UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner

v.

GENENTECH, INC.,
Patent Owner

Case IPR2017-01923
Patent 7,976,838 B2

PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107

LIST OF EXHIBITS

Exhibit[1]	Description
Ex.2001	International Application Publication No. WO 00/74718 A1 to David M. Goldberg *et al.* ("Goldenberg")
Ex.2002	Boardside "Chat with the Chief" presentation by Chief Administrative Patent Judge David P. Ruschke, titled "An Analysis of Multiple Petitions in AIA Trials," dated Oct. 24 2017
Ex.2003	J.K. Jenkins & K.J. Hardy, *Biological Modifier Therapy for the Treatment of Rheumatoid Arthritis*, 323(4) Am. J. Med. Sci. 197-205 (2002) ("Jenkins")
Ex.2004	Rituxan® (Rituximab) Prescribing Information dated February 2010
Ex.2005	Stanley B. Cohen et al., *Rituximab for Rheumatoid Arthritis Refractory to Anti-Tumor Necrosis Factor Therapy*, 54(9) Arthritis & Rheumatism, 2793-2806 (Sept. 2006) ("Cohen")
Ex.2006	"Arthritis Foundation Statement on Rituximab for Rheumatoid Arthritis" submitted, on May 10, 2012, by Genentech, Inc. to the European Patent Office as an exhibit (D61) to an appeal in the Opposition Proceedings in EP 1613350
Ex.2007	Prosecution History of U.S. Patent No. 7,976,838.
Ex.2008	Expert Report of Professor Dr. Bernardus (Ben) A.C. Dijkmans that was submitted by Petitioner, Pfizer, Inc., in a validity action involving European Patent EP 1951304
Ex.2009	Peter McLaughlin et al., *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, 16(8) J. of Clinical Oncology, 2825-33 (Aug. 1998) ("McLaughlin")
Ex.2010	Declaration of Megan Raymond

[1] Consistent with Petitioner's citation format, citations herein are to the stamped page numbers.

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Patent Owner Genentech, Inc. ("Genentech") submits this 37 C.F.R. § 42.107[2] Patent Owner Preliminary Response ("POPR") to the above-captioned Petition ("Petition" or "Pet."), which should be denied for failure to show a reasonable likelihood of prevailing on any asserted ground.

I. Introduction

This Petition is one of an onslaught of *six petitions* filed against U.S. Patent No. 7,976,838 (the "'838"), together with four others identified by Petitioner as "related." Three of the six '838 IPRs are currently pending as the latest wave of a systematic attempt to invalidate claims 1–14 ("the Challenged Claims") through iterative attacks, each making minor adjustments from the last in hopes of finding a challenge that will yield a different result. All six rely on overlapping art and arguments, including those already rejected by the original Examiner and this Board. While Petitioner attempts to suggest it offers something "new" with its combination of Takemura/Klimiuk/Ulfgren, these references add nothing: they do not disclose TNFα-inhibitor inadequate-responders ("TNFIRs"), let alone treatment of a human patient with rituximab or obtaining the claimed clinical responses (ACR50, ACR70 and no erosive progression). Indeed, Petitioner fails to point to anything they add to the art and arguments previously considered by the

[2] Unless otherwise stated, all emphasis/annotations added, and all statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates.

Office. But Petitioner never acknowledges the Board's discretion to deny institution under §§ 325(d) and 314(a) in such circumstances, and certainly does not identify anything in its overlapping art or arguments that is unique, or why the Board should devote its finite resources to yet another do-over. This alone is fatal to the Petition, and the Board should deny institution under §§ 325(d) and 314(a) for this repetitive attack on the same patent—a problem that has been repeatedly criticized as improper "gang tackling."

Even if Petitioner's rehashed arguments were considered on their merits, Petitioner fails to meet its burden. Petitioner's cited art fails to teach or suggest key limitations of every Challenged Claim, including, *e.g.*, the treatment of TNFIRs with two intravenous doses of 1000 mg of an antibody that binds to CD20 (claims 1, 2, and 4–7) or rituximab (claims 3, 8, and 9–14), and the specific clinical responses required by claims 2–7 and 10–14, namely an "ACR50 response," an "ACR70 response," and "no erosive progression." For at least these reasons, the Petition should be denied.

II. The Challenged Claims are Directed to a Non-Obvious Invention

Rheumatoid arthritis ("RA") is an autoimmune disorder. RA patients "suffer a chronic course of disease that, even with therapy, may result in progressive joint destruction, deformity, disability and even premature death." Ex.1001 4:4-7.

The goals of RA therapy are preventing or controlling joint damage, preventing loss of function, and decreasing pain. *Id*. 4:8-10. While RA patients are often initially treated with nonsteroidal anti-inflammatory drugs ("NSAIDs"), glucocorticoids, and/or low-dose prednisone, most patients are treated with synthetic disease-modifying antirheumatic drugs ("DMARDs") such as methotrexate or cyclosporine within three months of diagnosis. *Id*. 4:11-24. Before the claimed invention, if patients failed synthetic DMARDs, they could be treated with biologic drugs that inhibited tumor necrosis factor alpha ("TNFα"), including etanercept (ENBREL®), infliximab (REMICADE®), and adalimumab (HUMIRA™). *Id*. 4:25-56. However, not all RA patients respond to TNFα-inhibitors, which also have side-effects including infections, sepsis, and heart failure. *Id*. 4:28-40. These hard-to-treat RA patients needed other treatment options. Ex.2006 at 1; Ex.2007 at 412-413; Ex.2008 at 12.

Rituximab is an antibody that binds a B-cell-surface antigen, CD20, leading to the depletion of B cells. Ex.1001 2:32-48. Genentech originally obtained FDA approval of rituximab for non-Hodgkin's lymphoma ("NHL"), a cancer. Ex.1009 at 7. In treating NHL, rituximab was administered in body surface area ("BSA")-based doses of 375 mg/m^2 per week for four weeks. *Id*. at 8. The '838 inventors, though, saw the potential for rituximab to be used for treating other diseases.

The '838 discloses treating RA patients who have experienced an inadequate response to TNFα-inhibitors due to toxicity and/or inadequate efficacy ("TNFIRs") with rituximab. Ex.1001 4:60-65; 5:25-29. However, every Challenged Claim requires an anti-CD20 antibody/rituximab be administered in two doses of 1000 mg each to treat TNFIRs, rather than the dosing required to treat NHL. *Id*. 37:40-38:64.

In obtaining FDA approval of rituximab for treating RA, Genentech conducted a two-year double-blind Phase III clinical trial called "REFLEX" in more than 500 TNFIRs. Ex.2005. REFLEX patients showed marked improvements in ACR scores, which use a scale developed by the American College of Rheumatology. Ex.1019 at 6, Table 3. An ACR score generally corresponds to a percentage improvement in certain signs and symptoms of the disease.[3] *See* Ex.1010 at 5. Although the REFLEX trial patients were particularly hard to treat, many achieved ACR50 and ACR70 responses. Ex.2005 at 1. More surprisingly, a substantial number of patients had no progression in joint erosion at 24 weeks and beyond, even after two years. Ex.2004 at 27-28. The Challenged Claims refer to these important clinical outcomes, respectively, as an "ACR50

[3] For example, ACR50 corresponds to 50% improvement, and ACR70 to 70%.

response," an "ACR70 response," and "no erosive progression." Ex.1001 37:40-38:64.

III. Petitioner's Cited Art

Petitioner relies on seven references, in four combinations, to argue the Challenged Claims are unpatentable: Edwards 2001 (Ex.1004), Edwards 2002 (Ex.1003), Takemura (Ex.1005), Klimiuk (Ex.1006), Ulfgren (Ex.1007), the Rituxan® Label (Ex.1009), and Curd (Ex.1008). Pet. at 6-7. But as detailed below, each combination fails.

A. Edwards 2001

Edwards 2001 reports the results of an "open-label" study (where it is known which patients received the drug), using rituximab to treat five RA patients who did not respond to synthetic DMARDs such as gold, methotrexate, or prednisolone. Ex.1004 at 1-2. ***None*** of Edwards 2001's patients were TNFIRs. *Id*. at 2, Table 1 n.b.

Edwards 2001 used a protocol "based on the type of combination therapy used in B-cell lymphoma": Four rituximab infusions of 300 mg, 600 mg, 600 mg, and 600 mg administered on days 2, 8, 15, and 22, as well as oral prednisolone and cyclophosphamide. *Id*. at 2. All 5 patients achieved an ACR50 at 6 months, and patients 1–3 achieved ACR70. *Id*. at 3. However, in discussing its results, Edwards 2001 noted that because patients were treated with a drug combination, it

could not confirm that the results were due to rituximab alone. Instead, "[t]he further possibility, that steroid and cyclophosphamide contributed to the results, at least in part, through actions other than on B lymphocytes, seems very plausible." *Id*. at 6.

B. Edwards 2002

Edwards 2002 is an abstract reporting preliminary clinical trial results for 161 RA patients. As this Board has twice found, Edwards 2002 does not identify ***any*** patient as a TNFIR. *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc*., IPR2015-00417, Pap. 11 at 14-15 (July 14, 2015); *Celltrion, Inc. v. Genentech, Inc.*, IPR2016-01667, Pap. 15 at 10 (Mar. 2, 2017). Instead, Edwards 2002's target population was RA patients with "active disease" on methotrexate, a synthetic DMARD. Ex.1003 at 3. Patients were randomized to one of four treatment groups: (1) methotrexate; (2) rituximab (two 1000 mg infusions); (3) rituximab (two 1000 mg infusions) and cyclophosphamide (two 750 mg infusions); and (4) rituximab (two 1000 mg infusions) and methotrexate. *Id*. Edwards 2002 reports that all patients also received corticosteroids, although no specific steroid is identified. *Id*. ACR20, ACR50, and ACR70 results were reported for each of the rituximab-treated groups. The abstract is silent as to any impact from any treatment on erosive progression.

C. Takemura

Takemura examines the potential role of B-cells in synovial inflammation by treating chimeric mice with Rituxan® (rituximab). Human synovial tissue specimens used to generate human synovium-mouse chimeras were obtained from 15 patients with "RA with active synovitis." Ex.1005 at 2-3. No information is provided regarding the treatment history of these patients, and ***none*** are identified as TNFIRs. Takemura reports Rituxan® treatment inhibited T-cell activation, and inhibited production of IL-1β and IFN-γ. *Id*. at 6. However, Takemura does not provide any data showing whether this inhibition translated into clinical efficacy (*e.g*., ACR or x-ray data). Takemura also addresses the results reported in Edwards 2001, finding, "[b]ecause this study used a combination therapy, the relative contribution of B cell depletion to the treatment success is unclear." *Id*. at 9.

D. Klimiuk

Klimiuk reports the results of testing to "explore whether a correlation exists between the microscopic patterns of rheumatoid synovitis and *in situ* production of cytokines" based on tissue samples from 21 RA patients. Ex.1006 at 1. Klimiuk explained "[w]hether only T cells or only macrophages or both are the causative elements in RA remains a matter of controversy." *Id*. Klimiuk does not discuss the role of B-cells in RA. Nor does it discuss TNFα-inhibitors or that any patient

had undergone or had an inadequate response to TNFα-inhibitor therapy. Indeed, the past and current treatments for the patients studied were NSAIDs and synthetic DMARDs such as gold or methotrexate, not TNFα-inhibitors. *Id*. at 6, Table 4.

Instead, Klimiuk examines three categories of synovitis it classifies as (1) diffuse, (2) follicular, and (3) granulomatous. *Id*. at 1, 6. Diffuse synovitis was reportedly characterized by "low level transcription of INF-γ, IL-4, IL1β, and TNF-α." *Id*. at 1. Klimiuk reported diffuse synovitis was seen in patients with the mildest form of RA and is a "milder disease that is responsive to nonaggressive treatment." *Id*. at 1, 7. In discussing the results, Klimiuk acknowledged the PCR technique used "can have limitations that need to be considered when interpreting the data" and that its methods were not suitable "to determine quantitative differences" between the samples. *Id*. at 7.

E. Ulfgren

Ulfgren reports testing on eight RA patients treated with a single 10 mg/kg dose of TNFα-inhibitor infliximab to "investigate the hypothesis that [TNFα] blockade in rheumatoid arthritis (RA) diminishes synovial synthesis of TNFα, interleukin-1α (IL-1α) and IL-1β." Ex.1007 at 1. Synovial biopsy samples were obtained before treatment and 14 days later. *Id*. at 2. All patients had an ACR20 response and half had an ACR50 response. *Id*. at 3. Ulfgren reported "[p]atients meeting the ACR 50 were those with the highest baseline levels of TNFα

synthesis. There was a significant correlation between baseline levels of TNFα expression and change in TNFα levels in response to therapy." *Id*. at 1. Nowhere did Ulfgren identify any patient as a TNFIR or suggest alternative therapy was required.

F. Rituxan® Label

Petitioner's "1999 Rituxan® Label" document reports that rituximab, the active ingredient in Rituxan®, is an antibody directed against the CD20 antigen found on the surface of B-lymphocytes. Ex.1009 at 6. The Label reports rituximab binds to the CD20 antigen on B-lymphocytes and mediates B-cell lysis *in vitro*. *Id*. at 6-7. The Label states Rituxan® is indicated for certain *NHL* patients at a recommended dose of four 375 mg/m^2 infusions on days 1, 8, 15, and 22. *Id*. at 7-8. The Label reports on clinical studies administering Rituxan® in four weekly 375mg/m^2 intervals, and states such administration "resulted in a rapid and sustained depletion of circulated and tissue-based B cells." *Id*. at 7.

G. Curd

Curd discloses treating RA with rituximab in size-adjusted (varying based on BSA) and often dose-escalating regimens—all involving at least four doses of the drug. For instance, Example 1 teaches dosing using (1) 50 mg/m^2 on day 1, followed by 150 mg/m^2 on days 8, 15 and 22; (2) 150 mg/m^2 on day 1, followed by 375mg/m^2 on days 8, 15 and 22; and (3) 375 mg/m^2 on days 1, 8, 15 and 22.

Ex.1008 at 25:9-23. Curd notes adjunct therapies may be combined with rituximab, but "[p]referably however, the patient is only treated with RITUXAN®." *Id*. at 25:9-16. Curd says nothing about targeting or treating TNFIRs.

IV. The Petition Should Be Denied Under 35 U.S.C. §325(d)

In deciding whether to institute, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the [Patent and Trademark] Office," § 325(d), and the Board has repeatedly denied institution when—as here—the petition fails to explain why this discretion to deny should not be exercised. *See, e.g.*, *Unified Patents, Inc. v. Berman*, IPR2016-01571, Pap. 10 at 11-12 (Dec. 14, 2016) (informative).

Notwithstanding Petitioner's suggestion that its Petition is "different" (Pet. at 4), the Petition relies on substantially the same art and arguments previously presented in *both* prosecution and prior IPRs (IPR2015-00417 by Boehringer; IPR2015-01733 and IPR2016-01667 by Celltrion). Yet Petitioner never mentions § 325(d), despite the PTO's extensive prior consideration of the same and similar art. Regardless, Petitioner's substantive arguments here fare no better than those the Board rejected in IPR2016-01667, despite Petitioner's having the benefit not

only of the original prosecution and three prior IPR petitions filed against the '838, but also of Genentech's POPRs, and Board institution decisions.[4]

A. The Petition Should be Denied for Relying On Substantially the Same Art and Arguments Already Rejected by the Examiner and Board

In situations far less egregious than this, the Board routinely denies institution where a petition recycles substantially the same previously-considered art and arguments. For example, in applying § 325(d), the Board has repeatedly denied institution where, like here, the same or similar art was *either* before the original examiner *or* before the Board. *See Cultec, Inc. v. Stormtech LLC*, IPR2017-00777, Pap. 7 at 7-14 (Aug. 22, 2017) (informative) (previously considered by examiner); *Hospira, Inc. v. Genentech, Inc*., IPR2017-00739, Pap. 16 at 17-19 (July 27, 2017) (informative); *NetApp Inc. v. Crossroads Sys. Inc.*, IPR2015-00777, Pap. 12 at 7-8 (Sep. 3, 2015) (previously considered by Board); *Unilever Inc v. Procter & Gamble Co.*, IPR2014-00506, Pap. 17 at 6-8 (July 7, 2014). But here, *both* the Examiner *and* the Board have rejected the same or substantially the same art and arguments.

The Board has also been critical of petitioners who fail to offer any explanation why § 325(d) should not apply. *See, e.g.*, *Unified Patents*, IPR2016-

[4] Petitioner has also benefited from multiple papers involving challenges to related patents. *See infra* § V(C).

01571, Pap. 10 at 11-12. Here, Petitioner fails even to mention that its cited art (or art making substantially the same or more pertinent disclosures) was before the Examiner, who issued the Challenged Claims over this art, or that the same or substantially the same art and arguments were previously before—and rejected by—the Board. Petitioner's silence is particularly egregious given Petitioner's attempt to bury De Vita 2002—which was before both the original Examiner and the Board, and contradicts Petitioner's arguments regarding a reasonable expectation of success—in a single section at the end of the Petition (Pet. at 60-62 (acknowledging De Vita 2002 only in attacking a "teaching away" argument not at issue in this POPR)). *Infra* § VII(A)(2)(a). Instituting trial on these same arguments, in the face of Petitioner's silence with respect to § 325(d), would both waste the Board's limited resources and invite substantial abuse—encouraging petitioners to scour prior proceedings to mix and match previously-rejected material, using the Office's prior decisions as a roadmap to try to avoid the same fate.

Section 325(d) is meant to prevent just the sort of inefficiencies, harassment of patent owners, and abuse of process Petitioner invites here in repeating arguments already *twice* overcome by Genentech. The Board should exercise its discretion under § 325(d) and deny institution.

B. The Patent Examiner Considered and Rejected Substantially the Same Art and Arguments

Petitioner exclusively relies on seven references across its asserted combinations. Pet. at 6-7. But the substance of Petitioner's art was before the Examiner who allowed the Challenged Claims over it during prosecution.

Edwards 2001: Edwards 2001 was specifically relied upon during original prosecution by the Examiner who allowed the Challenged Claims. In particular, the pending claims were initially found obvious in light of *Edwards 2001*, Jenkins (Ex.2003), and Goldenberg (Ex.2001). Ex.2007 at 385-388. The Examiner asserted Edwards 2001 disclosed using rituximab in four infusions, at a total dose of 2100 mg, as a safe and effective for treating RA. *Id*. at 386. Further, the Examiner asserted Jenkins taught stopping TNFα-inhibitor therapy in RA patients who develop serious side effects, and Goldenberg taught that a patient experiencing only minor relief when treated with TNFα-inhibitor ENBREL® achieved improvement with rituximab. *Id*. at 386-387. The Examiner concluded Edwards 2001, combined with Jenkins and Goldenberg, rendered the claims obvious. *Id*. at 387-388. In particular, the Examiner found it obvious to treat patients who did not respond to TNFα-inhibitor therapies with rituximab, and that obtaining the claimed dosing regimen would be obvious dose optimization. *Id*.

The patentee overcame this rejection, pointing out that *none of the Edwards 2001 patients had been previously treated with a TNFα-inhibitor* and thus *none*

were TNFIRs. *Id*. at 411. The patentee further distinguished Edwards 2001 based on its use of four rituximab doses of 300 mg, 600 mg, 600 mg and 600 mg, not the two claimed doses of 1000 mg, explaining that the claimed dosing regimen was not merely optimization. *Id*. at 411-412. The Examiner thereafter withdrew the § 103 rejection and allowed the Challenged Claims. *Id*. at 465.

Edwards 2002: Edwards 2002 is identified in the '838 among "[p]ublications concerning therapy with Rituximab," and was also reviewed by the Examiner (after being cited in an IDS) during prosecution. Ex.1001 3:33-57; Ex.2007 at 394. At no point did the Examiner reject any Challenged Claim in light of Edwards 2002, alone or in combination with other cited art.

Takemura, Klimiuk, and Ulfgren: Pfizer relies on the combination of Takemura, Klimiuk, and Ulfgren as allegedly teaching a person of ordinary skill in the art ("POSITA"), that rituximab could be used to treat TNFIRs (*see, e.g*., Pet. at 37-42) in spite of the fact that *none of this art discloses TNFIRs or the use of rituximab to treat a human patient*. While these specific references were not considered by the Examiner, the Examiner did consider art that actually disclosed TNFIRs and use of rituximab in human patients. For example, discussed above, the pending claims were initially rejected under § 103 in light of Goldenberg's alleged disclosure of treating TNFIRs. But this rejection was overcome: the Challenged Claims were allowed over this (more pertinent) art.

During prosecution, the pending claims were also initially rejected under 35 U.S.C. § 102 as anticipated by De Vita 2002 (Ex.2007 at 383-384)—a more pertinent reference than Petitioner's references, as detailed below. The Examiner found De Vita 2002 taught methods of treating RA using rituximab in patients who did not respond to TNFα-inhibitor therapy. *Id*. at 384. But in overcoming the rejection, the patentee noted that De Vita *failed to disclose* both the *claimed dosing regimen* of two doses of 1000 mg (instead using four doses of 375 mg/m^2) as well as the *claimed clinical responses* of ACR50, ACR70, and no erosive progression. *Id*. at 406-407. Indeed, the patentee noted of De Vita 2002's two reported TNFIRs, one achieved only an ACR20 response and one "exhibited no improvement," while both actually saw an *increase* in the number of eroded joints. *Id*.; Ex.1016 at 2-4. The Examiner withdrew the rejection and allowed the Challenged Claims. Ex.2007 at 432, 465.

Given that art disclosing the actual *in vivo* treatment of TNFIRs was before the Examiner, Petitioner's substitution of other references merely alleged to *imply* that such treatment would be *possible* certainly offers nothing new or better than arguments already considered and rejected during prosecution.

Rituxan® Label: While Petitioner's 1999 Rituxan® Label itself was not before the Examiner, the disclosures argued by Petitioner were. The '838 discloses that rituximab is a genetically engineered murine/human monoclonal CD20

antibody approved for the treatment of certain forms of NHL. Ex.1001 2:32-39. That Rituxan® was administered in four weekly infusions of 375 mg/m^2 when treating NHL, as disclosed in the Label (Pet. at 49), was also before the Examiner. For example, De Vita 2002, in explaining its decision to administer four infusions of 375 mg/m^2 of Rituxan® to RA patients, noted that this was the same as "in treatment of B cell lymphoma." Ex.1016 at 2. The Examiner allowed the claims over these disclosures, and over the argument that one would optimize this dose to arrive at the claimed dosing regimen, even though De Vita 2002's disclosure, unlike the Label's, reported using this regimen to treat RA.

Curd: Curd is identified in the '838 as art "concerning CD20 antibodies," and was reviewed by the Examiner (after being cited in an IDS) during prosecution. Ex.1001 2:60-3:32; Ex.2007 at 393. The Examiner did not reject any Challenged Claim in light of Curd, either alone or in combination.

The Original Examiner Previously Considered Substantially the Same Art and Arguments: The Petition uses substantially the same art, in substantially the same way, as it was used and ultimately rejected by the Examiner.

For example, Petitioner's Ground II obviousness analysis relies on Edwards 2001, just as the Examiner's did, for disclosure of treating RA patients with rituximab to "effective" (ACR50 and ACR70) clinical responses. *Compare* Ex.2007 at 386, *with* Pet. at 47-48, 55. Under Ground I, Petitioner merely swaps in

Edwards 2002 for this same disclosure as in Edwards 2001. *See, e.g.*, Pet. at 37, 42-43.

Under both Grounds I and II, rather than relying directly on De Vita 2002 or Goldenberg for alleged disclosure of treating TNFIRs as the Examiner did in his anticipation and obviousness analyses, Petitioner swaps in the combination of Klimiuk, Ulfgren and Takemura. *See, e.g.*, Pet. at 40. Petitioner similarly swaps in the Label's disclosure of administering four doses of 375 mg/m^2 rituximab for that of De Vita 2002, which, as the Examiner noted, actually treated RA patients. *Compare* Ex.2007 at 384, 406-407, *with* Pet. at 49. This swapping of art offers nothing new. *See Cultec*, IPR2017-00777, Pap. 7 at 7-14 (finding denial of institution under § 325(d) warranted where prior art was cumulative of disclosure of art previously considered by Examiner). As discussed above, the Examiner ultimately withdrew his rejections and allowed the Challenged Claims—and he did so over *in vivo* disclosures more closely aligned with the Challenged Claims than those in Petitioner's art.

Petitioner's reliance on Curd also does not change the arguments previously considered and ultimately rejected by the Examiner, who relied on Goldenberg (methotrexate) and Edwards 2001 (prednisolone) for the same disclosures of the co-administration of rituximab with methotrexate and corticosteroids, including prednisone, that Petitioner cites from Curd. Ex.2007 at 386-387; Pet. at 46-47, 57.

Petitioner never reconciles its use of Edwards 2001, Edwards 2002, or Curd with the fact that the Challenged Claims were specifically allowed over the substance of these disclosures. Nor does Petitioner identify *any disclosure* in its cited art that was not previously before the Examiner, let alone how its arguments differ from those the Examiner abandoned. This is no surprise, because in acknowledging these facts, Petitioner would be conceding that its Petition should be denied.

C. The PTAB Considered and Rejected the Same (or Substantially the Same) Prior Art and Arguments in the *Celltrion* IPR

In IPR2016-01667, Celltrion unsuccessfully asserted obviousness in light of (1) Edwards 2002 and Tuscano (Ex.1017), and in light of (2) De Vita 2001, Curd, and Goldenberg. *Celltrion*, IPR2016-01667, Pap. 15 at 10-18. Petitioner makes substantially the same arguments here, removing art allegedly disclosing the actual treatment of RA patients with rituximab (*i.e.*, Tuscano, De Vita 2001, and Goldenberg) and replacing it with art that does not (Takemura Klimiuk, and Ulfgren)—hoping that by presenting art lacking disclosures about human dosing, Petitioner might somehow obscure the flaws in its arguments there, and thus avoid

repeating Celltrion's failure.[5] But Takemura, Klimiuk, and Ulfgren offer nothing new, and Petitioner cannot avoid these flaws by ignoring them.

Petitioner's Ground I relies on the same teachings in Edwards 2002 and Curd that the Board acknowledged and rejected in *Celltrion*. In particular, like Petitioner, the Board noted Edwards 2002 disclosed a study in which RA patients were separated into four treatment groups and that those receiving rituximab, alone or in combination with methotrexate or cyclophosphamide, received two 1000 mg doses of the drug. *Compare Celltrion*, IPR2016-01667, Pap. 15 at 8, *with* Pet. at 24. Like Petitioner, the Board noted that Edwards 2002 reported ACR50 and ACR 70 responses among its patients. *Compare Celltrion*, IPR2016-01667, Pap. 15 at 8, *with* Pet. at 24-25, 42-43. The Board also noted, like Petitioner, that Curd disclosed treating RA using various rituximab dosing schedules and optional further treatment with methotrexate and corticosteroids. *Compare Celltrion*,

[5] As Petitioner notes, in *Boehringer* the Board instituted under § 103 (Pet. at 3-4), but without the benefit of Genentech's fuller discussion of flaws in the dose optimization arguments underlying the obviousness arguments as provided in, *e.g.*, Genentech's later POPR in *Celltrion*. As detailed *infra* § VII(A)(2)(b)(i), when provided that information, the Board *denied* institution.

IPR2016-01667, Pap. 15 at 15, *with* Pet. at 46.[6] For the disclosure of TNFIRs, the Board read Tuscano as disclosing administering escalating doses of rituximab (100 mg, 375 mg/m^2, and two doses of 500 mg/m^2) to RA patients who previously failed multiple DMARDs, including the TNFα-inhibitor infliximab. *Celltrion*, IPR2016-01667, Pap. 15 at 11.

Ultimately the Board found a POSITA would not have combined the dosing regimen disclosed in Edwards 2002 with the TNFIRs discussed in Tuscano with a reasonable expectation of success. *Id.* at 11-14. It also rejected the argument that the claimed dosing regimen was a matter of "routine optimization." *Id*. The Board further rejected Celltrion's suggestion that the "claimed dosage is not critical," and held that "Petitioner has not explained persuasively why a person of skill in the art would have expected the regimen that was effective in Edwards' patients to be effective in Tuscano's inadequate responders." *Id.* at 13. Noting the differences between the Tuscano and Edwards 2002 dosing regimens, the Board concluded

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[6] While not discussed by the Board, Celltrion cited Curd as support for the limitations of Claim 6 in its Edwards 2002/Tuscano combination. *Celltrion*, IPR2016-01667, Pap. 2 at 50 (Aug. 24, 2016). Celltrion also asserted that Curd, in combination with Goldenberg and De Vita 2001, rendered obvious the Challenged Claims. *Id*. at 51-60.

"Petitioner has not addressed sufficiently why a person of ordinary skill in the art would have expected another treatment regimen, involving a reduced number of treatments, a reduced total dosage, and a dosage not based, in part, on a patient's size would have successfully treated RA in Tuscano's inadequate responders." *Id.* at 14.

Under Ground I, Petitioner relies on the same disclosures of Edwards 2002 and Curd as Celltrion did in its rejected petition. However, to avoid the Board's finding that Tuscano disclosed a different dosing regimen than claimed, Petitioner eliminates disclosure of dosing in TNFIRs altogether, swapping out Tuscano's alleged teaching of treating TNFIRs for the combination of Takemura, Klimiuk, and Ulfgren, which Petitioner alleges offers this same teaching or suggestion. *See, e.g.*, Pet. at 40. But the disclosure actually contained in these three substitute references is, at best, substantially the same as that in the art previously considered and rejected by the Board. If anything, Petitioner's newly cited art is less relevant because it lacks the alleged disclosure found in Tuscano: it fails to disclose any RA patient (let alone any TNFIRs) actually treated with rituximab.

Under Ground II, Petitioner swaps out Edwards 2002 for Edwards 2001, likely because, as discussed *infra* § VIII, Edwards 2002 is not prior art to the Challenged Claims. But there is nothing in Edwards 2001 that is not already disclosed in Edwards 2002. In fact, Edwards 2001 uses a dosing regimen—four

escalating doses—even further from the Challenged Claims. Ex.1004 at 2. Thus, Edwards 2001 provides nothing substantially different that was not already considered and rejected by the Board in *Celltrion*.

Nowhere does Petitioner reconcile its reliance on Edwards 2002 and Curd with the fact that the Board in *Celltrion* rejected institution on the Challenged Claims with respect to these references. Nor does Petitioner identify any disclosure in its cited art that was not before the Board when it last rejected essentially the same arguments, let alone how its Petition arguments are not "the same or substantially the same" as those rejected by the Board six months before the present Petition. That is because it cannot.

V. Petitioner's Unfair Use of the Office's Prior Decisions and Patent Owner's Arguments to Frame Its Challenge Warrants Denial Under § 314(a)

Even if the Petition did not raise substantially the same art and arguments as were raised by the Examiner and rejected in *Celltrion* (it does), the Board should separately deny institution under § 314(a). Petitioner is unfairly taking advantage of the PTO's prior actions and decisions, along with the Patent Owner's prior responses, using them as a "roadmap" to repeat and tweak previously-rejected arguments as part of a deliberate serial attack on the '838.

The Board applied both § 314(a) and § 325(d) to deny repetitive petitions long before its precedential decision in *General Plastic Industrial Co., Ltd. v.*

Canon Kabushiki Kaisha.[7] And, as the Board has repeatedly indicated, the Petition should have affirmatively addressed these issues. The Board in *General Plastic* explained "[a]lthough … an objective of the AIA is to provide an effective and efficient alternative to district court litigation, we also recognize the potential for abuse of the review process by repeated attacks on patents." IPR2016-01357, Pap. 19 at 16-17 (Sept. 6, 2017) (precedential). The Board cautioned against allowing petitioners "the opportunity to strategically stage their prior art and arguments in multiple petitions, using our decisions as a roadmap, until a ground is found that results in the grant of review," *id*. at 17—the very same opportunity Petitioner attempts to exploit here. The Board set forth a "non-exhaustive list of factors … the Board[] consider[s] in evaluating follow-on petitions," taking into account "undue inequities and prejudices to Patent Owner." *Id*. at 16-17. The *General Plastic* factors include:

1. whether the same petitioner previously filed a petition directed to the same claims;

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[7] *See Alarm.com Inc.* v. *Vivint, Inc.*, IPR2016-01124, Pap. 11 at 5-7 and n.3 (Dec. 5, 2016); *Nora Lighting, Inc. v. Juno Mfg., LLC*, IPR2015-00601, Pap. 13 at 11-12 (Aug. 12, 2015); *Conopco, Inc. v. Procter & Gamble Co*., IPR2014-00507, Pap. 17 at 7-8 (July 7, 2014).

2. whether at the time of filing of the first petition the petitioner knew or should have known of the prior art asserted in the second petition;
3. whether at the time of filing of the second petition the petitioner already received the POPR or Board's institution decision for the first petition;
4. the time between the petitioner learning of the prior art in the second petition and the filing of the second petition;
5. whether the petitioner provides adequate explanation for the time between the filings of the multiple petitions;
6. the Board's finite resources; and
7. the requirement under § 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution.

See id. at 16.

While *General Plastic* involved follow-on petitions by the same petitioner, the Board has applied these factors to petitions by separate petitioners. For example, in *Samsung Electronics Co. v. Elm 3DS Innovations, LLC*, the Board applied the *General Plastic* factors and denied institution where a new petitioner relied on three of the four references, as well as evidence and rulings, from prior proceedings. IPR2017-01305, Pap. 11 at 8-12, 16-23 (Oct. 17, 2017)

(informative). Recognizing that not all factors might be as directly applicable to new petitioners, *id*. at 20-23 (finding factors 2, 6, and 7 had little probative value), the Board considered the availability of prior petitions, patent owner responses, and Board decisions on the same and related patents, which the petitioner unfairly used to "improve its position." *Id*. at 21. In addition, the Board emphasized the petitioner's reliance on substantially the same art, in substantially the same manner, evidenced the unfair "benefit" petitioner derived from the prior proceedings. *Id*. at 20. Just as the *Samsung* Board found these factors warranted denial under § 314(a), the *General Plastic*/*Samsung* framework confirms the Petition here should also be denied.

A. Factor One: Same Petitioner

While not a party to the earlier '838 petitions, Petitioner is now an active party to a second wave of three petitions, filed over three days. These newest petitions include two Petitions by Sandoz using overlapping art (including Edwards 2001, Edwards 2002, and Curd). *See Sandoz, Inc. v. Genentech, Inc*., IPR2017-02036, Pap. 1 at 5 (Aug. 31, 2017); *Sandoz, Inc. v. Genentech, Inc*., IPR2017-02042, Pap. 1 at 6 (Aug. 31, 2017). In this Petition, Petitioner puts before the Board still more permutations of previously-considered art and arguments, hoping something will stick after six '838 attacks. These repeated attacks are particularly egregious given the additional repeated attacks by

Petitioner and others on *other* patents involving rituximab. *Infra* § V(C). This is the very abuse § 314(a) is meant to curb and exemplifies the type of repeated petitioning activity that has led to scrutiny by the Board itself. *See, e.g.*, Ex.2002 at 36.

Moreover, as in *Samsung*, the Petition here has a "high degree of similarity" with the three previously-filed '838 petitions, each of which included Edwards 2002 and Curd. IPR2017-01305, Pap. 11 at 19; *supra* § IV(C). Indeed, as discussed above, substantially the same art and arguments as set forth in the Petition were rejected by the Board six months before the Petition was filed.

B. Factor Two: Knowledge of Prior Art

While Petitioner knew or should have known of its cited art given that much of it was expressly raised before both the original Examiner and the Board, because Petitioner was not involved in prior '838 petitions, as in *Samsung*, this factor may have less probative value. IPR2017-01305, Pap. 11 at 20.

C. Factor Three: Availability of Information From Prior Proceedings

As in *Samsung*, this factor weighs strongly in favor of denying institution. *Id*. at 20-21.

Petitioner had the benefit of three other '838 petitions and Genentech's POPRs in *Boehringer* and *Celltrion* (along with multiple papers involving U.S. Patent No. 7,820,161 ("the '161") directed to methods of treating RA using

rituximab) in preparing the present Petition. The fact that Petitioner relies on substantially the same art in substantially the same manner (*see supra* § IV(C)) "evinces benefit Petitioner [ ] derived from those prior proceedings." *Samsung*, IPR2017-01305, Pap. 11 at 20. Petitioner clearly used Genentech's prior POPRs to try to preempt Genentech's arguments and strengthen Petitioner's position here. *See, e.g.*, Pet. at 31 (citing Genentech's arguments in *Celltrion* (Ex.1038) that Edwards 2002 is not prior art); *id*. at 59-66 (citing Genentech's *Boehringer* POPR (Ex.1036) and addressing Genentech's secondary considerations arguments). As the Board explained in *Samsung*, "[t]he *availability* of the Patent Owner's Response and Patent Owner's expert testimony from other proceedings also weights strongly in favor of exercising our discretion, as does Petitioner's *use* of such information in its Petition." IPR2017-01305, Pap. 11 at 21.

Petitioner also had available to it two prior '838 institution decisions and a decision denying reconsideration. As in *Samsung*, Petitioner used those prior decisions to try to improve its position here and would be able to do so further were the Board to institute review. "This also strongly weighs in favor of exercising [the Board's] discretion." *Id*.

Petitioner's ability to leverage prior statements by Genentech and the Board is not limited to the '838 IPRs. Instead, Petitioner also seeks to benefit from extensive attacks made on a variety of patents involving rituximab. For example,

the ’161, directed to methods of treating RA using rituximab, has been the subject of four petitions by Boehringer (IPR2015-00415), Celltrion (IPR2015-01744 and IPR2016-01614) and Pfizer (IPR2017-01115). Similarly, U.S. Patent No. 8,329,172 (“the ’172”), directed to methods of treating NHL using rituximab, has been the subject of three petitions by Boehringer (IPR2015-00418), Celltrion (IPR2017-01093) and Pfizer (IRP2017-01166). Petitioner cites statements made by Genentech in IPRs involving both the ’161 and ’172, even attaching Genentech’s filings as exhibits to the Petition. Pet. at 2-3, 21, 49-50, 65; Ex.1035; Ex.1040. Petitioner’s attempt to take advantage of these attacks against Genentech is not surprising given that the same counsel representing Petitioner here (including lead attorney Wong) also represented Petitioner in its petitions against the ’161 and ’172. Pet. at 5; *Pfizer, Inc. v. Biogen, Inc*., IPR2017-01115, Pap. 2 at 2 (Mar. 24, 2017); *Pfizer, Inc. v. Biogen*, IPR2017-01166, Pap. 2 at 5 (Apr. 21, 2017). Petitioner goes as far as characterizing the ’172 proceedings as a “related IPR,” but fails to list any ’172 proceedings in its mandatory notice of related matters, apparently hoping to obscure the full breadth of its multi-petition attack. Pet. at 3-5, 21. Petitioner should not be allowed to pick and choose among the filings and Board decisions in 13 IPRs across three patents to strengthen its case here.

D. Factor Four: Prior Art Asserted in Instant Petition

While Petitioner knew or should have known of the art cited in its Petition because much of it was expressly cited before the Examiner and Board in prior proceedings, *supra* §§ IV(B)-(C), the Board in *Samsung* found this factor to have little, if any, probative value where the petitioner had not filed prior petitions. IPR2017-01305, Pap. 11 at 22.

E. Factor Five: Petitioner's Explanation

Because Petitioner failed to mention, let alone address, § 314(a), it provided *no explanation* for its failure to file its Petition sooner. Indeed, Petitioner waited more than five months after filing its '161 petition (IPR2017-01115) before filing its '838 Petition. Thus, unlike in *Samsung*, where petitioner explained its delay, this factor weighs heavily in favor of denying institution. IPR2017-01305, Pap. 11 at 22-23.

F. Factors Six and Seven: Board Considerations of Finite Resources/One-Year Timeline

These related factors consider the "finite resources of the Board" and the timing requirement for the Board's final determination. As detailed *supra* §§ IV(B)-(C), both the Examiner and the Board have already expended significant effort to consider and reject similar art and arguments. Asking the Board to do so again does not conserve the Board's finite resources, and the Petition offers no justification. Thus, while factor seven (concerning the one-year timeline) may not

weigh significantly for or against institution, factor six weighs in favor of denying institution.

G. The Equities Support Denying Institution

For the reasons above, when all seven factors are considered, the balance of the equities clearly supports denying institution under § 314(a). This is a textbook example of Patent Owner harassment with iterative attacks superficially and incrementally tweaked to see what might stick.

VI. Claim Construction

A. Every Claim Requires the Recited Patient has Been, or is Being, Treated With a TNFα-Inhibitor

Every Challenged Claim requires treating a "patient who experiences an inadequate response to a TNFα-inhibitor." Ex.1001 37:40-38:64. The Board correctly construed this as a substantive limitation requiring the patient have actually experienced an inadequate response to a previous or current TNFα-inhibitor, not merely that such a person would experience such a result if treated. *Celltrion*, IPR2016-01667, Pap. 15 at 6-7; *see also Boehringer*, IPR2015-00417, Pap. 11 at 8-10; Ex.1001 5:25-29, 5:37-41, 28:45-55; Ex.2007 at 409, 412-13. Petitioner does not contest this construction. Pet. at 26.

B. The Clinical Response Limitations Cannot be Read Out

Claims 2–7 and 10–14 require achieving one of three clinical responses: ACR50 at week 24, ACR70 at week 24, and no erosive progression at weeks 24

and beyond. Petitioner mischaracterizes these limitations as merely "intended results" of the administered doses and argues they are not limitations. Pet. at 27-30. In doing so, Petitioner revives the same arguments presented by challengers in prior petitions and countered by Genentech, without addressing Genentech's prior responses. The Board did not accept those previous improper invitations to read out limitations of the Challenged Claims, and should not do so now. *Texas Instruments Inc. v. ITC*, 988 F.2d 1165, 1171 (Fed. Cir. 1993).

1. "achieving a clinical response selected from" (claims 11–14)

(a) The Applicant Used Both the Preamble and Body of Claim 11 to Define the Claimed Subject Matter

All words in a claim, whether in the preamble or body, may have patentable significance. "[W]hen the claim drafter chooses to use *both* the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." *Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995) (emphasis in original). In general, when a preamble recites essential structures or steps, it limits the invention. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999).

The body of claim 11 recites steps of administering rituximab and methotrexate in a specific dosing regimen. Ex.1001 38:51-58. The preamble recites an additional step of "achieving a clinical response selected from the group

consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond." *Id*. This step is not a necessary consequence or inherent result of the treatment set forth in the other claimed steps.

The fact that the additional step in the preamble necessary to achieve the intended response contains a Markush group further supports that it is limiting. *Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007) ("A Markush group … limit[s] the claim to a list of specified alternatives.").

(b) The Applicant Relied on the Clinical Response Limitations to Distinguish Art

That the claimed clinical responses limitations are limiting is further confirmed by Genentech's reliance on them in distinguishing art during prosecution, including art cited by Petitioner. Ex.2007 at 407, 409-410, 412-414 (distinguishing De Vita 2002, the Tuscano protocol, Edwards 2001, Jenkins, and Goldenberg based on failure to disclose claimed clinical responses in TNFIRs). In doing so the Applicant argued "these features of the invention … represent independently patentable features that further distinguish the claimed invention over the cited art." *Id.* at 412. This clear reliance on the preamble to distinguish the claimed invention from the prior art confirms it is limiting. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001); *see also Invitrogen Corp. v. Biocrest Mfg. LP*, 327 F.3d 1364, 1370 (Fed. Cir. 2003); *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003) (giving

weight to preamble phrases added to gain allowance); *Smith & Nephew, Inc. v. Bonutti Skeletal Innovations, LLC*, IPR2013-00605, Pap. 9 at 8-9 (Feb. 26, 2014). Nowhere does Petitioner address this prosecution history, in spite of being on clear notice of it through prior POPRs. *Boehringer*, IPR2015-00417, Pap. 9 at 20; *Celltrion*, IPR2016-01667, Pap. 13 at 13-14.

(c) Claims 12–14 Rely Upon, and Derive Antecedent Basis From, the Clinical Responses in Claim 11

That the clinical response limitations of claim 11 are limiting is further confirmed by dependent claims 12–14.

First, claims 12–14 each derive antecedent basis from the "achieving a clinical response" language of the claim 11 preamble by referring to "***the clinical response***": "The method of claim 11 wherein ***the*** clinical response is" one of the three alternatives set forth in claim 11. Ex.1001 38:59-64. Preamble language is limiting when, as here, "limitations in the body of the claim rely upon and derive antecedent basis from the preamble." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003).

In addition, the claim differentiation doctrine further confirms the clinical response language is limiting. The only difference among claims 12–14 is that each requires a different clinical response. If the clinical response limitations were ignored, claims 12–14 would be identical, reading "[t]he method of claim 11." Ex.1001 38:59-64. This would not only violate claim differentiation principles but

would also be nonsensical. *Versa Corp. v. Ag-Bag Int'l Ltd.*, 392 F.3d 1325, 1330 (Fed. Cir. 2004).

2. "wherein the patient has no erosive progression …" (Claim 10)

Petitioner's suggestion that claim 10's limitation "wherein the patient has no erosive progression at weeks 24 and beyond" (Ex.1001 38:45-50) is non-limiting is without merit.

Again, "wherein" clauses like this are regularly found limiting. For example, in *BioDelivery Sciences International, Inc. v. RB Pharmaceuticals Ltd.*, claim 15 recited "an orally dissolving film formation, 'wherein said formulation provides' specific pharmacokinetic profiles." IPR2014-00325, Pap. 43 at 4 (June 30, 2015). The Board agreed "that the pharmacokinetic ranges recited in the wherein clause 'give crucial meaning to, and provide defining characteristics provided by the film formulation at issue.'" *Id.* at 5. This language required a formulation "capable of producing the pharmacokinetic profile recited in the wherein clause of the claim." *Id.* at 6 (citing *Griffin v. Bertina*, 285 F.3d 1029, 1033-34 (Fed. Cir. 2002)); *see also 10X Genomics, Inc. v. Univ. of Chicago*, IPR2015-01162, Pap. 14 at 12-13 (Nov. 16, 2015) ("wherein" clause limiting because it was informative about how steps were performed) (citing *Griffin*, 285 F.3d 1033-34); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Pap. 17 at 22-24 (Jan. 29, 2016) ("wherein" clause limiting

because it set forth a "specific, quantitative test" for determining if process fell within scope of claim).

The "wherein" clause's limiting nature is further confirmed by it giving "meaning and purpose" to the step of administering two intravenous doses of 1000 mg. *See, e.g.*, *Griffin*, 285 F.3d 1033-34 ("wherein" clause limiting where it gave "meaning and purpose to the manipulative steps"). Claim 10 is directed to a "method of treating rheumatoid arthritis." Thus, like claims 11–14, its method is used to achieve a therapeutic effect or invoke a clinical response in a TNFIR patient, rather than just administration of an antibody as intravenous doses. And the "wherein" clause defines a specific, quantitative test for determining what that therapeutic effect or clinical response is, requiring achievement of "no erosive progression at 24 weeks and beyond." The '838 explicitly states a "primary endpoint" of treatment is "the portion of patients with an ACR20 response at Week 24"; "secondary endpoints" include "[p]roportion of patients with ACR50 and 70 responses at Week 24"; and "[e]xploratory endpoints" involve "ACR(20/50/70 and ACR n) . . . over Weeks 8, 12, 16, 20, 24, and beyond . . . non erosive progression . . . at weeks 24 and beyond." Ex.1001 31:42-32:34. It further teaches that beneficial clinical response is determined "according to one or more of the[se] endpoints." *Id*. 32:40-43. This determination is a fundamental characteristic of the claimed invention, as evidenced by the patentee's reliance on endpoint limitations

in distinguishing art during prosecution. *Supra* § VI(B)(1)(b). Claim 10, like claims 11–14, requires a specific endpoint. Like those claims, its antibody administration step would have little meaning or utility, and would be a mere academic exercise, unless placed within the context of the specific purpose of achieving the endpoints, defined by its wherein clause.

3. "an amount that is effective to provide" (Claims 2–7)

Claim 2 recites administering an antibody which binds to CD20 in "an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond." Ex.1001 37:46-52. Claims 3–7 depend from claim 2. *Id*. 37:53-65. In asking the Board to ignore this limitation, Petitioner attempts to equate two different terms in the same claim: the clinical response limitation ("in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond") and the administering limitation ("the antibody is administered as two intravenous doses of 1000 mg"). Pet. at 27-28; Ex.1001 46-52. This invitation to error should be rejected: "In the absence of any evidence to contrary, we must presume that the use of [] different terms in claims connotes different meanings." *CAE Screenplates Inc. v. Heinrich Fiedler GmbH Co. Kg*, 224 F.3d 1308, 1317 (Fed. Cir. 2000). There is no contrary evidence.

Furthermore, the claim language demonstrates that the "amount that is effective to provide [a clinical response]" clarifies the "two intravenous doses of 1000 mg" phrase. Petitioner ignores that an amount of antibody cannot be "effective to provide" the recited clinical responses unless administering the antibody to the patient actually provides such a response. Indeed, as prior petitioners admitted, the claimed treatment produces a clinical response in "some but not all patients." *Celltrion, Inc. v. Genentech, Inc*., IPR2015-01733, Pap. 2 at 48 (Aug. 14, 2015). Merely claiming "two intravenous doses of 1000 mg" would not have required any particular clinical response be achieved. Thus, Petitioner's argument should be rejected.

VII. The Petition Fails to Establish that the Challenged Claims are Obvious in Light of the Cited Art

To justify institution, Petitioner must make a *prima facie* showing that, as a factual and legal matter for its asserted grounds, Petitioner's submitted evidence and arguments have a reasonable likelihood of proving at least one Challenged Claim unpatentable. § 314. Even if Edwards 2002 were assumed to be prior art,[8]

[8] As Petitioner has likely anticipated given its use of alternative grounds of invalidity that do *not* rely on Edwards 2002 (Pet. at 6-7), Petitioner will not show its § 102(a) reference, Edwards 2002, is prior art to the Challenged Claims. That is because, as detailed in Genentech's POPR in *Celltrion*, the

the Petition fails to establish a *prima facie case* that any of its prior art combinations render obvious each and every limitation of *any* Challenged Claim. Thus, Petitioner has failed again to meet its burden for institution.

A. The Petition Fails to Demonstrate that it Would Have Been Obvious to Treat TNFIRs Using Two 1000 mg Rituximab Doses

Every challenged claim requires treating RA "in a human patient who experiences an inadequate response to a TNFα-inhibitor" by administering "two intravenous doses of 1000 mg" of "an antibody that binds to CD20" (claims 1, 2, and 4–7) or of "rituximab" (claims 3, 8, and 9–14). Ex.1001 37:40-38:64.

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subject matter of Challenged Claims 1–3 and 7–9 was reduced to practice earlier. If Petitioner's claims were instituted, in addition to addressing the numerous other substantive errors and shortcomings that underlie Petitioner's arguments and purported evidence, Genentech anticipates presenting that same evidence to swear behind Petitioner's art. *See Celltrion*, IPR2016-01667, Pap. 13 at 19 (Dec. 6, 2016); *see also id.* at 20-29, Exs.2001-2004, 2007, 2010, 2023, 2036-2037, 2041, 2057, 2061-2062, 2085, 2088-2089, 2091-2096, 2098-2099. However, because all of Petitioner's arguments fail even without this showing, and in light of § 42.108(c), Patent Owner reserves those issues until its § 42.120 Response, if one is required.

Petitioner fails to establish that its asserted combinations of art render these claim limitations obvious.

1. The Cited Art Does Not Disclose TNFIRs

While Petitioner's cited art does disclose attempts to treat RA using rituximab, Petitioner failed to show that any art disclosed the hard-to-treat TNFIRs who are the focus of the Challenged Claims.

Under Ground I, Petitioner relies on the combination of Edwards 2002, Takemura, Klimiuk, Ulfgren and Curd. Pet. at 6. But *each* of these references is *silent as to whether any patients were TNFIRs*. Indeed, as Petitioner has acknowledged, and as this Board has twice held, Edwards 2002 does not disclose, explicitly or inherently, treating TNFIRs. Pet at 1; *Boehringer*, IPR2015-00417, Pap. 11 at 14-15; *Celltrion*, IPR2016-01667, Pap. 15 at 8-10.

The Board previously rejected the idea that the claim term "a patient who experiences an inadequate response to a TNFα-inhibitor" encompassed patients who would be TNFIRs due to some inherent condition of the patient but who had not actually experienced an inadequate response to a previous or current treatment with a TNFα-inhibitor. *Celltrion*, IPR2016-01667, Pap. 15 at 6-7. Instead, consistent with the '838 specification, TNFIRs are those patients who have actually been treated with and had an inadequate response to a TNFα-inhibitor. *Id*. But neither Klimiuk nor Takemura identifies ***any*** patient as having undergone

TNFα-inhibitor therapy, let alone as having an inadequate response to it. Takemura is silent as to any prior treatments undergone by its patients and Petitioner has not shown that any was a TNFIR. *In re Rijckeaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993). And, while Klimiuk reports on its patients' prior therapies, none was a TNFα-inhibitor. Ex.1006 at 6, Table 4. This is true even for patients with diffuse synovitis (*id*.), which as discussed below Petitioner attempts to improperly equate to being a TNFIR. Petitioner has failed to even identify any TNFα-inhibitor FDA approved for the treatment of RA as of Klimiuk's asserted 1997 publication date. (Understandably so, because there were none.) Thus, Petitioner's suggestion that "Klimiuk explained why many patients did not respond to TNFis" (Pet. at 14), even though it nowhere disclosed such patients, is an improper hindsight reading of the art.

To overcome these deficiencies, Petitioner attempts to equate "diffuse synovitis," discussed in both Klimiuk and Takemura, with the patient being an inadequate-responder. *See, e.g.*, *id*. at 39-40. Setting aside that this is contrary to the Board's uncontested prior reading of the claims as requiring actual previous or current TNFα-inhibitor treatment, not merely that the patient "would be" a TNFIR (*supra* § VI(A)), neither publication equates "diffuse synovitis" with being a TNFIR, as required to support Petitioner's post-hoc attempt to link Ulfgren with Klimiuk and Takemura. In fact, Klimiuk's description of diffuse synovitis is

inconsistent with such a conclusion. Klimiuk reports that diffuse synovitis RA is a "clinically milder disease that is responsive to nonaggressive treatment." Ex.1006 at 7. But, as Petitioner's own expert explained in European proceedings, TNFIRS are "difficult-to-treat RA patients." Ex.2008 at 1, 12. This is consistent with the description of TNFIRs in the file history and the Arthritis Foundation's description of TNFIRs, at the time of Rituxan®'s approval for treating RA, as a "difficult-to-treat patient population." Ex.2006 at 1; Ex.2007 at 412-413. Petitioner has not, and cannot, reconcile Klimiuk's own description of diffuse synovitis as a mild disease responsive to standard treatments (such as NSAIDs and synthetic DMARDs (Ex.1006 at 6-7)) with its position that these are simultaneously the same patients who are hard-to-treat TNFIRs requiring a non-standard treatment like rituximab.

The sole reference cited under Petitioner's Ground I that discusses patients treated with a TNFα-inhibitor is Ulfgren. But Ulfgren reports that, after a single 10 mg/kg infusion of TNFα-inhibitor infliximab, all eight patients "met the American College of Rheumatology 20% improvement response criteria (ACR 20) at 2 weeks, and half of these patients met the ACR 50." Ex.1007 at 1. Contrary to Petitioner's repeated assertion that Ulfgren "taught that RA patients with low levels of TNFα respond inadequately to TNFis" (Pet. at 40), nowhere does Ulfgren characterize any of its patients as a TNFIR. Indeed, Petitioner affirmatively points

to ACR20 among the possible "improvement" scores and suggests changes in therapy *only* if there is *no* improvement or scores *decline*. Pet. at 9. Moreover, while Ulfgren notes a "correlation" between the amount of TNFα and the observed response to the study's single dose of TNFα-inhibitor (Ex.1007 at 5-6), it does not report a causal relationship between the two. Nor does it report that the amount of TNFα present will result in any patient being a TNFIR. Despite premising its arguments on such a relationship, Petitioner fails to identify any teaching in Ulfgren of a causal relationship.

Petitioner fares no better in its Ground II combinations, which replace Edwards 2002 with Edwards 2001 and the Rituxan® Label. Pet. at 6-7. The only use of rituximab disclosed in the Label is for the treatment of NHL. Ex.1009 at 7. And while Edwards 2001 targeted patients whose RA was not adequately controlled using at least five synthetic DMARDs, it said nothing of TNFIRs. In fact, Edwards 2001 explicitly listed the DMARDs previously tried by each of its patients—none is a TNFα-inhibitor. Ex.1004 at 2, Table 1 n.b.

Because *each of Petitioner's cited references is silent as to TNFIRs*, Petitioner has failed to show that the cited art renders obvious the treatment of TNFIRs with an anti-CD20 antibody or rituximab. Thus, the Petition should be denied.

2. The Cited Art Does Not Teach or Suggest the Claimed Dosing Regimen For Treating TNFIRs

Even assuming it would have been obvious to treat TNFIRs using an anti-CD20 antibody or rituximab to begin with (it was not), Petitioner has failed to show it would have been obvious to treat these patients using the particular dosing regimen—two intravenous doses of 1000 mg—required by every Challenged Claim.

(a) Ground I Art

Instead, under Ground I, Petitioner argues a POSITA would be motivated to use the two 1000 mg doses of rituximab disclosed in Edwards 2002 to treat TNFIRs. Pet. at 36-42. But the Board in *Celltrion* previously rejected the idea that a POSITA would be motived to use the dosing disclosed in Edwards 2002 to treat TNFIRs. *Celltrion*, IPR2016-01667, Pap. 15 at 12-14; *id*., Pap. 19 at 5 (Aug. 18, 2017). In doing so, the Board emphasized the significant differences in the dosing regimens used in Edwards 2002 and Tuscano, which Celltrion alleged taught the treatment of TNFIRs using rituximab. *Celltrion*, IPR2016-01667, Pap. 15 at 13-14. Using the Board's prior opinion as a roadmap, Petitioner cynically attempts to avoid this problem by *omitting any disclosure of dosing for TNFIRs*. Thus, instead of arguing that the motivation to treat TNFIRs and reasonable expectation of success in doing so comes from art that actually discussed TNFIRs, as Tuscano allegedly did, Petitioner argues that it comes from the combination of Takemura,

Klimiuk and Ulfgren which, as discussed *supra* § VII(A)(1), do not discuss TNFIRs at all.

Petitioner's position is impermissible hindsight. Indeed, as set forth *supra* § VII(A)(1), none of Takemura, Klimiuk, or Ulfgren discuss TNFIRs, let alone their treatment with the claimed antibodies. And, while Petitioner attempts to equate "diffuse synovitis" in Klimiuk and Takemura with being a TNFIR (Pet. at 39-40), Petitioner cannot reconcile Klimiuk's own description of diffuse synovitis (Ex.1006 at 7) with its position that these patients represent the same hard-to-treat TNFIRs, or that a POSITA would be motivated to look to a non-conventional treatment like rituximab for these patients. Indeed, neither Klimiuk or Takemura report any clinical data showing efficacy of any drug in patients, and Petitioner's attempt to bridge this gap based on *in vitro* models of the disease cannot meet its burden as this is not how the impact of an RA drug is measured. Instead, as even Petitioner acknowledges, it is based on actual improvement seen in the patient. *See* Pet. at 9.

Petitioner's analysis also fails for the additional reason that it does not account for differences in dosing disclosed even in its own art. For example, under Ground I(b), Petitioner further relies on Curd. Pet. at 6, 46-47. But Curd's disclosed dosing differs from that in Edwards 2002 in terms of (i) dose-sizing, (ii) the total dosage amount, (iii) the number of doses, and (iv) the amount of drug

in each individual dose. Unlike Edwards 2002, which used fixed dosing, Curd teaches size-based (*i.e.*, variable) dosing, based on the patient's BSA. *See, e.g.*, Ex.1008 at 25:17-23. Curd also discloses using at least four doses instead of two, and includes examples of escalating doses rather than doses of equal amounts like Edwards 2002. Ex.1008 at 23:23-27, 25:17-23. For example, in Example 1, Curd discloses three RA dosing regimens, all of which are four-dose, BSA-based regimens with individual doses including 50 mg/m^2, 150 mg/m^2 and 375 mg/m^2. *Id*. at 25:9-23.[9] As discussed below, it is only through the use of impermissible hindsight that a POSITA would arrive at the claimed dosing regimen for treating TNFIRs from Petitioner's cited art.

Petitioner's argument that a POSITA would be motived to, and expect success in, using Edwards 2002's dosing to treat TNFIRs is premised on the assumptions that a POSITA would expect all RA patients to respond the same way

[9] While Curd does not disclose the actual amount of any individual dose or total final dosage of any proposed BSA-based regimen, using Petitioner's asserted BSA average of 1.6 m^2 (Pet. at 19), the lowest total dose disclosed in Curd's Example 1 would be 809.6 mg (dosing A (50 mg/m^2 x 1.6 m^2) + (150 mg/m^2 x 1.6 m^2 x 3) = 809.6 mg), and the highest disclosed would be 2400 mg (dosing C (375 mg/m^2 x 1.6 m^2 x 4) = 2400 mg).

to rituximab and that there is no relationship between being a TNFIR and how a patient responds to rituximab. *See* Pet. at 17, 41-42, 54. But Petitioner itself acknowledges that by no means was everything known regarding RA and why certain patients did and did not respond to therapy: "[a]s rheumatologists gained new insights into RA's etiology, new treatments emerged." Pet. at 11. And what was known from the art at the time, including the explicit teachings of De Vita 2002 did not support Petitioner's conclusion. Instead, De Vita's results show the assumptions underlying Petitioner's arguments are unsupported. Petitioner does not even acknowledge De Vita until page 60 of its Petition, and then only to anticipate an argument from *Boehringer* that De Vita taught away from the claimed invention. Pet. at 60-62. But that is not the issue here (nor was it the issue in *Celltrion* when the Board last denied institution). The issue is what a POSITA would have understood about the likelihood of success in treating TNFIRs with rituximab: De Vita 2002 taught that TNFIRs responded differently, and worse, to rituximab treatment than other RA patients.

In De Vita 2002, TNFIRs saw (1) no response or (2) only a transient ACR20 response with subsequent relapse, together with worsened joint erosion, when administered four rituximab doses of 375 mg/m^2, while other RA patients saw ACR50 and ACR70 responses. Ex.1016 at 2-4. In other words, contrary to Petitioner's assumption, the two populations of patients did *not* react in the same

way to rituximab treatment. De Vita 2002 does not disclose the BSA of any participant or the total rituximab dosage administered to any patient. But, assuming as Petitioner does an average BSA of 1.6 m^2 (Pet. at 19), De Vita's patients would have received a total rituximab dose of approximately 2400 mg (375 mg/m^2 x 1.6 m^2 x 4 doses), not 2000 mg as claimed. Petitioner offers no explanation of how or why a POSITA, who would be aware of De Vita's results, would believe the key to successfully treating TNFIRs, which De Vita itself showed were *more difficult* to treat, would be to (1) abandon BSA-based dosing tailored to the patient's size, (2) start with the dose that *did not successfully treat TNFIRs*, (3) *reduce* the number of doses of rituximab by 50% (from four to two), and, at the same time, (4) *reduce* the total dosage of rituximab by 400 mg (from 2400 mg to 2000 mg (2 x 1000 mg)) or nearly 20%. The reason is simple: they would not, and Petitioner's failure to explain this means it has failed to make the threshold showing required for institution.

(b) Ground II Art

Petitioner's Ground II art similarly fails to teach or suggest using the claimed dosing regimen to treat TNFIRs. Under Ground II, Petitioner replaces Edwards 2002 with Edwards 2001 and the Label. As set forth *supra* § VII(A)(1), none of the cited Ground II art discloses the use of an anti-CD20 antibody or

rituximab to treat TNFIRs. Nor does any piece of Ground II art disclose the use of two 1000 mg infusions of rituximab to treat any disease, let alone TNFIRs.

Faced with the fact that none of the cited art teaches or suggests the claimed dosing regimen, Petitioner argues that a POSITA would have arrived at the claimed dosing regimen as a matter of "routine optimization." Pet. at 48-55. In doing so, however, Petitioner ignores both the Examiner and Board's prior rejection of this argument, as well as the case law on "routine optimization."

(i) Petitioner's "Routine Optimization" Arguments Have Already Been Properly Rejected

Petitioner is not the first to attempt to overcome the deficiencies in its cited art by arguing that the claimed dosing regimen was simply a matter of routine optimization. But this argument was rejected both by the original Examiner during prosecution and by the Board in *Celltrion*.

During prosecution, the Examiner rejected the pending claims under § 103 based on Edwards 2001, Jenkins, and Goldenberg. Ex.2007 at 385-388. While none of the cited art disclosed the claimed dosing regimen, the Examiner initially argued that regimen was obvious as a matter of routine optimization. *Id*. at 387-388. However, the Examiner ultimately withdrew those rejections, allowing the Challenged Claims. *Id*. at 465.

In *Boehringer*, the Board accepted Boehringer's routine optimization argument in instituting claim 6. *Boehringer*, IPR2015-00417, Pap. 11 at 20-22.

The Board's opinion, however, focused only on Boehringer's argument that the number of doses would be reduced from four in the prior art to the two claimed to "solve the problem of patient compliance." *Id*. at 22. Nowhere did the Board specifically address how or why the other dosing parameters ((i) dose-sizing, (ii) the total dosage amount, and (iii) the amount of drug in each individual dose)) would be arrived at as a matter of routine optimization.

However, when the Board examined these additional parameters two years later in *Celltrion* with the benefit of briefing on the facts and law concerning "optimization" in Genentech's POPR, it came to the opposite conclusion, *rejecting* the idea that the claimed dosing regimen would result from mere routine optimization:

> [T]he claimed dosing regimen involves a number of variables that differ from the cited prior art, such as: dose-sizing option, i.e., fixed dosing vs. dosing based on body surface area (Curd and De Vita); total dose; number of infusions; and amount of each infusion. [ ] Petitioner has not demonstrated that each of those parameters represents a result-effective variable, such that a person of skill in the art would have had a reason to optimize it. . . . . Moreover, Petitioner has not explained adequately that the alleged routine optimization would result in modifying each parameter in a manner so as to arrive at the claimed dosage regimen.

Celltrion, IPR2016-01667, Pap. 15 at 17. For the same reasons, the same argument now repeated in this Petition should be rejected.

(ii) The Petition Fails to Address the Requirements for "Routine Optimization" Arguments

In spite of having in hand Genentech's *Celltrion* POPR (of which Petitioner was aware (Pet. at 38, Ex.1038)), Petitioner fails to address these requirements in the case law. For Petitioner to show "routine optimization" applies, and thus to argue that some "optimum value" of "a result effective variable" in a "known process" or composition is obvious, *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977), Petitioner must show at least five requirements are satisfied. But Petitioner (like Celltrion before it) fails to address any of these requirements with respect to any of the four variables reflected in the claimed dosing regimen (discussed *infra* §§ VII(A)(2)(b)(iii)-(vii)).

First, for "routine optimization" to apply, the resulting value must be the "*optimum value*" for the variable. *In re Antonie*, 559 F.2d at 620; *In re Aller*, 220 F.2d 454, 458 (C.C.P.A. 1955) ("No invention is involved in discovering *optimum* ranges of a process by routine experimentation."). Nowhere though does Petitioner even assert that any of the four dosing variables is in fact an "optimum."

Second, the variable being optimized must have been *"known" to be "result-effective." In re Antonie*, 559 F.2d at 620; *In re Yates*, 663 F.2d 1054, 1056 (C.C.P.A. 1981) (rejecting routine optimization argument where allegedly optimized variable "was not recognized to be a result-effective variable"). Nowhere does Petitioner assert that any, let alone every one of the four dosage

variables were "result-effective," or that a POSITA would have known by the '838's priority date, how each of these variables would interact in treating TNFIRs. In fact, the words "result-effective" appear nowhere in the Petition. But the Board highlighted *this same deficiency* in *Celltrion*, noting "Petitioner has not demonstrated that each of those parameters represents a result-effective variable, such that a person of skill in the art would have had a reason to optimize it." *Celltrion*, IPR2016-01667, Pap. 15 at 17. Despite having this decision, Petitioner repeats the same failure here, and the same rejection from the Board is warranted.

Third, for "routine optimization" to apply, the evidence must show that the *experimentation needed to optimize the variable was known* in the art. *In re Fay*, 347 F.2d 597, 602 (C.C.P.A. 1965). Nowhere does Petitioner present evidence describing the experimentation process that would have allegedly been needed to arrive at the claimed dosing regimen, let alone evidence that such experimentation was known as of the '838's priority date.

Fourth, the *prior art* must "have *suggested to one of ordinary skill in the art that this [experimentation] process should be carried out* and would have a *reasonable likelihood of success*, viewed in light of the prior art." *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989). Petitioner identifies no such suggestion. Indeed, as discussed *supra* § VII(A)(1), none of Petitioner's cited art discusses TNFIRs. Yet De Vita 2002, acknowledged by Petitioner only *after* its

obviousness analysis, reported that *more frequent dosing* and a *higher total dose* than claimed in the '838, resulted in no response or only an ACR20 response in TNFIRs, while other RA patients saw higher ACR50 and ACR70 responses. Ex.1016 at 2-4. Moreover, De Vita's TNFIRs also saw an *increase* in joint erosion. *Id*. at 4. Petitioner has not attempted to, and cannot, reconcile its assertions of a reasonable expectation of success from *decreasing* the total amount and frequency of dosing for TNFIRs (*supra* § VII(A)(2)(a)) with the teachings of its own cited art.

Fifth, the *experimentation required* to arrive at the claimed optimum must be "*nothing more than routine*." *Merck & Co.*, 874 F.2d at 809. But nowhere does Petitioner provide evidence that any required experimentation—which it never describes to begin with—would have been merely routine.

In sum, because Petitioner has failed to show a POSITA would have arrived at the claimed dosing regimen through "routine optimization," just as in *Celltrion*, this argument fails, and Petitioner has failed to show that the claimed dosing regimen—required in every Challenged Claim—would have been obvious.

(iii) Petitioner's Routine Optimization Arguments are Impermissible Hindsight

Petitioner's dosage optimization arguments, made in support of its Ground II combinations, fail for the additional, independent reason that they are the result of impermissible hindsight.

Arriving at the claimed dosing regimen requires making choices about at least four variables. As set forth below, the dosing in ***every one*** of Petitioner's Ground II references that disclose administering rituximab to humans differs from the claimed dosing regimen in at least three of the four dosing variables. Indeed, Curd and the Label differ in ***all four*** variables. Thus, arriving at the claimed dosing regimen would require the POSITA to *ignore* the disclosed dosing and instead pluck out and combine elements in a way that contradicts the very references on which Petitioner relies.

Dosing Variables	'838 Claimed Dosing Regimen	Edwards 2001	Curd	Rituxan® Label for NHL
Dose-Sizing (Fixed v. BSA-Based Dosing)	Fixed	Fixed	BSA	BSA
Total Dosage Amount	2000 mg	2100 mg	Not disclosed ~ 809.6 mg to ~2,400 mg assuming 1.6 m^2	Not disclosed ~2400 mg assuming 1.6 m^2
Number of Doses	2	4	4	4
Amount Per Dose	1000 mg	300 mg, 600 mg, 600 mg, 600 mg	(1) 50 mg/m^2, 150 mg/m^2, 150 mg/m^2, 150 mg/m^2 (2) 150 mg/m^2, 375mg/m^2, 375mg/m^2, 375mg/m^2 (3) 375 mg/m^2	375 mg/m^2

As set forth in detail below, looking at this art together, it is only through impermissible hindsight using the '838 as a roadmap that Petitioner, from this art, purports to "optimize[]" the dosing in this art (Pet. at 48-53) to arrive at the claimed dosing regimen. This cannot support obviousness. *See In re NTP, Inc.*, 654 F.3d 1279, 1298-99 (Fed. Cir. 2001) (reversing obviousness finding based on improper "hindsight reasoning to piece together elements to arrive at the claimed

invention"); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); *Janssen Pharms., Inc. v. Watson Labs., Inc.*, No. 08-cv-5103, 2012 WL 3990221, at *24 (D.N.J. Sept. 11, 2012) (finding claimed dosing regimen non-obvious where obviousness argument "appears persuasive only from the perspective of the rear-view mirror" and "appears to start with the invention and work backwards").

(iv) Dose-Sizing

Under Petitioner's theory, to arrive at the claimed dosing regimen, there is first a choice among dose-sizing options. Among the available options are (i) fixed dosing for all patients as claimed in the '838; (ii) size-based dosing based on, *e.g.*, a patient's BSA as was used for treating NHL according to the Label and taught in Curd; or (iii) a combination of the two.

While Petitioner suggests a POSITA would prefer fixed dosing (Pet. at 50), the totality of Petitioner's cited art overwhelmingly suggests otherwise. Of Petitioner's Ground II art, only Edwards 2001 uses fixed dosing. Ex.1004 at 2. Both Curd and the Label teach only BSA-based dosing. Ex.1008; Ex.1009. Petitioner fails to explain why or how, if it is correct that the preference was for fixed dosing, most of its cited art used BSA-based dosing instead.

(v) Total Dose

Second, for Petitioner to achieve the claimed dosing regimen, the proper total dose of the anti-CD20 antibody (claims 1, 2, and 4–7) or of rituximab (claims 3, 8, and 9–14) must be selected. Even assuming a POSITA would have gone against the majority of Petitioner's own relied-upon art to select fixed dosing to the exclusion of any BSA-based dosing, it is undisputed that *none of the Ground II cited art teaches the claimed 2000 mg total dose*. Petitioner does not specifically address how or why a POSITA (without the benefit of the '838) would select the total dosage administered to match the '838 claims. And, Petitioner fails to reconcile its conclusion with its own cited art, including Edwards 2001, Curd and the Label.

(vi) Number of Doses

Third, arriving at the claimed dosing regimen as Petitioner suggests would additionally have required determining the number of doses over which to divide the total dose. While each Challenged Claim requires ***two*** infusions, *every one of Petitioner's Ground II cited references teaches using at least* ***four*** *infusions*. Ex.1004 at 2; Ex.1008 at 25:17-23; Ex.1009 at 8. Petitioner's assertion that a POSITA would be motived to use fewer infusions (Pet. at 49-51) is thus belied by the very art it cites, *none* of which identified such a need, let alone acted on it.

Petitioner attempts to justify its hindsight-based selection of two doses by arguing that reducing the number of doses would improve patient compliance. Pet. at 51. Nowhere does Petitioner identify any actual patient compliance problem with respect to RA drugs, let alone with those administered intravenously. Indeed, the claims of the '838 are directed to patients that had previously taken, but did not adequately respond to, TNFα-inhibitor injections and were now trying the claimed therapy. That these patients continue to seek treatment after an inadequate response to prior TNFα-inhibitor treatment suggests they are complying with attempts to treat their RA. This is particularly true given that TNFα-inhibitors, including REMICADE® and ENBREL®, were administered using significantly more than four doses. Ex.1048 at 6; Ex.1050 at 10. Moreover, Petitioner fails to explain how subjecting a patient to two infusions each using significantly more drug than any single infusion in the cited art, thus lengthening infusion time, would increase patient compliance or be more convenient for patients. Unlike oral drugs that can be swallowed in an instant, infused therapies like rituximab are administered slowly, with duration depending on the amount administered. Indeed, one article reports the mean time required for a first infusion of only 375 mg/m^2 of rituximab in cancer patients (well below what Petitioner argues would be obvious) was 5.2 hours, with values ranging from 2.5 to 20 hours. Ex.2009 at 4-5.

Petitioner attempts to justify its position on decreasing the number of total doses based on statements by Genentech in proceedings involving the '172. Pet. at 49-50. But those statements regarding *modifications* for NHL maintenance therapy dosing are irrelevant here. The '172 claims methods of treating NHL, not RA, and two-year maintenance therapy, not dosing as claimed. Ex.1035 at 17, 20-23. What one would have done to alter dosing in that context is irrelevant to what one would do for treating hard-to-treat TNFIRs, and Petitioner's attempt to distort these out-of-context statements should be rejected.

And even if it were assumed that a POSITA would be motivated to decrease the total number of doses from the four in Petitioner's art, Petitioner does not explain why or how a POSITA would have selected exactly two doses instead of three doses or even a single dose. This same deficiency was identified in *Celltrion*, where the Board rejected petitioner's dose optimization arguments: "[Petitioner] has not explained why a skilled artisan would not have considered an optimized dose to include three infusions or some number of infusions with differing, e.g., escalating, dosage amounts." IPR2016-01667, Pap. 15 at 18. Even with that decision in hand, Petitioner here does nothing to address this same shortcoming, and this new Petition should similarly be rejected.

(vii) Amount of Each Dose

Finally, arriving at the claimed dosing regimen under Petitioner's argument requires selecting the amount of each infusion. While every Challenged Claim requires two doses of 1000 mg, *none of the Ground II cited art identifies a specific initial dose* of an anti-CD20 antibody or rituximab for treating RA *greater than 375 mg/m^2* which, assuming an average BSA of 1.6 m^2 (Pet. at 19), would be 600 mg. This is not surprising given that 375 mg/m^2 is the individual infusion dosage for treating NHL and, as Petitioner's own Edwards 2001 explained, protocols using rituximab for treating RA were based on the therapy used for treating NHL. Ex.1004 at 2; Ex.1009 at 11. Petitioner has not explained why a POSITA would increase the maximum disclosed individual dose for rituximab in treating RA, as well as the maximum individual dose approved to treat cancer (NHL), by more than 40% to arrive at the claimed dosage sizes. Nor has Petitioner explained why a POSITA would have used two infusions of equal size instead of escalating dosage amounts as taught in Edwards 2001 and Curd to avoid adverse reactions. Indeed, in *Celltrion*, there was additional evidence (which Petitioner ignores) regarding the risk of adverse reactions during the initial dosing of rituximab. Ex.1038 at 66-67 (citing Exs.2066, 2077, 2079, and 2090).

Petitioner's additional assertion that two doses of 1000 mg were an obvious choice because rituximab was already supplied in 500 mg and 100 mg vials (Pet. at

51-53) ignores (1) Petitioner's own prior art references, some of which teach dosages that conflict with this argument,[10] and (2) all of the intermediate dosage amounts—including the amounts that were actually used in Petitioner's cited references—one can obtain from combining vials of 100 mg or of 100 mg and 500 mg. For example, the four doses disclosed in Edwards 2001 (300 mg, 600 mg, 600 mg and 600 mg) can all be obtained using these vial amounts. Nothing about these vial sizes (or about Edwards 2001's actual use of 300 mg and 600 mg dosages that contradict Petitioner's arguments here) suggests the claimed 1000 mg doses.

Finally, Petitioner's argument that two doses of 1000 mg were obvious to try because rituximab's known pharmacokinetic profile suggested that the total dosage could be decreased to treat RA (Pet. at 20-22, 49-53) is, at best, improper hindsight. Even assuming a POSITA would have considered such a calculation in determining dosing—and nothing in Petitioner's POSITA definition (Pet. at 7) suggests a POSITA would possess such pharmacokinetic expertise—Petitioner

[10] For example, in dosing schedule A of Curd Example 1, the 50 mg/m^2 dosage would be an 80 mg dose for a 1.6 m^2 person (50 mg/m^2 x 1.6 m^2) and the 150 mg/m^2 dosage would be a 243.2 mg dose for a 1.6 m^2 person (150 mg/m^2 x 1.6 m^2).

failed to allege, let alone show, that any such equivalence was known prior to the '838. Petitioner has also failed to reconcile its position with De Vita 2002 which taught that TNFIRs saw an increase in joint erosion and achieved only (1) a transient ACR20 response or (2) no response when administered four doses of 375 mg/m^2 rituximab, the same dosage disclosed in the label for NHL. Ex.1016 at 2-4.

Because Petitioner has filed to show that the cited art teaches or suggests treating TNFIRs with the claimed dosing regimen of two 1000 mg doses, Petitioner's obviousness claims fail and institution should be denied.

B. The Petition Fails to Establish that the Claimed Clinical Response Limitations Were Obvious

Challenged Claims 2–7 and 10–14 each require an "ACR50 response at week 24," an "ACR70 response at week 24," or "no erosive progression at weeks 24 and beyond." Ex.1001 37:40-38:64; *supra* § VI(B). However, none of Petitioner's art teaches or suggests the claimed clinical responses ***in TNFIRs***. The Petition should be denied for this additional reason.

No Disclosure of ACR50 or ACR70 Responses: Petitioner seemingly acknowledges that none of Klimiuk, Ulfgren, Takemura, Curd or the Label disclose any clinical response for patients treated with anti-CD20 antibodies or rituximab whatsoever. Instead, Petitioner's sole bases for arguing that the claimed clinical responses are disclosed in the prior art is Edwards 2002 (Ground I) and

Edwards 2001 (Ground II). Pet. at 42-45, 58-59. But the ACR50 and ACR70 responses disclosed in Edwards 2002 and Edwards 2001 are ***not disclosed in TNFIRs***. Indeed, as detailed *supra* §§ III(A)-(B), VII(A)(1), both Edwards 2002 and Edwards 2001 are ***silent as to whether the patients were TNFIRs***.

Petitioner's suggestion that a POSITA would have expected the same responses disclosed in this art from TNFIRs ignores what the art (eventually acknowledged on page 60 of the Petition) actually taught. TNFIRs, as Petitioner has acknowledged, are hard-to-treat patients. Ex.2008 at 1, 12; *see also* Ex.2006 at 1. And, as discussed above, De Vita 2002 reported that while other RA patients obtained ACR50 and ACR70 responses, the two TNFIRs in its study achieved (1) only a transient ACR20 response (with subsequent relapse) and (2) no response. Ex.1016 at 2-4. Thus, De Vita 2002 itself suggested that TNFIRs respond differently (and less well) to rituximab than other RA patients such that obtaining ACR50/ACR70 responses in certain RA patients did not correlate to achieving those responses in TNFIRs. This directly contradicts Petitioner's argument (Pet. at 41-42, 54-55) that a POSITA would expect the same responses in both populations or would have a reasonable expectation of success in achieving the same responses in both populations. Nowhere does Petitioner even attempt to explain this inconsistency in its arguments.

No Disclosure of No Erosive Progression: Tellingly, Petitioner also remains silent regarding any alleged teaching or suggestion in the art of the claimed "no erosive progression at 24 weeks and beyond," as specifically required by claims 10 and 14. Indeed, the TNFIRs in De Vita 2002 actually saw an ***increase*** in joint erosion. Ex.1016 at 4. Even if one were to accept Petitioner's argument that the cited art rendered obvious the claimed dosing regimen (and as set forth above it does not), Petitioner makes no attempt to explain why a POSITA would have a reasonable expectation of success in obtaining *no erosive progression* in the very patients De Vita 2002 reported as experiencing an *increase*.

Because Petitioner has failed to show that the cited art teaches or suggests the claimed clinical responses in TNFIRs, Petitioner's claim 2–7 and 10–14 arguments fail and institution should be denied for this additional reason.

VIII. Conclusion

Petitioner has failed to show that there is a reasonable likelihood that it will prevail in proving any Challenged Claim unpatentable, and the Petition should be denied in its entirety.[11]

[11] Patent Owner reserves the right to make additional arguments based on the Supreme Court's decision in *Oil States* (No. 16-712, now pending).

Respectfully submitted by: Dated: January 5, 2018

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 complies with the type-volume limitation in 37 C.F.R. § 42.24(b)(1). According to the word-processing system's word count, the brief contains 13,990 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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