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Paper 23
Date: January 6, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC, and
FRESENIUS KABI SWISSBIOSIM GMBH
Petitioners,

v.

CHUGAI SEIYAKU KABUSHIKI KAISHA,
Patent Owner.

IPR2021-01025
Patent 10,744,201 B2

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

FRANKLIN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Fresenius Kabi USA, LLC, Fresenius Kabi SwissBioSim GmbH. ("Petitioners") filed a Petition requesting an *inter partes* review of claims 1–15 of U.S. Patent No. 10,744,201 B2 (Ex. 1001, "the '201 patent"). Paper 3 ("Petition" or "Pet."). Chugai Seiyaku Kabushiki Kaisha, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). With our authorization, Ex. 3001, Petitioners filed a Reply to the Preliminary Response to address further issues raised by Patent Owner involving the Board's discretion to deny institution under 35 U.S.C. § 314(a). Paper 13. Patent Owner filed a Sur-reply in response. Paper 14.

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314 (2018). Upon considering the parties' arguments and evidence, we determine that Petitioners have demonstrated a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review.

A. Real Parties-in-Interest

Petitioners identify the real parties-in-interest as Fresenius Kabi USA, LLC, Fresenius Kabi SwissBioSim GmbH, Fresenius Kabi AG, Fresenius Kabi Pharmaceuticals Holding, Inc., Fresenius Kabi Deutschland GmbH and Fresenius SE & Co. KGaA. Pet. 3. Patent Owner identifies itself as the real party-in-interest, noting that it is also called Chugai Pharmaceutical Co., Ltd. Paper 5, 1. Patent Owner further identifies Genentech, Inc., as a real party-in-interest. *Id.*

B. Related Matters

Petitioners assert that the '201 patent is not currently the subject of any litigation or post-grant proceedings. Pet. 3. Petitioners note that they

are seeking *inter partes* review of US Patent No. 7,521,052 ("the '052 patent") to which the '201 patent claims priority. *Id.*, *see* IPR2021-01024, Paper 3 (petition seeking *inter partes review* of the '052 patent).

Patent Owner identifies a number of patent applications and issued patents that relate to US Patent Application No. 15/919,429, which issued as the '201 patent. Paper 5, 1–3. Patent Owner also notes that the '052 patent is the subject of IPR2021-01024. *Id.* at 2.

C. The '201 Patent

The '201 patent relates to methods for treating interleukin-6 (IL-6) related diseases with a combination of an IL-6 antagonist and immunosuppressants. Ex. 1001, 1:25–29. IL-6 is a multifunctional cytokine which affects functions of various cells, including inducing maturation of T lymphocyte lineage cells. *Id.* at 1:38–42. The IL-6 receptor, a ligand binding protein, is one manner by which IL-6 transmits its biological activity. *Id.* at 1:44–47.

The use of anti-IL-6 receptor antibodies, such as humanized anti-IL-6R antibodies and chimeric anti-IL-6R antibodies, to prevent or treat rheumatoid arthritis and other diseases attributed to IL-6 production has been known in the art. *Id.* at 1:53–2:17. The Specification describes the specific preferable anti-IL-6R antibody for the present invention is, for example, humanized PM-1 antibody. *Id.* at 2:46–53.

According to the Specification, it was not previously known that: (a) synergistic effects can be obtained when treating IL-6 related diseases by using a combination of an anti-IL-6R antibody with immunosuppressants, such as methotrexate (MTX); (b) an immunosuppressant, such as MTX, can reduce or prevent allergic reactions when treating rheumatoid arthritis with an anti-IL-6R antibody; and (c) high dose anti-IL-6R antibody treatment of rheumatoid arthritis can reduce or prevent allergic reactions associated with the use of an IL-6 antagonist for the treatment of IL-6 related diseases, including rheumatoid arthritis. *Id.* at 2:17–26.

D. Illustrative Claim

Petitioners challenge claims 1–15 of the '201 patent. The independent claims challenged are claims 1, 6, and 11. For purposes of this Decision on Institution, independent claim 1, set forth below, is illustrative of the claimed subject matter.

> 1. A method for increasing the likelihood of achieving an America College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone, comprising administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously, and (ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg.

Ex. 1001, 22:30–39.

E. Asserted Grounds of Unpatentability

Petitioners assert that claims 1–15 are unpatentable on the following two grounds:

Claims Challenged	32 U.S.C. §[1]	Reference(s)
1–15	102(b)	Nishimoto[2]
1–15	103(a)	Nishimoto and Weinblatt[3]

Petitioners also rely upon the Declaration of Thomas M. Zizic, M.D. (Ex. 1002).

II. ANALYSIS

A. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 18–34. We have discretion to deny review when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In that respect, § 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office.[4] *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH,* IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

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[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the '201 patent issued has an effective filing date prior to that date, the pre-AIA version of §§ 102 and 103 applies.

[2] Nishimoto, *Anti-IL-6 Receptor Antibodies, Usefulness and Issues in Rheumatoid Arthritis*, THERAPEUTICS 36(12):1264-1267 (2002) (certified English Translation) (Ex. 1006, "Nishimoto").

[3] Weinblatt et al., *Adalimumab, a Fully Human Anti-Tumor Necrosis Factor α Monoclonal Antibody, for the Treatment of Rheumatoid Arthritis in Patients Taking Concomitant Methotrexate*, ARTHRITIS & RHEUMATISM 48(1):35–45 (2003) (Ex. 1008, "Weinblatt").

[4] The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a); *Advanced Bionics*, Paper 6 at 7 n.7.

In evaluating matters under § 325(d), the Board uses the following two-part framework: (1) determining 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; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics* at 8.

In applying the two-part framework, we consider several nonexclusive factors, including:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;

(e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*").

Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics* at 10. Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.* "[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9.

1. Part One of the § 325(d) Analysis

We first consider whether Petitioners assert the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8.

a) Petitioners' Anticipation Ground

Patent Owner asserts that Petitioners' anticipation ground relies on the same art and arguments that were already considered by the Examiner during prosecution of the '201 patent. Prelim. Resp. 19. In particular, Patent Owner asserts that Petitioners' anticipation challenge relies on two disclosures in Nishimoto, i.e., (1) a recommended monotherapy dosage of 8mg/kg of body weight every 4 weeks for MRA, and (2) a phase II study of the coadministration of MRA with MTX that was currently underway. *Id.* (citing Ex. 1006, 5). Referring to the Petition, Patent Owner asserts that Petitioners rely on those disclosures in Nishimoto to contend that the prior art disclosed combining MRA and MTX in the manner required by the challenged claims. *Id.* (citing Pet. 2). According to Patent Owner, the

Examiner considered Nishimoto, as indicated on the IDS. *Id.* at 20 (citing Ex. 1004, 172 (A285)). Additionally, Patent Owner asserts that the Examiner considered, at length, a second reference, Okuda, which discloses the same recommended MRA dosage and the same phase II study of the co-administration of MRA with MTX that Petitioners rely upon Nishimoto as disclosing. *Id.* at 20–21 (citing Ex. 2020,[5] 20–22; Ex. 1004, 173–174 (A302)).

Petitioners assert that, although Nishimoto was disclosed on the IDS during prosecution, it was never substantively evaluated by the Examiner. Pet. 59–60. Additionally, Petitioners essentially assert that Okuda is not substantially similar to Nishimoto because Okuda does not disclose either the claimed MRA dosing regimen of 8 mg/kg every four weeks, or the claimed MTX dosing regimen of 10–25 mg every week. *Id.* at 60–61. According to Petitioners, Nishimoto expressly discloses the claimed MRA regimen and implicitly discloses the claimed methotrexate regimen. *Id.* at 61.

Based on our review of the record, we find that Patent Owner has shown persuasively that the Examiner considered the same or substantially the same art that Petitioners rely upon for its anticipation challenge. Specifically, Patent Owner demonstrates that Nishimoto and Okuda were presented to the Office, as noted in the IDS. The Examiner discussed a Nishimoto reference in an obviousness rejection, finding that reference discloses administering MRA at a dose of 8mg/kg every 4 weeks, and is silent with respect to administering MTX with MRA and the dosage of

[5] Okuda, *Anti-IL-6 receptor antibody MRA*, Chugai Pharm. Co., Ltd., Project Promotion Dep't (2003) (A302) (Ex. 2020, "Okuda").

MTX. Ex. 1004, 153. It is unclear if that Nishimoto reference is the one relied upon by Petitioners, as a number of Nishimoto references were included in the IDS, and the specific Nishimoto reference discussed by the Examiner is not clearly identified. In any event, Patent Owner has demonstrated that the Examiner also considered and discussed Okuda in an obviousness rejection, finding that it disclosed treating RA by administering 8mg/kg of MRA every 2 weeks, and administering MTX in combination with MRA, without disclosing the dosage of MTX. Prelim. Resp. 20 –21 (citing Ex. 1004, 156). Additionally, Patent Owner has argued persuasively that Okuda also teaches administering 8mg/kg of MRA every 4 weeks, similarly to Nishimoto. *Id.* at 21 (citing Ex. 2020, 20–22). Those disclosures in Okuda are the same disclosures in Nishimoto that the Petitioners rely upon for their anticipation ground.

Thus, we determine that the same or substantially the same prior art relied upon in the Petition for the anticipation ground was previously presented to the Office.

b) Petitioners' Obviousness Ground

Patent Owner asserts that Petitioners' obviousness ground, based on a combination of Nishimoto and Weinblatt, relies on the same art and arguments that were already considered by the Examiner during prosecution of the '201 patent. Prelim. Resp. 27. In particular, Patent Owner asserts that, like Nishimoto, discussed above, Weinblatt was also cited in an IDS and considered during prosecution. *Id.* (citing Ex. 1004, 175 (A330)).

Additionally, Patent Owner asserts that the Examiner considered, at some length, substantially identical art, i.e., the combination of Okuda and

Maini.[6] *Id.* at 27–28. Patent Owner asserts here again that Nishimoto and Okuda contain identical disclosures of the 8 mg/kg dosing for MRA every four weeks and the European phase II study of the combination of MRA and MTX to treat RA, relied upon by Petitioners. *Id.* at 28.

Patent Owner asserts that Maini contains the same disclosures in Weinblatt relied upon in Petitioners' obviousness challenge because Maini similarly discloses a clinical trial for the treatment of RA comprising the administration of MTX with an antibody targeting TNF-α and concludes that such combination therapy was "effective and well tolerated." *Id.* (citing Ex. 1015, 1). Patent Owner acknowledges that Maini disclosed using a lower MTX dose, i.e., 7.5 mg per week, than disclosed in Weinblatt and recited by the challenged claims, i.e., 10–25 mg per week. *Id.* at 28–29. According to Patent Owner, that difference is nominal and should not matter because the Examiner rejected the claims, based in part on, finding that a skilled artisan would have found it obvious to increase the MTX dose used in Maini to, e.g., 10 to 25 mg, to "increase the clinical efficacy of MRA." *Id.* at 29 (citing Ex. 1004, 157–158). Patent Owner notes that it did not challenge the rejection based on that finding, but instead traversed the rejection by successfully arguing that data from the trial involving TNF-α inhibitor was not predictive of biologics like MRA. *Id.* (citing Ex. 1004, 771).

Petitioners repeat their assertion that Nishimoto was not substantively evaluated by the Examiner and Okuda is not substantially the same as Nishimoto. Pet. 61. Petitioners acknowledge that Weinblatt was disclosed

[6] Maini et al., *Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis*, ARTHRITIS & RHEUMATISM 41(9):1552-63 (1998) (Ex. 1015, "Maini").

to the Examiner, but assert that it was not the subject of any rejection. *Id.* As for Maini, Petitioners assert only that it disclosed administering a different, lower dose of MTX than disclosed in Weinblatt and that the Examiner relied on Maini's dosing as a starting point for optimization to the claimed dosing range of MTX. *Id.* at 61.

Based on our review of the record, we find that Patent Owner has shown persuasively that the Examiner considered the same or substantially the same art that Petitioners rely upon for its obviousness challenge. As explained above, we have found that Patent Owner demonstrates that the Examiner considered the same or substantially the same prior art as Nishimoto. Regarding Weinblatt, we find that Patent Owner has shown that the Examiner considered that reference, as it is cited in an IDS, and further that the Examiner considered and based an obviousness rejection, in part, on substantially the same art, i.e., Maini. Petitioners and Patent Owner both acknowledge a difference in the dosing of MTX in those two references, however, Patent Owner has argued persuasively that such difference is nominal in view of the Examiner's finding that it would have been obvious to optimize Maini's MTX dosage to 10–25 mg, as disclosed in Weinblatt and recited in the challenged claims.

Thus, we determine that the same or substantially the same prior art relied upon in the Petition for the obviousness ground was previously presented to the Office.

Because we have determined that the same or substantially the same art or arguments raised in the anticipation and obviousness challenges in the Petition were presented previously to the Office, we proceed to step two of the *Advanced Bionics* framework.

2. Part Two of the § 325(d) Analysis

a) Petitioners' Anticipation Ground

The Examiner did not reject the challenged claims based on anticipation. Petitioners assert that the Examiner erred by failing to appreciate that Nishimoto anticipates the challenged claims. Pet. 60–61. According to Petitioners, Nishimoto expressly discloses administering MTX with MRA, expressly discloses the claimed MRA regimen of 8mg/kg every four weeks, and implicitly discloses the dosage of MTX. *Id.* We disagree with Petitioners. In particular, as explained below, Petitioners have not shown persuasively that Nishimoto implicitly discloses administering a dosage of 10–25 mg, as recited in the challenged claims. Nishimoto does not describe or discuss the dosage of MTX used in the European phase II study. Nor does Nishimoto confirm that its recommended MRA dosage was used in that ongoing phase II study.

Accordingly, we determine that Petitioners have not demonstrated that the Office erred in a manner material regarding the patentability of the challenged claims by not rejecting the claims as anticipated by Nishimoto.

b) Petitioners' Obviousness Ground

Petitioners assert that Weinblatt was not the subject of any rejection and that the Examiner did not identify any reference as disclosing the 10–25 mg once weekly dosage for MTX that Weinblatt discloses. Pet. 61–62. Petitioners assert that the Examiner allowed the challenged claims in view of alleged unexpected results that administering MRA in combination with MTX increased the likelihood of an ACR70 response as compared to methotrexate alone. *Id.* at 61 (citing Ex. 1004, 2094–2095). In that regard, Petitioners assert that additional evidence and facts presented in the Petition warrant reconsideration of the asserted prior art. *Id.* at 62. Specifically,

Petitioners assert that the Examiner was without the benefit of Nishimoto Abstract B, Ex. 1017,[7] which Petitioners contend discloses that "administering MRA in accordance with the claimed regimen provided an ACR70 response in a substantial percentage of patients," which would have suggested the results that the Examiner considered to be unexpected. *Id.*

Patent Owner argues that Okuda discloses the same phase II clinical trial results detailed Nishimoto Abstract B. Prelim. Resp. 33. According to Patent Owner, the Examiner refused to rely on those trial results to reject Patent Owner's claims of unexpected properties. *Id.* Patent Owner contends that the disclosed trial results in Nishimoto Abstract B and Okuda are not relevant to the claimed combination therapy because they are based on administering MRA by itself, and not in combination with MTX. *Id.* (citing Ex. 1017, 2). Further, Patent Owner asserts that, if anything, the results in Nishimoto Abstract B confirm the alleged unexpected properties of the claimed combination therapy. *Id.* at 33–34. In support of that contention, Patent Owner asserts:

> The abstract discloses that 4 mg/kg MRA was just as effective (if not more) than 8 mg/kg MRA in achieving ACR 70 responses (achieving such responses in 20.4 percent of patients versus 16.4 percent, respectively). *Id.* Yet Patent Owner discovered that combining 4 mg/kg MRA with MTX made patients, if anything, *less likely* to achieve an ACR 70 response compared to administration of MTX alone, while combining 8 mg/kg MRA with MTX made patients *far more likely* to achieve such a response.

[7] Nishimoto et al., *A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Humanized Anti-interleukin-6 (IL-6) Receptor Monoclonal Antibody (MRA) in Rheumatoid Arthritis (RA)*, ARTHRITIS & RHEUMATISM 46(9 Supplement):S559 (2002) (Ex. 1017, "Nishimoto Abstract B").

Id. at 34 (citing Ex. 1001, Table 1).

Based on our review of the record, we determine that additional evidence and facts presented in the Petition warrant reconsideration of the asserted prior art. Specifically, we agree with Petitioners that Nishimoto Abstract B provides such evidence. Although Patent Owner asserts that Okuda discloses the same test results as Nishomoto Abstract B, Patent Owner has not supported its contention, with any citation in the record, that the Examiner considered those results and refused to rely on them. *See* Prelim. Resp. 33.

Moreover, we are not persuaded that the disclosed trial results in Nishimoto Abstract B and Okuda are not relevant to the claimed combination therapy because they are based on administering MRA as monotherapy and not in combination with MTX. *See id.* (citing Ex. 1017, 2). Further, we are not persuaded that the results in Nishimoto Abstract B confirm Patent Owner's alleged unexpected properties of the claimed combination therapy, insofar Patent Owner asserts that those results demonstrate that "combining 8 mg/kg MRA with MTX made patients *far more likely* to achieve such a response." *See id.* at 34. In that regard, Petitioners have supported the Petition with the declaration of Dr. Zizic, who provides testimony contradicting those assertions by Patent Owner and the findings of the Examiner that the prior art fails to teach or suggest the alleged unexpected results that administering MRA in combination with MTX increases the likelihood of an ACR70 response as compared to methotrexate alone. Ex. 1004, 2094–2095. Dr. Zizic's testimony, unrebutted on the current record, describes the MRA trial disclosed in Nishimoto Abstract B and provides his opinion that, based on those results, a POSA would have reasonably expected that administering the combined

MRA and MTX regimen would increase the likelihood of achieving an ACR70 response as compared to treatment with MTX alone. *See, e.g.*, Ex. 1002 ¶¶ 38, 80–83, 158. Thus, we also find that Dr. Zizic's testimony regarding Patent Owner's alleged unexpected results and how a POSA would have viewed the results disclosed in Nishimoto Abstract B, warrants reconsideration of the asserted prior art. Based on the preliminary record here, we determine that it was error to allow the claims on the basis of the asserted unexpected results.

Accordingly, we determine that Petitioners have demonstrated that additional evidence and facts presented in the Petition to support the obviousness challenge of claims 1–15 are sufficient to warrant reconsideration of the asserted prior art and patentability of those challenged claims. On balance, this determination outweighs the outcome of our analysis of the anticipation ground.

3. Conclusion

Based on the foregoing analysis, we decline to exercise our discretion to deny the Petition under § 325(d).

B. Discretion to Institute under 35 U.S.C. § 314(a)

Institution of *inter partes* review is discretionary:

> The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that 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). This language provides the Director with discretion to deny institution of a petition. *See Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 273 (2016) ("[T]he agency's decision to deny a petition is a matter

committed to the Patent Office's discretion."); Patent Trial and Appeal Board Consolidated Trial Practice Guide ("CTPG") at 55 (November 2019), *available at* https://www.uspto.gov/TrialPracticeGuideConsolidated. The Director has delegated his authority under § 324(a) to the Board. 37 C.F.R. § 42.4(a) ("The Board institutes the trial on behalf of the Director.").

The Leahy-Smith America Invents Act was "designed to establish a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs." H.R. Rep. No. 112−98, pt. 1, at 40 (2011), 2011 U.S.C.C.A.N. 67, 69 (reviews were meant to be "quick and cost effective alternatives to litigation"); *see also* S. Rep. No. 110−259, at 20 (2008); CTPG 56. The Board recognized these goals, but also "recognize[d] the potential for abuse of the review process by repeated attacks on patents." *General Plastic Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 16−17 (PTAB Sept. 6, 2017) (precedential).

In *NHK Spring Co. v. Intri-Plex Technologies, Inc.*, IPR2018-00752, Paper 8 (PTAB Sept. 12, 2018) (precedential), the Board determined that the advanced state of a parallel proceeding is an additional factor weighing in favor of denying institution under 35 U.S.C. § 314(a). *Id.* at 19–20. In *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019 ("*Fintiv*"), Paper 11 (PTAB Mar. 20, 2020) (precedential), the Board articulated a list of factors that we consider in determining whether to exercise discretion to deny institution based on an advanced stage of a parallel proceeding:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
>
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;

> 3. investment in the parallel proceeding by the court and the parties;
>
> 4. overlap between issues raised in the petition and in the parallel proceeding;
>
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Fintiv, Paper 11, 5–6. "These factors relate to whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding." *Id.* at 6. In evaluating these factors, we take "a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* (citing CTPG 58).

Patent Owner asserts that we should decline to institute under *NHK Spring/Fintiv*. Prelim. Resp. 54–57. However, as Patent Owner admits, there is no pending litigation between the parties. *Id.* at 54. Nevertheless, Patent Owner urges that we could deny institution under *Fintiv* "because of the near-certainty of parallel, duplicative proceedings." *Id.* In particular, Patent Owner asserts that "[t]he absence of any pending litigation between the parties does not mean they do not have a dispute." *Id.* According to Patent Owner, "[t]he statutory scheme governing biosimilars like Petitioners' copy of Actemra® [Patent Owner's product comprising tocilizumab, i.e., MRA] all but guarantees patent litigation between Petitioners and Patent Owner." *Id.* Specifically, Patent Owner contends,

> Once Petitioners seek approval from FDA for their copy of Actemra®, the parties' patent disputes are likely to explode into full-blown district court litigation, including, potentially, preliminary injunction proceedings on patents like the '052 patent. By refusing to hold off serving its notice of intent to

> market until this proceeding concludes, Petitioners virtually guarantee that the trial court and the Board will be addressing the '052 patent in parallel.

Id. at 55.

As noted above, the Board's discretionary denial analysis, set forth in *NHK Spring/Fintiv* pertains to matters before us that involve a parallel proceeding—typically an ongoing lawsuit in court. Here, Patent Owner has identified, at best, a hypothetical future district court litigation. Because Patent Owner has not identified an existing parallel proceeding to consider, we decline Patent Owner's invitation for us to consider discretionary denial of institution under *Fintiv*.

C. Person of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioners assert that a person of ordinary skill in the art (POSA) at the time of the invention "would have had been an individual with an M.D. specializing in the treatment of autoimmune disorders and having several years of experience treating patients with such disorders, including rheumatoid arthritis, or having several years of experience researching treatments for autoimmune disorders, including rheumatoid arthritis." Pet. 16 (citing Ex. 1002 ¶ 30). At this stage in the proceeding, Patent Owner does not dispute Petitioners' description of the level of ordinary skill in the art. Prelim. Resp. 17 n.3.

Because Petitioners' uncontested definition of one of ordinary skill in the art is reasonable and consistent with the '201 patent and the prior art of record, we adopt Petitioners' definition for purposes of this Decision.

D. Claim Construction

The Board applies 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. § 100(b) (2019). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioners assert that all the preambles of the challenged claims are limiting and that the claims should be given their ordinary and customary meaning, as understood by a POSA as of the invention date of the '201 patent. Pet. 2 n.4, 17. Patent Owner asserts that it agrees with both of those assertions by Petitioners, for purposes of this proceeding. Prelim. Resp. 16–17.

Based upon our review of the current record, we determine that no claim terms require express construction for purposes of deciding whether to institute an *inter partes* review of the challenged claims. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed.

Cir. 2017) (Only those terms that are in controversy need be construed, "and only to the extent necessary to resolve the controversy.").

E. Anticipation by Nishimoto

Petitioners assert that Nishimoto anticipates claim 1. Pet. 17–31. Patent Owner disagrees. Prelim. Resp. 35–40.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Schering Corp. v. Geneva Pharms*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

1. Nishimoto

Nishimoto is a journal article that discusses the role of IL-6 in the pathology of rheumatoid arthritis and the usefulness of anti-IL-6 receptor antibodies as a novel treatment for the disease. Ex. 1006, 3–4.[8] Nishimoto explains that, prior to clinical studies, MRA was used at Osaka University from 1995 to 1997 "to treat patients with intractable rheumatism who were resistant to anti-rheumatics including methotrexate." *Id.* at 4. That MRA treatment was administered by drip infusion of 50 mg twice a week or 100 mg once a week. *Id.* Nishimoto discloses that such MRA treatment "not only caused a dramatic normalization of inflammatory markers . . . but also rapidly improved joint symptoms and general symptoms." *Id.*

According to Nishimoto, based on the effectiveness of MRA treatment observed in those patients as Osaka University, phase I clinical studies were initiated in 1997 in healthy individuals in Japan and in

[8] We refer to page numbers assigned to Exhibit 1006 by Petitioners.

rheumatism patients in the United Kingdom. *Id.* Nishimoto describes the phase I study in the United Kingdom as "a double-blind study by single administration of 0.1, 1.5 or 10 mg/kg of body weight of MRA or a placebo." *Id.* Nishimoto states that "[o]n day 2 after MRA administration in the 5 mg/kg dose group, efficacy was observed with about 56% of patients satisfying the American College of Rheumatology Criteria ACR 20." *Id.*

Nishimoto also describes a phase I/II study of MRA in rheumatoid arthritis patients in Japan that began in 1999. *Id.* In that open-label study, patients were administered 2, 4, or 8 mg/kg body weight of MRA every two weeks by intravenous drip infusion. *Id.* Nishimoto reports that "[t]he percentage achieving ACR 20 was 60% in week 6 and 80% in month 6, and the percentage achieving ACR 50 was 6.7% in week 6 and 40% in month 6, confirming excellent treatment efficacy." *Id.* at 4. Nishimoto explains that, based on these study results, "a placebo-controlled late phase II study was performed in Japan and on the basis of its results, treatment with 8 mg/kg of body weight of MRA every 4 weeks was recommended." *Id.*

Additionally, Nishimoto mentions that "a phase II study of coadministration with methotrexate is currently underway in several European countries." *Id.*

2. Discussion

Petitioners identify the disclosures in Nishimoto that Petitioners assert disclose each limitation of the challenged claims. Pet. 24–29. In particular, Petitioners assert that "Nishimoto discloses a clinical study of MRA in combination with MTX, involving administering MRA according to the recommended regimen, i.e., 8 mg/kg administered intravenously every four weeks." *Id.* at 19 (citing Ex. 1002 ¶ 124), *see also id.* at 25 (citing Ex. 1002 121–125). Petitioners support that assertion by referring to two disclosures

in Nishimoto: first, that based on earlier clinical trial results, the recommended dosage regimen of MRA for treating RA is 8mg/kg administered intravenously every four weeks; and second, that there is an ongoing clinical study in which MRA is co-administered with methotrexate to treat RA. *Id.* (citing Ex. 1006, 5). Nishimoto describes that ongoing study by stating only that "a phase II study of coadministration [of MRA] with methotrexate is currently underway in several European countries." Ex. 1006, 5.

We focus also on Petitioners' contentions regarding the dosage range of methotrexate recited by the challenged claims, i.e., 10–25 mg once per week. Petitioners assert that a POSA would have known that methotrexate was administered at a dose of between 7.5 mg and 25 mg once weekly to treat RA. Pet. 19–20 (citing Ex. 1002 ¶ 126–128). Petitioners assert also that a POSA would have known that same dosage range was used for clinical trials involving methotrexate in combination with other RA drugs. *Id.* at 20 (citing Ex. 1002 ¶ 127). Additionally, Petitioners assert that a POSA would have known that the dosage of methotrexate would be titrated up from 7.5 mg to at least 10 mg if a patient was not responsive to the low dose. *Id.* (citing Ex. 1002 ¶ 128). Based on those assertions, Petitioners contend that "a POSA would therefore have understood that the reference in Nishimoto to 'a phase II study of coadministration with methotrexate' necessarily means that some patients would be treated with a dosage from 10 mg to 25 mg of methotrexate." *Id.*

Patent Owner argues that Petitioners have not shown that Nishimoto anticipates the challenged claims because, among other things, Nishimoto does not disclose the MRA or MTX dosing used in the phase II study involving the coadministration of those two drugs that was currently

underway in several European countries. Prelim. Resp. 35. We agree. Nishimoto provides no details about the clinical course of the combination therapy in the European phase II study beyond the fact that it involved coadministration of MRA and MTX. *See* Ex. 1006, 5. As Patent Owner asserts, it is unclear whether the MRA dosage amount disclosed by Nishimoto was known, much less employed, by those conducting the phase II study in Europe. *See* Prelim. Resp. 35–36. Additionally, there is no indication in Nishimoto that the phase II study employed a MTX dosage amount used in conventional treatment. Based on those deficiencies, we determine that Petitioners have not shown sufficiently for institution that Nishimoto discloses each limitation of the challenged claims.

Accordingly, based on the information presented at this stage of the proceeding, we determine that Petitioners have not demonstrated a reasonable likelihood that it would prevail in showing that claims 1–15 are anticipated by Nishimoto.

F. Obviousness over Nishimoto and Weinblatt

Petitioners assert that claim 1 would have been obvious over the combined teachings of Nishimoto and Weinblatt. Pet. 31–58. Patent Owner disagrees. Prelim. Resp. 40–54. We incorporate our description of Nishimoto in Section II.E.1. here.

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

"An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)). "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc.,* 821 F.3d at 1367. A reasonable expectation of success "does not require absolute predictability of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988)).

1. Weinblatt

Weinblatt is a journal article describing a 24-week, randomized double-blind, placebo-controlled trial of adalimumab with concomitant MTX therapy performed in the United States and Canada, i.e., the "ARMADA" trial. Ex. 1008, 1–2.[9]

As background, Weinblatt explains that, although methotrexate had become the treatment of choice for RA, many patients continue to have some degree of disease activity despite receiving therapeutic doses of that drug. *Id.* at 2. "To enhance the clinical response, MTX is frequently combined with one or more other traditional disease-modifying antirheumatic drugs (DMARDs)." *Id.* Specifically, Weinblatt describes "the development of biologic DMARDs that bind to and inactivate the

[9] We refer to page numbers assigned to Exhibit 1008 by Petitioners.

proinflammatory cytokine tumor necrosis factor α (TNFα)." *Id.* Weinblatt notes that there are two TNFα blockers that are commercially available, infliximab, a chimeric monoclonal antibody to TNFα, and etanercept, a recombinant human TNF receptor fusion protein. *Id.*

The focus of the current study discussed by Weinblatt was to evaluate the efficacy and safety of the first fully human monoclonal tumor necrosis factor α antibody, adalimumab. *Id.* at 1–2. In the study, patients with active rheumatoid arthritis, despite treatment with MTX, were randomly assigned to receive injections of 20 mg, 40 mg, or 80 mg of adalimumab subcutaneously, or placebo, every other week "while continuing to take their long-term stable dosage of MTX," i.e., 12.5–25 mg, or 10 mg if intolerant to higher doses). *Id.* at 1–2.

Weinblatt reports that "the addition of adalimumab (subcutaneously every other week) to the MTX (orally or subcutaneously every week) therapy achieved significant, rapid, and sustained responses." *Id.* at 9. In particular, "[t]he 20-mg, 40-mg and 80-mg adalimumab dosage plus MTX groups achieved statistically superior ACR20 and ACR50 response rates compared with placebo plus MTX group." *Id.* According to Weinblatt, "[t]aken together, these findings indicate that addition of adalimumab to MTX therapy substantially and rapidly improves standard measures of disease activity, including signs and symptoms, the acute-phase response, functional parameters, fatigue scales, and quality of life scores in RA patients not adequately responding to therapy with MTX alone." *Id.*

2. Discussion

a) Motivation and Reasonable Expectation of Success

The parties dispute whether a POSA would have been motivated by the combined teachings of Nishimoto and Weinblatt to administer the

claimed MRA-MTX regimen to a RA patient, and would have had a reasonable expectation of success in doing so. As in its anticipation challenge, Petitioners here again rely on Nishimoto's disclosure that "a phase II study of the coadministration [of MRA] with methotrexate is currently underway in several European countries" and Nishimoto's recommended treatment of RA with 8mg/kg of body weight of MRA every four weeks. Pet. 34 (citing Ex. 1006, 5). Petitioners assert that "[e]ven if Nishimoto did not expressly disclose the amounts or frequencies of administration of the combined regimen, selection of theses parameters [as claimed] would have been obvious." *Id.* at 35–36.

Specifically, regarding MRA, Petitioners assert that a POSA would have been motivated to use that recommended dosing that Nishimoto discloses for MRA, which is the same dosage recited in claim 1, in a MRA-MTX combination therapy because it was known that "DMARDs are generally administered in the same dosage amount and frequency when given in combination with methotrexate as they are when given alone, and a POSA would have expected this to be the case for MRA." *Id.* at 36 (citing Ex. 1002 ¶150).

Regarding methotrexate, Petitioners assert that a POSA would have been motivated to maintain the patient's existing methotrexate dosing regimen as disclosed in Weinblatt, which was a common practice when supplementing methotrexate with a new drug. *Id.* (citing Ex. 1008, 2; Ex. 1002 ¶ 154). In particular, Petitioners point to Weinblatt's teaching that typical inadequate methotrexate responders receive oral doses between 10 and 25 mg once per week, which is the same dosage range recited in claim 1. *Id.* (citing Ex. 1008, 2); Ex. 1002 ¶¶ 149–154.

Petitioners contend that a skilled artisan would have had a reasonable expectation that the combined regimen would successfully treat RA "because both MRA and methotrexate were known to be individually effective for treating RA, and combining methotrexate with other RA drugs was known to 'improve disease control.'" *Id.* at 37 (citing Ex. 1002 ¶ 155). In other words, Petitioners assert that a POSA would have had a reasonable expectation that a combination of known efficacious regimens of MRA and methotrexate could be used to treat a patient with RA. *Id.* at 37–38 (citing *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1074 (Fed. Cir. 2019) ("[T]he record shows that a PHOSITA would have a reasonable expectation of success in combining abiraterone and prednisone because they were both together and individually considered promising prostate cancer treatments at the time.").

Additionally, Petitioners contend that a skilled artisan would have been motivated, with a reasonable expectation of success, to achieve the claimed results of, e.g., increasing the likelihood of an ACR70 response and achieving an ACR70 response, which Petitioners also assert are "the 'natural result' of following the claimed method steps, and hence inherent in the method itself." *Id.* at 31, 38–40 (citing Ex. 1002 ¶¶ 156–158; Ex. 1017, 2). In particular, Petitioners contend that achieving an ACR70 response was known to be desirable for an RA regimen and treatment with MRA was known to provide such a response in some patients resistant to DMARD therapy, even without coadministration of methotrexate. *Id.* at 39–40. According to Petitioners, a POSA would have thus been motivated to increase the likelihood of achieving an ACR70 response, compared to administration of methotrexate alone, by combining methotrexate with

MRA, and would have had a reasonable expectation of success in doing so. *Id.* at 40.

Patent Owner responds that "Petitioners' references establish only that the POSA might have been motivated to find a successful combination of [MRA] and MTX." Prelim. Resp. 47. However, Patent Owner asserts that, "[i]n light of the field's limited understanding of the pathology of RA, the mixed and unpredictable experience with prior MTX combination treatments, and the novelty and complexity of anti-cytokine treatments for RA, Petitioners have not shown a reasonable likelihood of meeting [their] burden" of proving that a skilled artisan would have reasonably expected success that the combination of MRA and MTX would be more effective in treating RA than MTX alone, as required by the challenged claims. *Id.* at 40–47 (arguing that the track record of treating RA with MTX in combination with another compound was "replete with mixed and unpredictable results").

Patent Owner argues also that a skilled artisan would not have been motivated to administer 8 mg/kg MRA in combination with methotrexate because "with combination treatments for RA 'the individual agents tended to be prescribed at the minimal effective therapeutic dosage'" based on potential toxicity concerns. Prelim. Resp. 47–48 (quoting Ex. 2010,[10] 4–5). According to Patent Owner, "[c]onsistent with settled practice, therefore, the POSA contemplating a novel combination of MRA with MTX would have selected the 'minimal effective therapeutic dosage'" of MRA, which Patent Owner contends was understood to be 4 mg/kg. *Id.*

[10] Felson et al., *The Efficacy and Toxicity of Combination Therapy in Rheumatoid Arthritis*, ARTHRITIS & RHEUMATISM, 37(10):1487–1491 (1994) (Ex. 2010, "Felson").

Further, Patent Owner argues that the POSA would not have had a reasonable expectation of success in combining a higher dose of MRA with MTX because little was known about the mechanism of action of each drug, or the potential toxicity involved with combining them. *Id.* at 49–50.

Having considered the parties' arguments and evidence, at this stage in the proceeding, we conclude that Petitioners have shown persuasively that, in view of Nishimoto and Weinblatt, a POSA would have had a reason to administer 8 mg/kg of MRA every four weeks, and a weekly dose of 10–25 mg of MTX, as a combination therapy for an RA patient to increase the likelihood of achieving an ACR 70 response, as compared to treating the patient with MTX alone, with a reasonable expectation of success. To begin, Petitioners have provided ample support for its contention that Nishimoto alone, and in view of Weinblatt, would have provided sufficient motivation for a POSA to combine MRA and MTX to treat RA. *See* Pet. 31–41. Indeed, Patent Owner does not challenge Petitioners' contention in that regard, at this stage in the proceeding. *See* Prelim. Resp. 47 (acknowledging the motivation provided by Petitioners' cited references to combine MRA and MTX).

As for the dosage of MRA, Petitioners have shown that Nishimoto discloses a recommended dosage of MRA, i.e., 8 mg/kg of body weight every 4 weeks, to treat RA. Pet. 35–36, 40–41; Ex. 1006, 5. As Petitioners assert, Nishimoto explains that such dose was recommended based on study results that confirmed such treatment provided excellent efficacy. *See* Pet. 36; Ex. 1006, 4–5. Based on those disclosures of Nishimoto, we find that Petitioners have shown sufficiently, on the current record, that Nishimoto teaches or suggests the precise amount of MRA to treat RA, as required by claim 1.

We have considered Patent Owner's argument that a skilled artisan would not have been motivated to administer 8 mg/kg MRA in combination with methotrexate. However, we do not find that assertion adequately supported on the current record insofar as it Patent Owner relies on Felson to assert that "with combination treatments for RA 'the individual agents tended to be prescribed at the minimal effective therapeutic dosage'" based on potential toxicity concerns. Prelim. Resp. 47–48 (quoting Ex. 2010, 4–5). That characterization by Felson applied only to the trials reported in that journal article and does not appear to be a statement of any general practice in the field. *See* Ex. 2010, 4 (explaining that, in "the trials reported here . . . the individual agents tended to be prescribed at the minimal effective therapeutic dosage."). Indeed, Felson suggest that "[i]t is possible that higher doses of each drug in the combination could have been more effective, but the toxicity might also have been greater." *Id.* at 5. Such potential toxicity is not described as being at an unacceptable level. Further, the combination treatments discussed by Felson did not include the combination of MTX with a cytokine antagonist, such as MRA.

Absent expert testimony regarding the relevance of Felson to the motivation of combining Nishimoto's recommended dosage of MRA with MTX, we remain persuaded by Petitioners' assertion that Nishimoto provides motivation to administer the same MRA dosage recited by claim 1. Moreover, we credit Dr. Zizic's currently unrebutted testimony that "DMARDs are generally administered in the same dosage amount and frequency when given in combination with methotrexate as they are when given alone, and a POSA would have expected this to be the case for MRA." Ex. 1002 ¶ 150.

As for the dosage of MTX, Petitioners have demonstrated persuasively, at this stage in the proceeding, and based on the teachings of at least Weinblatt and the testimony of Dr. Zizic, that a POSA would have maintained a patient's existing methotrexate dosing regimen when supplementing that medication with an additional drug, including MRA. *See* Pet. 36 (citing Ex. 1008, 2; Ex. 1002 ¶ 154). Additionally, Petitioners have shown sufficiently at this stage that the typical dosage of methotrexate used to treat RA was between 10 and 25 mg once per week, as disclosed, for example, in Weinblatt. *Id.* Based on that showing, we find that Petitioners have shown persuasively, on the current record, that Weinblatt and the knowledge in the art teaches or suggests administering the same dosage range of MTX to treat RA as required by claim 1.

Based on the current record, we also find that Petitioners have shown that a POSA would have had a reasonable expectation of success in increasing the likelihood of achieving an ACR 70 response in RA patients by administering the known recited amounts of MRA and MTX, as compared to treatment with MTX alone. For example, Petitioners have argued persuasively that a POSA would have known that both drugs had been shown, individually, to be effective for treating RA, and that "combining methotrexate with other RA drugs was known to 'improve disease control.'" *See* Pet. 37 (citing Ex. 1002 ¶ 155; Ex. 1008, 2). Additionally, Petitioners demonstrate persuasively that achieving the recited ACR 70 response is only a function of the administering the same combination therapy suggested by the combined prior art, and is, thus, an inherent result of the such combination therapy. *Id.* at 39.

We have considered Patent Owner's arguments that Petitioners have not demonstrated a reasonable expectation of success. However, we do not

find those arguments to be sufficient at this stage of the proceeding to deny the Petition. In particular, Patent Owner has not identified evidence sufficient to establish that concerns regarding potential toxicity or the unpredictability involved in certain other combination therapies would have caused a POSA not to *reasonably* expect to achieve better therapeutic results with a different combination of two drugs known to individually be safe and effective for treating RA.

Accordingly, based on the information presented at this stage of the proceeding, we determine that Petitioners have shown persuasively that the combination of Nishimoto and Weinblatt teach or suggest each limitation of claim 1 and provide motivation for combining the recited dosages of MRA and MTX to treat RA with a reasonable likelihood of success in increasing the likelihood of achieving an ACR70 response over treatment with MTX alone.

We continue our analysis below with a discussion of Patent Owner's asserted secondary considerations of nonobviousness.

b) Secondary Considerations

Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the patent's invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the challenged claims would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Objective evidence of nonobviousness, so called "secondary considerations," may include long-felt but unsolved need, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17–18;

Leapfrog Enters., Inc. v. Fisher–Price, Inc., 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Here, Patent Owner asserts that "unexpected properties of the claimed dosing regimen confirm the nonobviousness of the claims." Prelim. Resp. 50. In particular, Patent Owner asserts that its clinical trial data, disclosed in the '201 patent, reveals that: (a) patients receiving 8mg/kg MRA with MTX had far more frequent ACR 70 responses than patients receiving MTX alone; (b) "[w]hen the [MRA] dose was increased from 4mg/kg to 8 mg/kg, the ACR 70 score for the combination therapy more than tripled, even though the increase from 2mg/kg to 4 mg/kg . . . saw almost no additional patients scoring at that level;" and (c) "[t]he ACR 70 score at the claimed combination dosages (36.7 percent) exceeded the aggregate scores achieved for monotherapies at those same dosages of MRA (15.7 percent) and MTX (16.3 percent), the opposite of what was observed at the lower MRA dosages." *Id.* at 49–51.

Referring to Patent Owner's allegations of unexpected results during prosecution, Petitioners assert that Patent Owner did not compare results of the claimed methods to the closest prior art. Pet. 51. Petitioners contend that the closest prior art to the claimed invention is Nishimoto, which discloses a recommendation to administer MRA at a dosage of 8 mg/kg every four weeks to treat RA, and a phase II study for treating RA with a combination of MRA and MTX. *Id.* Thus, Petitioners assert that Patent Owner improperly compares the results of the claimed regimen to combinations of MTX with lower dosages of MRA than disclosed Nishimoto. *Id.*

Additionally, Petitioners assert that Patent Owner's relied upon results of combining 8 mg/kg MRA with MTX would have been expected based on

Nishimoto's disclosure that its recommended dosing for MRA resulted in an ACR70 response in a substantially greater percentage of patients that what MTX was known to yield. *Id.* at 52–53 (citing Ex. 1002 ¶¶ 179–180; Ex. 1008, 5; Ex. 1017, 2).

Patent Owner responds to Petitioners' argument by challenging Petitioners' characterization of Nishimoto. However, Patent Owner does not identify clearly what it considers to be the closest prior art. Nor do we see that Patent Owner provides a comparison of the results of such prior art to those asserted for the claimed invention.

As our reviewing court has instructed, to properly evaluate whether a superior property was unexpected, we must first consider what properties were expected. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). To do so, we consider the results of the closest prior art and compare them to those asserted for the claimed invention. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Thus, we reserve any further analysis of Patent Owner's alleged evidence of unexpected results until the arguments and record are more fully developed during trial.

c) Summary

Accordingly, based on the current record, we determine that Petitioners have shown sufficiently for institution that there is a reasonable likelihood that it would prevail in showing that claim 1 is rendered obvious by the combination of Nishimoto and Weinblatt.

Petitioners also challenge claims 2–15 in this ground. Patent Owner does not raise any separate or additional arguments regarding those claims.

See Prelim. Resp. We have reviewed Petitioners' evidence and arguments relating to the remaining challenged claims and determine, at this stage in the proceeding, that Petitioners have demonstrated a reasonable likelihood that those claims are also rendered obvious by the combined references, largely for the same reasons discussed regarding claim 1.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioners have established a reasonable likelihood of prevailing in its assertion that at least one challenged claim of the '201 patent is unpatentable. Accordingly, in light of *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348, 1354 (2018), and the Patent Trial and Appeal Board Consolidated Trial Practice Guide 64 (Nov. 2019), *available at* https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf, we institute an *inter partes* review of the challenged claims on all asserted grounds.

Our determination in this Decision is not a final determination on either the patentability of any challenged claims or the construction of any claim.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–15 of the '201 patent on all grounds set forth in the Petition is instituted, commencing on the entry date of this decision; 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 review.

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