/files/documents/tpgnovpdf.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted on all challenged claims of the '752 patent based on all the asserted grounds set forth in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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