UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.
Petitioner

v.

GENENTECH, INC.
Patent Owner.

CASE IPR2016-01667
Patent 7,976,838

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

TABLE OF CONTENTS

Page

I. INTRODUCTION 1

II. BACKGROUND 6

A. '838 Patent Prosecution History 6

B. Rituximab 6

III. CLAIM CONSTRUCTION 8

A. The Plain Meaning Of The Claims Requires That The Recited Patient Has Been, Or Is Being, Treated With A TNFα-Inhibitor. 8

B. Clinical-Response Limitations Cannot Be Read Out Of The Claims. 10

1. "achieving a clinical response selected from…"(Claims 11-14) 12

a) The Applicants Chose To Use Both The Preamble And The Body Of Claim 11 To Define The Claimed Subject Matter. 12

b) The Bodies of Dependent Claims 12-14 Rely Upon, And Derive Antecedent Basis From, The Clinical Responses Recited In The Preamble Of Claim 11 13

c) The Applicants Relied On The Clinical Responses Recited In The Preamble Of Claim 11 To Distinguish Cited Art. 13

d) Celltrion Fails To Address The Above Points Even Though Genentech Raised Them Previously. 14

Page

2. "wherein the clinical response is…" (Claims 12-14) and "wherein the patient has no erosive progression…" (Claim 10) 15

a) The "wherein" Clauses Relate Back To And Clarify The "administering" Steps. 16

b) Construing the "wherein" Clauses As Non-Limiting Would Create Absurd Outcomes. 17

c) Reliance During Prosecution On Limitations In The Disputed "wherein" Clauses to Distinguish Cited Art Further Confirms That Those Clauses Are Limiting. 18

3. "an amount that is effective to provide..."(Claims 2-7)..... 18

IV. PRIOR INVENTION..... 19

A. The Collaboration Between Genentech and Roche 20

[redacted]

Page

V. CELLTRION FAILS TO ESTABLISH THAT IT LIKELY WOULD PREVAIL BASED ON THE REFERENCES IT RELIES ON UNDER 35 U.S.C. §102(a). 29

A. Ground 1: Edwards 2002 Does Not Anticipate Claims 1-5 and 7-14 30

1. Edwards 2002 Is Not Prior Art As To Claims 1-3 and 7-9 ... 30

2. Edwards 2002 Does Not Anticipate Any Claims 30

a) Edwards 2002 Does Not Disclose Treating A "Patient Who Experiences An Inadequate Response To A TNFα-Inhibitor." 31

(i) Inherency Cannot Be Established By Probabilities 31

(ii) Celltrion's Probability Argument Relies On Its Incorrect Claim Construction 32

b) Edwards 2002 Does Not Disclose Achieving "No Erosive Progression At Weeks 24 And Beyond." 32

c) Edwards 2002 Does Not Disclose Achieving ACR50 Or ACR70 Responses In Patients Who Experience An Inadequate Response To A TNFα-Inhibitor. 33

B. Ground 2: The Combination Of Edwards 2002 In View Of Tuscano Does Not Render The Claims Obvious. 34

1. Edwards 2002 And Tuscano Do Not Constitute Prior Art As To Claims 1-3 and 7-9. 34

2. Claims 2-7 and 10-14 Are Not Rendered Obvious By Edwards 2002 In View Of Tuscano. 35

a) Neither Edwards 2002 nor Tuscano discloses the claimed clinical responses. 35

Page

b) Celltrion fails to establish that a PHOSITA would have combined Edwards 2002 and Tuscano with a reasonable expectation of success. 35

(i) The art taught that erosive progression continues in TNFα-inadequate-responders despite treatment with rituximab. 36

(ii) The art disclosed that TNFα-inadequate-responders could not achieve ACR50 or ACR70 responses with rituximab. 37

(iii) Celltrion's expectation-of-success arguments lack evidentiary and legal support. 38

VI. CELLTRION FAILS TO ESTABLISH THAT IT LIKELY WOULD PREVAIL ON THE REFERENCES IT RELIES ON UNDER 35 U.S.C. §102(b) – GROUND 3. 41

A. Goldenberg, Curd, and De Vita Fail To Disclose Key Limitations. 42

1. None of Goldenberg, Curd or De Vita discloses two 1000 mg infusions of an anti-CD20 antibody, as required by all claims. 42

a) Celltrion's "routine optimization" arguments ignore the "routine optimization" case law. 42

b) Celltrion's "routine optimization" arguments rely on hindsight reconstruction, which is impermissible. 46

(i) Celltrion ignores the variable requiring a choice between size-based dosing, fixed dosing, or a combination of both. 48

Page

(ii) Celltrion's argument concerning the total dose variable relies on erroneous characterizations of the prior art. 48

(iii) Celltrion's argument concerning the number of rituximab infusions fails. 51

(iv) Celltrion's "routine optimization" argument ignores the variable of infusion amounts. 54

c) Celltrion admits that safety concerns would have led a PHOSITA away from using a dosing regimen as claimed here. 54

(i) Celltrion admits that a PHOSITA would not have made the infusion sizes equal. 54

(ii) Celltrion admits that the prior art warned against a first infusion as high as 1000 mg 55

2. None of the Ground 3 references discloses achieving the clinical responses required by claims 2-7 and 10-14. 56

B. Celltrion Fails To Establish A Motivation To Combine The Cited References To Arrive At The Claimed Invention. 57

1. Goldenberg teaches away from at least the invention of claim 7. 57

2. Celltrion's motivation-to-combine arguments with respect to claims 1-14 do not withstand scrutiny. 58

C. Celltrion Fails To Establish A Reasonable Expectation Of Success In Achieving What Is Claimed. 59

1. De Vita and Goldenberg would not have inspired in a PHOSITA a reasonable expectation of success in treating the patients of claims 1-14. 60

Page

2. Celltrion fails to establish a reasonable expectation of success in specifically achieving the clinical responses required by claims 2-7 and 10-14. 60

VII. CONCLUSION 61

CERTIFICATE OF SERVICE 64

TABLE OF AUTHORITIES

Page(s)

Cases

Abbott Labs. v. Andrx Pharm., Inc.,
473 F.3d 1196 (Fed. Cir. 2007) 12

AK Steel Corp. v. Sollac & Ugine,
344 F.3d 1234 (Fed. Cir. 2003) 17

In re Aller,
220 F.2d 454 (C.C.P.A. 1955) 43

In re Antonie,
559 F.2d 618 (C.C.P.A. 1977) 42, 43

Ex Parte Behzad,
Appeal 2011-007124, 2014 WL 1311619 (P.T.A.B. Mar. 28, 2014) 17

Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.,
55 F.3d 615 (Fed. Cir. 1995) 12

In re Boesch,
617 F.2d 272 (C.C.P.A. 1980) 43

Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.,
246 F.3d 1368 (Fed. Cir. 2001) 11, 14, 16

CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co. Kg,
224 F.3d 1308 (Fed. Cir. 2000) 19

Catalina Mktg. Int'l Inc. v. Coolsavings.com, Inc.,
289 F.3d 801 (Fed. Cir. 2002) 18

Cooper v. Goldfarb,
154 F.3d 1321 (Fed. Cir. 1998) 25

Eaton Corp. v. Rockwell Int'l Corp.,
323 F.3d 1332 (Fed. Cir. 2003) 13

Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.,
471 F.3d 1369 (Fed. Cir. 2006) 57

Page(s)

In re Fay,
347 F.2d 597 (C.C.P.A. 1965) 44

Ferrum Ferro Capital, LLC v. Allergan Sales, LLC,
IPR2015-00858 (Paper 10) (Sep. 21, 2015) 11

Funai Elec. Co. v. Daewoo Elecs. Corp.,
616 F.3d 1357 (Fed. Cir. 2010) 17

Griffin v. Bertina,
285 F.3d 1029 (Fed. Cir. 2002) 15, 16

In re Gurley,
27 F.3d 551 (Fed. Cir. 1994) 57

Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.,
821 F.3d 1359 (Fed. Cir. 2016) 35, 59

Invitrogen Corp. v. Biocrest Mfg. LP,
327 F.3d 1364 (Fed. Cir. 2003) 13

Life Techs., Inc. v. Clontech Labs., Inc.,
224 F.3d 1320 (Fed. Cir. 2000) 41

Loral Fairchild Corp. v. Matsushita Elec.,
266 F.3d 1358 (Fed. Cir. 2001) 25

Mahurkar v. C.R. Bard, Inc.,
79 F.3d 1572 (Fed. Cir. 1996) 30

MEHL/Biophile Int'l Corp. v. Milgraum,
192 F.3d 1362 (Fed. Cir. 1999) 30

Merck & Co. v. Biocraft Labs., Inc.,
874 F.2d 804 (Fed. Cir. 1989) 44, 45, 46

In re Montgomery,
677 F.3d 1375 (Fed. Cir. 2012) 31

In re Peterson,
315 F.3d 1325 (Fed. Cir. 2003) 42, 43, 51

Page(s)

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007) 51

REG Synthetic Fuels, LLC v. Neste Oil OYJ,
No. 2015-1773, 2016 WL 6595978 (Fed. Cir. Nov. 8, 2016) 25

In re Saether,
492 F.2d 849 (C.C.P.A. 1974) 46

Schering Corp. v. Geneva Pharms.,
339 F.3d 1373 (Fed. Cir. 2003) 50

Smith & Nephew, Inc. v. Bonutti Skeletal Innovations, LLC,
IPR2013-00605, Paper 9 13

St. Jude Med., Inc. v. Access Closure, Inc.,
729 F.3d 1369 (Fed. Cir. 2013) 53

Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.,
806 F.3d 1356 (Fed. Cir. 2015) 8, 10

Texas Instruments Incorporated v. ITC,
988 F.2d 1165 (Fed. Cir. 1993) 11

Unigene Labs., Inc. v. Apotex, Inc.,
655 F.3d 1352 (Fed. Cir. 2011) 57

In re Urbanksi,
809 F.3d 1237 (Fed. Cir. 2016) 44

Ex parte Whalen,
89 U.S.P.Q.2d 1078 (B.P.A.I. 2008) 46

In re Yates,
663 F.2d 1054 (C.C.P.A. 1981) 43

Statutes

35 U.S.C. §102(a) 1, 19, 29, 30

35 U.S.C. §102(b) 1, 3, 41

Page(s)

MPEP § 2143.02(III).....41

MPEP § 2164.02 50

I. INTRODUCTION

The Board should decline to institute IPR2016-01667 because the petition fails to establish a reasonable likelihood that Celltrion would carry its burden to show that any claim of U.S. Patent No. 7,976,838 ("'838 patent") is not patentable.

Celltrion's petition advances three grounds of challenge. Grounds 1 and 2 are based on references that Celltrion contends are prior art under §102(a), and Ground 3 is based on references that Celltrion contends are prior art under §102(b). Pet. 30. All three grounds fail.

Ground 1

Celltrion argues that claims 1-5 and 7-14 are inherently anticipated by "Edwards 2002." But Edwards 2002 does not even qualify as prior art with respect to a number of claims. Specifically, the subject matter of at least claims 1-3 and 7-9 was conceived and actually reduced to practice by the inventors at least by July 2002 and no later than September 2002—before the alleged October 2002 publication date of Edwards 2002.[1] Indeed, one inventor of the '838 patent—Dr. Randall Stevens—describes some of his prior inventive work in Edwards 2002, which he co-authored.

[1] The rules in effect during the previous IPR did not allow Genentech to submit evidence of actual reduction to practice in its POPR.

Even if Edwards 2002 were prior art with respect to all claims, Ground 1 would still fail because all claims require treating a rheumatoid arthritis ("RA") patient who experiences an inadequate response to a TNFα-inhibitor (a "TNFα-inadequate-responder" or "TNF failure"). Claims 2-7 and 10-14 additionally require achieving one of three specific clinical responses in such a patient. Neither requirement is disclosed in Edwards 2002.

Relying solely on probabilities, Celltrion argues that Edwards 2002 *inherently* discloses this missing subject matter. The Federal Circuit has repeatedly held, however, that inherency cannot be established by probabilities, as the Board found previously. Therefore, Edwards 2002 does not disclose every limitation of claims 1-5 and 7-14, and Ground 1 fails.

Ground 2

Celltrion contends that all claims are rendered obvious by Edwards 2002 in combination with Tuscano. Here again, neither reference qualifies as prior art with respect to many claims. The alleged publication date of Edwards 2002 (October 2002) is later than the inventors's actual reduction to practice of claims 1-3 and 7-9, as discussed in connection with Ground 1, and the alleged publication date of Tuscano (December 2002) is later still. Ground 2 therefore fails as to those claims.

Ground 2 also fails as to all of the other claims. Like Edwards 2002, Tuscano does not disclose achieving the specific clinical responses required by

claims 2-7 and 10-14 in a TNFα-inadequate-responder. Even assuming that a PHOSITA would have been motivated to combine and modify Edwards 2002 and Tuscano in the way Celltrion suggests, Celltrion offers no reason (much less evidence) that a PHOSITA would have had a reasonable expectation of success in achieving the claimed clinical responses in such patients. Instead, Celltrion attempts to read the clinical-response limitations out of the claims, contrary to fundamental principles of claim construction. Celltrion also ignores evidence demonstrating that a PHOSITA would *not* have had a reasonable expectation of success in achieving the claimed clinical responses.

Thus, Ground 2 fails because Edwards 2002 and Tuscano do not constitute prior art as to claims 1-3 and 7-9, and do not render claims 2-7 and 10-14 obvious given the clinical response limitations in those claims.

Ground 3

Celltrion argues that three alleged §102(b) references—Goldenberg, Curd, and De Vita—render all claims obvious. But all claims require administering two 1000 mg infusions of anti-CD20 antibody (such as rituximab), and none of the references discloses this dosing. Celltrion expressly concedes this point. Pet. 52.

Celltrion argues that skilled artisans nonetheless would have arrived at the claimed dosing regimen by "routine optimization." But the claimed dosing regimen reflects choices with respect to at least four different variables—dose sizing (e.g.,

fixed, based on the size of the patient ("size-based"), or a combination of both), total dose, number of infusions, and infusion amount(s)–and Celltrion fails to establish that any of the claimed choices can be characterized as an optimum. Nor does Celltrion establish that any variable is result-effective or that any process for optimizing those variables was known and would have been routine, as required by the case law. Celltrion does not even address the controlling case law.

Celltrion does not even address two of the four variables (dose sizing and infusion amount(s)). For the remaining variables (total dose and number of infusions) Celltrion relies on erroneous characterizations of the alleged prior art, or ignores the art altogether. For example, to support its argument that the total dose claimed—though undisclosed by the alleged prior art—nevertheless falls within a prior art range, Celltrion represents that "Goldenberg discloses successful treatment of RA with a total dose of 1500 mg (Ex. 1038 at 22[[2]]) and De Vita discloses successful treatment of RA with a total dose of 2550 mg." Pet. 53. But that is wrong. Goldenberg discloses a dose of anti-B cell antibodies totaling 3000 mg, and De Vita discloses a size-based dose of four 375 mg/m^2 infusions, where the units of m^2 refer to patient body surface area (BSA). Even if De Vita were deemed to teach an absolute dose of 2550 mg, the claimed total dose of 2000 mg

[2] Celltrion pincites to native page numbers in Exhibit 1038. This POPR pincites to exhibit-label page numbering throughout.

would be substantially lower than the total doses taught by either reference, and therefore well outside any range that could be constructed from those doses.

Thus, only by reliance on hindsight, not routine optimization, can Celltrion argue that the Ground 3 references would have led a PHOSITA to the claimed dosing of two 1000 mg infusions. This reliance on hindsight is even more starkly evidenced by the fact that Celltrion's "routine optimization" argument runs contrary to Celltrion's own admissions that safety concerns would have led a PHOSITA *away* from the claimed dosing of two equal 1000 mg infusions. Elsewhere, Celltrion admits that a PHOSITA would *not* have made the infusion sizes equal because a PHOSITA "would have been motivated to administer an initial dose of rituximab that is *lower* than a subsequent dose of rituximab in accordance with the general medical principle that patients should be titrated up slowly on medications to minimize unwanted side effects." Ex. 2068 at 38-39 (emphasis added).

Celltrion also admits that a PHOSITA would not have chosen a first infusion that is higher than the FDA-approved first infusion for treating cancers—375 mg/m^2 (about 640 mg based on an average BSA of 1.7 m^2)—because the literature "warns the skilled person against increasing the *first* dose" over 375 mg/m^2 "in order not to increase infusion-related side effects." Ex. 2066 at 31-32 (emphasis in original). Consistent with Celltrion's admission, each Ground 3 reference teaches

using a first rituximab infusion equal to or lower than 375 mg/m^2 (~640 mg on average). The claimed 1000 mg infusion, by contrast, is significantly higher than that. Celltrion's admissions expose its "routine optimization" argument as textbook hindsight, which is impermissible to prove obviousness.

Celltrion is unable to establish a reasonable likelihood of prevailing on any of Grounds 1, 2, or 3. The Board should decline to institute IPR.

II. BACKGROUND

A. '838 Patent Prosecution History

Prosecution of the '838 patent began with the filing of a provisional application on April 9, 2003, Ex. 2097, followed by a nearly-identical non-provisional application on April 6, 2004, Ex. 2064, claiming priority thereto. The patent issued from a continuation of the non-provisional application, Ex. 2065, listing Dr. Mark Benyunes as inventor. Ex. 1001. A certificate of correction later issued identifying Dr. Randall Stevens as a co-inventor. Ex. 2067.

All references on which Celltrion grounds its challenge were cited during prosecution of the patent and considered by the Office, with only one exception. Ex. 1001. Instead of the "De Vita" abstract (Ex. 1051), a full-length, 2002 article reporting on the same study (Ex. 1032) was cited and considered by the Office.

B. Rituximab

Rituximab is an antibody that binds to a B-cell-surface antigen designated CD20, leading to the depletion of B cells. Ex. 1001 at 1:54-62, 2:32-34. In 1997,

Genentech first obtained FDA approval for rituximab to treat certain non-Hodgkin's lymphomas (NHLs) at a size-based dose of 375 mg/m^2 BSA per week for four weeks. Ex. 1027 at 4.

In collaboration with the F. Hoffmann-La Roche family of companies ("Roche") and IDEC Pharmaceuticals, Inc. ("IDEC"), Genentech also developed an additional rituximab indication for treatment of RA patients who experience an inadequate response to a TNFα-inhibitor, which typically was prescribed only after a patient already "failed at least 2-3 conventional RA therapies." Ex. 1004 ¶6. Genentech's two-year Phase III clinical trial in more than 500 of these difficult-to-treat patients was called "REFLEX," Ex. 2085, and it lead to FDA approval. Ex. 2084.

Patients in the REFLEX trial showed marked improvements in ACR scores, which are measured using a scale developed by the **A**merican **C**ollege of **R**heumatology. Ex. 1014. An ACR20 score, for example, generally corresponds to a 20% improvement in certain signs and symptoms of the disease. *Id.* Although patients in the REFLEX study were particularly hard to treat, Ex. 1004 at ¶¶6, 12, many achieved ACR50 and ACR70 responses. Ex. 2085 at 1.

More surprisingly, a substantial number of the REFLEX patients who received rituximab therapy had no progression in joint erosion at 24 weeks and beyond, *id.* at 1, and even after two years. Ex. 2073 at 27-28. Joint erosion, which

is measured using x-rays, is the progressive destruction of bone and cartilage associated with RA. Ex. 2060 at 2, 8. Preventing erosive progression is critical for an RA patient because destruction of bone and cartilage ultimately leads to permanent disabilities, *id.* at 9, even if the patient's symptoms are controlled by other agents. Ex. 1018 at 1. Indeed, "a substantial proportion of patients continue to show radiographic progression, even though clinically they are in a state of low disease activity." *Id.* at 1.

III. CLAIM CONSTRUCTION

A. The Plain Meaning Of The Claims Requires That The Recited Patient Has Been, Or Is Being, Treated With A TNFα-Inhibitor.

All of the claims require treating "a patient who experiences an inadequate response to a TNFα-inhibitor." Celltrion and another petitioner previously sought to broaden the claims by arguing that this language is not limiting. Ex. 2076 at 15-16; Ex. 2069 at 16-18. The Board rejected that argument. Ex. 2075 at 8-10. Celltrion now tries again to broaden the claims, this time by impermissibly redefining the language contrary to its plain meaning. *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356 (Fed. Cir. 2015).

The "Definitions" section of the specification expressly defines "inadequate response to a TNFα-inhibitor" as "an inadequate response to *previous or current* treatment with a TNFα-inhibitor because of toxicity and/or inadequate efficacy," Ex. 1001 at 5:25-28 (emphasis added), and states that "[t]he inadequate response

can be assessed by a clinician skilled in treating the disease in question." *Id.* at 5:28-29. Celltrion concedes this definition. Pet. 6. Because a patient cannot experience an inadequate response to previous or current treatment unless the patient has actually received such treatment, "a patient who experiences an inadequate response to a TNFα-inhibitor" therefore is, by definition, someone who has been, or is being, treated with a TNFα-inhibitor.

Celltrion asserts that this language extends to patients who *have never* received treatment with a TNFα-inhibitor, but who *hypothetically* would not respond, or *hypothetically* would experience toxicity, if they were to receive such treatment. This runs contrary both to the plain language of the claims themselves, and to the express definition quoted above, which establishes that the response must be real, not hypothetical—e.g., it "can be assessed by a clinician." Ex. 1001 at 5:28-29; *id.* at 5:37-41 ("A mammal who experiences 'inadequate efficacy' continues to have active disease following previous or current treatment with a TNFα-inhibitor.").

Celltrion argues that its hypothetical-response theory is consistent with a portion of the specification that mentions a patient who may be considered prone to experience toxicity from, or unlikely to respond to, a TNFα-inhibitor. Ex. 1001 at 28:45-61. But that portion of the specification expressly juxtaposes such a patient with one "who experiences an inadequate response to previous or current treatment

with a TNFα-inhibitor." *Compare id.* at 28:45-55 ("previous or current treatment") *with id.* at 28:55-61 ("prone to experience"). Nowhere does the patent describe an individual who is prone to experience toxicity, or is unlikely to respond to therapy with a TNFα-inhibitor, as "a patient who experiences an inadequate response to a TNFα-inhibitor," as recited in the claims. "The plain meaning of the claim language is therefore not overridden by the specification." *Straight Path*, 806 F.3d at 1362.

Celltrion's hypothetical-response theory also is inconsistent with the prosecution history, in which Genentech distinguished a claim to a method of treating a patient "who experiences an inadequate response to a TNFa-inhibitor" from a cited reference on the ground that "there is nothing in [the reference] to indicate that a patient who had an inadequate response to a TNF-α-inhibitor was actually treated with RITUXAN®." Ex. 1045 at 8; *see Straight Path*, 806 F.3d at 1362-63 ("And the plain meaning is positively confirmed by the prosecution history, which we have indicated is to be consulted even in determining a claim's broadest reasonable interpretation.").

B. Clinical-Response Limitations Cannot Be Read Out Of The Claims.

Claims 2-7, 10, and 11-14 describe a TNFα-inadequate-responder achieving one of three clinical responses to rituximab treatment: ACR50 at week 24, ACR70 at week 24, and no erosive progression at weeks 24 and beyond. Celltrion calls

these clinical responses "results" and repeatedly argues that, according to *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001), "results" do not count as claim limitations. Pet. 26-29. But as the Board has acknowledged, "[n]either that case law," nor other authority, "indicates that we should consider a recited result not to be a limitation in a method claim simply because it recites a result." *Ferrum Ferro Capital, LLC v. Allergan Sales, LLC*, IPR2015-00858 (Paper 10) at 7-8 (Sep. 21, 2015) (finding that a "'without loss of efficacy' . . . result is recited and required in claim 4, and is a limitation.").

Celltrion and another petitioner previously argued that the clinical-response limitations in the claims are not limiting, and Genentech responded to those arguments in its previous POPR with points articulated below. Ex. 2082 at 24-31. Celltrion's new petition ignores those points. The Board did not read the clinical-response limitations out of the claims previously, Ex. 2075 (IPR2015-00417, Paper 11) at 7-10 (declining to address the issue), and it should not do so now. *Texas Instruments Incorporated v. ITC*, 988 F.2d 1165, 1171 (Fed. Cir. 1993) (stating that "read[ing] an express limitation out of the claims" is something "we will not do").

1. "achieving a clinical response selected from…"(Claims 11-14)

a) The Applicants Chose To Use Both The Preamble And The Body Of Claim 11 To Define The Claimed Subject Matter.

"[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).

The body of claim 11 recites certain steps and the preamble recites the 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." This additional step is not a necessary consequence, or inherent result, of the treatment described in the other claimed steps. Indeed, as Celltrion acknowledged in its previous IPR petition, the claimed "treatment will produce a clinical response in some but not all patients." Ex. 2076 at 52.

That the additional step in the preamble includes a Markush group—"the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond"—further signifies that the term is limiting. "A Markush group . . . limit[s] the claim to a list of specified alternatives." *Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007).

b) The Bodies of Dependent Claims 12-14 Rely Upon, And Derive Antecedent Basis From, The Clinical Responses Recited In The Preamble Of Claim 11.

Preamble language is limiting "[w]hen 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). Here, each of dependent claims 12-14 has the form: "The method of claim 11 wherein ***the*** clinical response is . . . ." These references to "the clinical response" derive antecedent basis from the "achieving a clinical response" language in the preamble of independent claim 11. The preamble phrase is therefore limiting.

c) The Applicants Relied On The Clinical Responses Recited In The Preamble Of Claim 11 To Distinguish Cited Art.

Reliance on a preamble term to distinguish cited art during prosecution indicates that the term is a limitation of the claimed invention. *Invitrogen Corp. v. Biocrest Mfg. LP*, 327 F.3d 1364, 1370 (Fed. Cir. 2003) (holding that "the applicants clearly relied on the preamble term 'improved competence' to distinguish [the] Hanahan [reference]," so the preamble term "thus limits the claims and is not merely a statement of intended advantage"); *Smith & Nephew, Inc. v. Bonutti Skeletal Innovations, LLC*, IPR2013-00605, Paper 9 at 8-9.

Here, Celltrion acknowledges that, during prosecution, "[t]he applicant distinguished the cited prior art by noting that neither the claimed dosage amount nor the results of the treatment (i.e., ACR50, ACR70, and no erosive progression at

24 weeks) had been disclosed." Pet. 7. Indeed, when Genentech added claim 11 (original claim 37) during prosecution, it distinguished a reference by Tuscano on the ground that it "nowhere mentions 'an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond.'" Ex. 1045 at 9. The clinical-response language in the preamble is therefore limiting.

d) Celltrion Fails To Address The Above Points Even Though Genentech Raised Them Previously.

Celltrion ignores all of this previously-identified evidence showing that the invention is not "set forth fully in the body of the claim" and that the preamble of claim 11 does not merely "state[] the purpose or intended use" of the invention. Pet. 29. And Celltrion still fails to establish that the steps recited in the body of claim 11—including the step of "administering to the patient . . . methotrexate" in a discretionary amount—are actually "performed in the same way regardless of whether the intended result recited in the preamble is achieved," Pet. 29, much less that the preamble would be non-limiting even if they were.

Celltrion's reliance on *Ben Venue* is misplaced for the reasons explained above, and because, in *Ben Venue*, the steps of the method were "performed in the same way regardless" and "the language of the claim itself strongly suggest[ed] the independence of the preamble from the body of the claim." *Ben Venue*, 246 F.3d at 1375. Here, Celltrion does not, and cannot, assert that there is any such suggestion in the language of claim 11.

2. "wherein the clinical response is…" (Claims 12-14) and "wherein the patient has no erosive progression…" (Claim 10)

Claims 12-14 all read: "The method of claim 11 wherein the clinical response is [ACR50 at week 24, ACR70 at week 24, or no erosive progression at weeks 24 and beyond, respectively]." Claim 10 similarly recites administering rituximab "wherein the patient has no erosive progression at weeks 24 and beyond."

Celltrion argues that these "wherein" clauses are not limiting, just as it did in its previous petition. But Celltrion still fails to cite any case in which a "wherein" clause was found to be non-limiting. Instead, Celltrion cites a case addressing a "whereby" clause. Pet. 28. A "whereby" clause is not the same as a "wherein" clause. *Griffin v. Bertina*, 285 F.3d 1029, 1034 (Fed. Cir. 2002) (commenting on cases addressing "whereby" clauses and pointing out that "[a]side from the fact that 'wherein' is an adverb and 'whereby' is a conjunction, those cases are all fact-specific").

Even if the test for "whereby" clauses were applicable, the "wherein" clauses here still could not be read out of the claims. Celltrion argues that "a '"whereby" clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim.'" Pet. 28. But as explained in Section III.B.1.a), the "wherein" clauses here do not merely state necessary results of other claim limitations. Indeed, Celltrion admits that the claimed treatments will

not necessarily produce a clinical response. Ex. 2076 at 52 ("This treatment will produce a clinical response in some but not all patients.").

Celltrion again relies on *Ben Venue*, and again that reliance is misplaced. *Ben Venue* does not even address "wherein" clauses (or even "whereby" clauses). Moreover, in *Ben Venue*, the language found to be non-limiting from the body of the claims "essentially duplicate[d]" other language in the claims based on the teaching of the specification. *Ben* Venue, 246 F.3d at 1375. Here, the "wherein" clauses disclose clinical-response requirements that do not duplicate other terms and are not necessary consequences of the other terms, as discussed above.

a) The "wherein" Clauses Relate Back To And Clarify The "administering" Steps.

"Wherein" clauses in claims are routinely recognized as limiting. For example, in *Griffin*, the Federal Circuit refused to read "wherein" clauses out of the claims. 285 F.3d at 1033. The court observed that the "wherein" clauses there "relate back to and clarify what is required by the [claim]." *Id.* So do the claimed "wherein" clauses here. They relate back to and clarify the step that involves "administering to the patient . . . methotrexate," requiring that the amount of methotrexate administered must be such that the claimed treatment as a whole yields the claimed clinical response.

b) Construing the "wherein" Clauses As Non-Limiting Would Create Absurd Outcomes.

If the "wherein" clauses in claims 12-14 were deemed non-limiting, then those claims would, as shown below, be reduced to simply: "The method of claim 11."

> **12.** The method of claim **11** ~~wherein the clinical response is ACR50 response at week 24~~.
> **13.** The method of claim **11** ~~wherein the clinical response is ACR70 response at week 24~~.
> **14.** The method of claim **11** ~~wherein the clinical response is no erosive progression at weeks 24 and beyond.~~

Ex. 1001 (strikethrough added). Accordingly, claims 12-14 would become identical to each other, and would also become identical to claim 11, giving the dependent claims the same scope as the independent claim. Such an outcome would be contrary to the principle of claim differentiation. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). Such an outcome also would violate the rule that "claims should be interpreted such that each word is given meaning." *Ex Parte Behzad*, Appeal 2011-007124, 2014 WL 1311619, at *2 (P.T.A.B. Mar. 28, 2014); *Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1372 (Fed. Cir. 2010) ("We must give meaning to all the words in [the] claims.").

c) Reliance During Prosecution On Limitations In The Disputed "wherein" Clauses to Distinguish Cited Art Further Confirms That Those Clauses Are Limiting.

As noted above, Celltrion itself acknowledges that during prosecution, Genentech distinguished cited references by relying on the clinical-response limitations that appear in the "wherein" clauses at issue. Pet. 7; Ex. 1045 at 6, 9. Such reliance "indicates use of the [wherein limitations] to define, in part, the claimed invention," which means they are limiting. *Catalina Mktg. Int'l Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002).

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." Celltrion argues that this language is non-limiting because claim 2 elsewhere includes a "wherein" clause that specifies a particular amount ("two intravenous doses of 1000 mg") of the anti-CD20 antibody. Setting aside Celltrion's inconsistent positions regarding whether "wherein" clauses are limiting, Celltrion's attempt to eliminate the clinical-response limitation by equating it with the "wherein" clause should be rejected because "[i]n the absence of any evidence to the contrary, we must presume that the use of [] different terms in the claims connotes different

meanings." *CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co. Kg*, 224 F.3d 1308, 1317 (Fed. Cir. 2000). There is no evidence to the contrary here.

Moreover, the claim language itself demonstrates that the "amount that is effective to provide [a clinical response]" term adds meaning over the "two intravenous doses of 1000 mg" term. Celltrion would ignore critical language in the limitation requiring the claimed clinical responses: 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 in the patient. Celltrion admits that administering two 1000 mg doses "will produce a clinical response in some but not all patients." Ex. 2076 at 52. Thus, merely claiming "two intravenous doses of 1000 mg" would not have required that any particular clinical response be achieved.

IV. PRIOR INVENTION

As Celltrion anticipated, no doubt given that one of the authors on the Edwards 2002 reference is one of the inventors of the '838 patent, the subject matter claimed in the '838 patent was invented before the dates of Celltrion's §102(a) references. Genentech can, in Celltrion's words, "swear behind the prior art date for the art relied on in Grounds 1 and 2 (i.e., Edwards 2002 and Tuscano)." Pet. 30-31.

A. The Collaboration Between Genentech and Roche

In 1995, Genentech and Roche executed a collaboration agreement for the development of certain pharmaceutical agents to which Genentech possessed rights. Ex. 2003; Ex. 2092 ¶¶3-5. Such agents included the antibody now known as "rituximab," Ex. 2092 ¶3, referred to in the agreement as the "IDEC Product" because it was created by Genentech's collaborator IDEC, which in turn referred to it as C2B8. Ex. 2001 at 8-9; Ex. 2003 at 8; *see also* Ex. 2002 at 40. The companies collaborated on using rituximab to treat RA, among other things.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Claim	Excerpts from Evidence of Actual RTP
1. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody that binds to CD20, wherein the antibody is administered as two intravenous doses of 1000 mg.	[redacted]

Claim	Excerpts from Evidence of Actual RTP
2. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient 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, wherein the antibody is administered as two intravenous doses of 1000 mg.	See entry for claim 1 above. Additionally: [redacted]
3. The method of claim 2 wherein the antibody comprises rituximab.	See entry for claim 2, and incorporated material, above. Additionally: [redacted]
7. The method of claim 2 wherein the CD20 antibody is the only B-cell surface marker antibody administered to the patient.	See entry for Claim 2, and incorporated material, above. [redacted]

Claim	Excerpts from Evidence of Actual RTP
8. A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient rituximab, wherein rituximab is administered as two intravenous doses of 1000 mg.	See entry for claim 1 above. Additionally: [redacted]
9. The method of claim 8 further comprising administering methotrexate to the patient.	See entry for claim 8 above. Additionally: [redacted]

[redacted] Success in treating such patients with rituximab was reported in publications after the filing date. Ex. 2085.

V. CELLTRION FAILS TO ESTABLISH THAT IT LIKELY WOULD PREVAIL BASED ON THE REFERENCES IT RELIES ON UNDER 35 U.S.C. §102(a).

Because the '838 patent was filed before the AIA was enacted, the pre-AIA version of Title 35 applies. "Grounds 1 and 2, which are based on 102(a) prior art," Pet. 30, request "cancellation of claims 1-5 and 7-14 as anticipated by Edwards 2002" (Ground 1) and "cancellation of claims 1-14 as obvious over

Edwards 2002 in view of Tuscano" (Ground 2). *Id*. Neither ground supports institution.

A. Ground 1: Edwards 2002 Does Not Anticipate Claims 1-5 and 7-14

1. Edwards 2002 Is Not Prior Art As To Claims 1-3 and 7-9

"Section 102(a) explicitly refers to invention dates, not filing dates." *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996). "Thus, under section 102(a), a document is prior art only when published before the invention date." *Id.*

Celltrion contends that Edwards 2002 was "published in October 2002." Pet. 23. But the evidence shows that the subject matter of at least claims 1-3 and 7-9 was actually reduced to practice by the inventors no later than September 4, 2002, as explained in Section IV above. Because September 4, 2002 is before the alleged Edwards 2002 publication date of "October 2002," Pet. 23, Celltrion cannot carry its burden of establishing that Edwards 2002 is prior art.

2. Edwards 2002 Does Not Anticipate Any Claims

"To anticipate, a single reference must teach every limitation of the claimed invention." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Even if it were §102(a) prior art, Edwards 2002 falls far short of this standard for all claims.

a) Edwards 2002 Does Not Disclose Treating A "Patient Who Experiences An Inadequate Response To A TNFα-Inhibitor."

All claims of the '838 patent require treating RA "in a human patient who experiences an inadequate response to a TNFα-inhibitor." Ex. 1001. Celltrion does not contend that Edwards 2002 expressly discloses this element. As the Board previously concluded, "neither Edwards [2002] nor Genentech Press Release describes any study participant as a TNFα-inadequate responder." Ex. 2075 (IPR2015-00417, Paper 11) at 14.

(i) Inherency Cannot Be Established By Probabilities

Celltrion argues that "[t]his element is inherent in Edwards 2002" because "at least 30-40% of RA patients experience an inadequate response to a TNFα-inhibitor." Pet. 32. This is the same argument that the Board rejected previously because "there is only a possibility that treatment according to [the] method disclosed in the prior art would result in the claimed method." Ex. 2075 at 15. Celltrion's reliance on a statistician's declaration in an attempt to quantify the possibilities does not change anything—Celltrion is still trying to establish inherency through probabilities, which is impermissible. "It is well established," the Board wrote, "that 'inherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention.'" *Id.* (quoting *In re Montgomery*, 677 F.3d 1375, 1384 (Fed. Cir. 2012)). None of the cases cited by Celltrion says otherwise. Pet. 35-36.

(ii) Celltrion's Probability Argument Relies On Its Incorrect Claim Construction

Celltrion's probability argument also fails under the proper construction of the claim term "a patient who experiences an inadequate response to a TNFα-inhibitor." As explained in Section III.A above, this language requires that the patient actually has been, or is being, treated with a TNFα-inhibitor. Celltrion's statistical analysis ignores this requirement. Celltrion's analysis is based on its position that the patient need *not* previously have received treatment with a TNFα-inhibitor. Celltrion therefore does not even purport to calculate the probability that any patients reported on in Edwards 2002 had in fact been treated with a TNFα-inhibitor and had failed that treatment. Thus, even if anticipation by probabilities were legally permissible, Celltrion's argument would fail because Celltrion calculates the wrong probability.

b) Edwards 2002 Does Not Disclose Achieving "No Erosive Progression At Weeks 24 And Beyond."

Claims 10 and 14 require that the TNFα-inadequate-responder achieve "no erosive progression at weeks 24 and beyond." Ex. 1001. Edwards 2002 does not even address erosive progression, much less report that any such patient achieved no erosive progression at weeks 24 and beyond. Ex. 1033.

Celltrion does not contend otherwise. Rather, Celltrion contends that "the element is inherently disclosed by Edwards 2002, as later references report that

some patients who are treated with the regimen disclosed in Edwards 2002 had no erosive progression at week 24." Pet. 41 (emphasis added). This is just another, less elaborate, attempt by Celltrion to establish inherency through probabilities, which fails as a matter of law.

c) Edwards 2002 Does Not Disclose Achieving ACR50 Or ACR70 Responses In Patients Who Experience An Inadequate Response To A TNFα-Inhibitor.

Claims 2-7 and 11-14 require a clinical response of either an ACR50 response at week 24 week, an ACR70 response at week 24, or no erosive progression at weeks 24 and beyond in a TNFα-inadequate-responder. Edwards 2002 fails to disclose no erosive progression, as explained in Section V.A.2.b) above. It also fails to disclose achieving an ACR50 or ACR70 response in a TNFα-inadequate-responder. Ex. 1033.

Celltrion argues that this limitation is met because Edwards 2002 discloses ACR50 and ACR70 responses in some patients. Pet. 42, 44. But Edwards 2002 does not describe any patient as a TNFα-inadequate-responder, as discussed in Section A.2.a) above. Celltrion does not even try to articulate a probability that the methotrexate partial responders in Edwards 2002 who achieved ACR50 or ACR70 scores were also TNFα-inadequate-responders. And any such argument would fail because anticipation cannot be proven by probabilities.

B. Ground 2: The Combination Of Edwards 2002 In View Of Tuscano Does Not Render The Claims Obvious.

Neither Edwards 2002 nor Tuscano is prior art as to claims 1-3 and 7-9, and neither reference discloses achieving any of the claimed clinical responses in a TNFα-inadequate-responder, as required by claims 2-7 and 10-14. Celltrion states that the Board instituted on this ground in IPR2015-00417, but the Board did not then have before it the present evidence showing that neither Edwards 2002 nor Tuscano is prior art, and the Board did not address the clinical-response limitations of claims 2-7 and 10-14.

1. Edwards 2002 And Tuscano Do Not Constitute Prior Art As To Claims 1-3 and 7-9.

Celltrion cannot carry its burden of establishing that Edwards 2002 is prior art with respect to claims 1-3 and 7-9, as discussed in Section V.A.1 above.

As for Tuscano, Celltrion alleges that it was "published in December 2002." Pet. 20. That is after September 4, 2002, the latest date by which the subject matter of claims 1-3 and 7-9 was actually reduced to practice, as explained in Section IV above. Thus, Celltrion cannot carry its burden of establishing that Tuscano is prior art with respect to claims 1-3 and 7-9 either and its obviousness challenge fails.

2. Claims 2-7 and 10-14 Are Not Rendered Obvious By Edwards 2002 In View Of Tuscano.

a) Neither Edwards 2002 nor Tuscano discloses the claimed clinical responses.

As discussed in Sections V.A.2.b) and V.A.2.c), Edwards 2002 does not disclose achieving any of the claimed clinical responses in a TNFα-inadequate-responder. Nor does Tuscano contain any mention of such clinical responses. Ex. 1034. Edwards 2002 and Tuscano do not even mention erosive progression. Celltrion does not argue to the contrary. Thus, Celltrion cannot show that all the elements of claims 2-7 and 10-14 can be found in prior art, much less that a PHOSITA would have been motivated to combine the prior art to arrive at the claimed inventions.

b) Celltrion fails to establish that a PHOSITA would have combined Edwards 2002 and Tuscano with a reasonable expectation of success.

Even assuming that a PHOSITA would have been motivated to combine Edwards 2002 and Tuscano to arrive at the claimed inventions, Celltrion fails to show that a PHOSITA would have had a reasonable expectation of success of achieving what is claimed.

"The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Here, Celltrion's obviousness challenge to claims 2-7 and 10-14 requires showing a reasonable expectation of achieving an "ACR50 response at week 24," an "ACR70 response at week 24," or "no erosive progression at weeks 24 and beyond" in a TNFα-inadequate-responder. Because neither Edwards 2002 nor Tuscano discloses achieving such responses, *see supra* Section V.B.2.a) and V.A.2.c), neither reference would have inspired the requisite expectation of success in a PHOSITA.

Celltrion does not argue that such an expectation was provided by any other reference, and in fact, the alleged prior art created precisely the opposite expectation, as explained below.

(i) The art taught that erosive progression continues in TNFα-inadequate-responders despite treatment with rituximab.

Only one reference from before the effective filing date—De Vita 2002—addresses whether TNFα-inadequate-responders exhibit erosive progression at weeks 24 and beyond following treatment with rituximab. The reference discloses that they do exhibit erosive progression—the exact opposite of the claim language. Ex. 1032.

De Vita 2002 discloses a study in which two patients—patients 3 and 4—had "been treated unsuccessfully (nonresponse) with anti-TNFα." Ex. 1032 at 2. Both patients were administered "4 weekly intravenous infusions of 375 mg/m^2" of rituximab, and "underwent close clinical and laboratory followup," including

"assessment of joint involvement by means of conventional radiography, magnetic resonance imaging (MRI), and ultrasonography." *Id.*

De Vita 2002 reports that "[t]he number of eroded joints as seen on hand and foot radiographs ***increased*** . . . from 14 (baseline) to 15 (month 6) in patient 4, and from 20 (baseline) to 23 (month 6) in patient 3." *Id.* at 2-4 (emphasis added). Thus, De Vita 2002 reports erosive progression at 24 weeks and beyond in rituximab patients who are TNFα-inadequate-responders. Accordingly, a PHOSITA would not have had a reasonable expectation of success in meeting the "no erosive progression" limitations of claims 2-7, 10, and 11-14.

(ii) The art disclosed that TNFα-inadequate-responders could not achieve ACR50 or ACR70 responses with rituximab.

De Vita 2002 discloses that one of the TNFα-inadequate-responders (patient 3) "exhibited no improvement with the anti-CD20 treatment," and in the other (patient 4), only an "ACR 20% response was observed from month 3 to month 5." Ex. 1032 at 2-4. Similarly, none of the patients of Tuscano could achieve an ACR50 or ACR70 response. Ex. 1034. Accordingly, a PHOSITA would not have had a reasonable expectation that the corresponding clinical-response limitations of claims 2-7 and 11-13 could successfully be met in the claimed TNFα-inadequate-responders.

(iii) Celltrion's expectation-of-success arguments lack evidentiary and legal support.

Celltrion nowhere argues that a PHOSITA would have had a reasonable expectation of success in achieving ACR50 and ACR70 responses in TNFα-inadequate-responders. Instead, Celltrion asserts that Edwards 2002 *actually discloses* such responses. But Edwards 2002 does not describe any patients as TNFα-inadequate-responders. *See* Section V.A.2.c) above.

Citing the declaration of Dr. Boers, Celltrion further asserts that "a POSA would have understood from the ACR50 and ACR70 responses disclosed in Edwards 2002 that there would be no erosive progression at week 24 and beyond. (Ex. 1002 ¶¶122, 126)." Pet. 47-48. But Dr. Boers merely states in his declaration that "based on experience with traditional DMARDs and TNFa-inhibiotrs [sic] available as of 2003, a person of ordinary skill in the art would expect a *reduction or* arrest of erosive progression *commensurate with or exceeding that expected with the clinical response measured* by ACR20, 50 or 70." Ex. 1002 ¶122 (citing Ex. 1054) (emphasis added). This fails to support Celltrion's assertion for at least two reasons:

First, the plain language of the claim requires "no erosive progression." Just as slowing down is not the same thing as stopping, a "reduction" of erosive progression is not the same thing as "no erosive progression."

Second, nowhere does Dr. Boers establish what "reduction or arrest" of erosive progression allegedly would have been "expected with the clinical response measured by ACR20, 50 or 70" in the first place. Ex. 1002 ¶122. Describing it as "commensurate with or exceeding" the undisclosed "expected" reduction or arrest adds nothing.

The paper cited by Dr. Boers at ¶122 of his declaration does not cure either of these deficiencies. It neither addresses treatment with rituximab nor even mentions arresting erosive progression. Rather, the paper addresses treatments that merely "retard[] progression of joint damage." Ex. 1054 at 1.

If anything, the paper cited by Dr. Boers undermines the premise that ACR scores predict no erosive progression because the paper reports that retardation of joint damage progression after treatment "was apparent both in patients who were responders and those who were nonresponders according to the American College of Rheumatology (ACR) 20% criteria for improvement." *Id*. In other words, the reported ACR scores did not predict even retardation, much less halting, of joint damage progression.

Celltrion's argument would fail even assuming that the ACR50 and ACR70 scores in the patient population of Edwards 2002 would have predicted an absence of any erosive progression for patients in Edwards's population of methotrexate partial responders. Celltrion offers no evidence that the absence of erosive

progression in that unclaimed population would have been predictive of the absence of erosive progression in the claimed population of TNFα-inadequate-responders. Celltrion cannot assume that a PHOSITA would have expected these two patient populations to respond the same way, particularly given Celltrion's contention that TNFα-inadequate-responders were known to be inherently different from other patients. Pet. 25 ("As Dr. Boers explains, a POSA as of 2003 would have understood that whether a patient will or will not respond to TNF-inhibitor treatment is an inherent characteristic of the patient herself.").

Moreover, references like De Vita 2002 suggest that the two patient populations do not respond the same way to rituximab. In De Vita 2002, patients who *were not* TNFα-inadequate-responders achieved ACR50 and ACR70 scores after treatment with rituximab, whereas patients who *were* TNFα-inadequate-responders did not respond, or achieved only an ACR20 response after the very same treatment. Ex. 1032. Celltrion fails to identify any prior art showing an ACR50 or ACR70 response in a TNFα-inadequate-responder.

Celltrion argues in a footnote that the "no erosive progression at weeks 24 and beyond" limitation "is inherently met by the method disclosed in Edwards 2002" based on probabilities. Pet. 48 n.9. But that argument fails for the reasons discussed in Section V.A.2.b) above.

Nor can Celltrion argue that such probabilities would have inspired a reasonable expectation of success. Celltrion calculates the probabilities based only on information in "later references"—published more than three years after the effective filing date. *Id.* at 41 (relying on Ex. 1041, allegedly published in 2006). Celltrion therefore fails to establish any expectation of success *at the time of the invention*, as required in an obviousness analysis (as opposed to inherent anticipation). *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000) ("For the Johnson article to render the claimed invention obvious, there must have been, at the time the invention was made, a reasonable expectation of success in applying Johnson's teachings."); MPEP § 2143.02(III).

VI. CELLTRION FAILS TO ESTABLISH THAT IT LIKELY WOULD PREVAIL ON THE REFERENCES IT RELIES ON UNDER 35 U.S.C. §102(b) – GROUND 3.

Ground 3, based on the combination of Goldenberg, Curd and De Vita, was not asserted in either of the prior IPRs and has never been addressed by the Board. Indeed, Goldenberg, was not even an exhibit in the prior IPRs.

The Board should reject Ground 3 because the three references on which it is based fail to disclose key claim limitations, leaving non-obvious gaps between the claims and the alleged prior art. Celltrion also fails to establish a motivation to modify and combine the cited references to arrive at the claimed inventions, and fails to establish a reasonable expectation of success in achieving what is claimed.

In short, Ground 3 relies on self-serving hindsight, not an objective analysis of what a PHOSITA actually would have found obvious at the time the invention as made.

A. Goldenberg, Curd, and De Vita Fail To Disclose Key Limitations.

1. None of Goldenberg, Curd or De Vita discloses two 1000 mg infusions of an anti-CD20 antibody, as required by all claims.

Celltrion concedes that "[t]he prior art does not teach the exact claimed dose of rituximab." Pet. 52. It attempts to remedy this deficiency by arguing that the prior art "does teach a range of total doses reported to treat RA successfully, and the claimed dose falls within this range." *Id.* Celltrion argues that a PHOSITA would therefore have arrived at the claimed regimen by "routine optimization." *Id.* But that is just hindsight-driven hand waving.

a) Celltrion's "routine optimization" arguments ignore the "routine optimization" case law.

"Routine optimization" cases state that discovery of an "optimum value" of "a result effective variable" in a "known process" or composition is normally obvious. *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977). For example, in the field of alloys having multiple components, it may be a matter of routine optimization to select a smaller optimum range of component percentages from within a broader range of component percentages disclosed by a prior art reference. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). "The normal desire of scientists or artisans to improve upon what is already generally known provides the

motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Id.* (quoting *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980)).

There are at least five requirements that must be satisfied in order for "routine optimization" to apply to a variable, and Celltrion fails to establish that these requirements are satisfied with respect to any of the four variables (addressed in subsection b) below) reflected in the claimed dosing:

First, the result of the "optimization" process must in fact be an "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.") (emphasis added). Celltrion never even asserts, much less submits evidence demonstrating, that any—let alone every one—of the *claimed* choices for these 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 (rejecting a routine optimization argument because "the parameter optimized was not recognized to be a result-effective variable") (emphasis added). Celltrion does not contend that each of the four variables was considered "result effective," much less that a PHOSITA knew the way in which each of those variables allegedly affects results or how they interact with each other. *See id.*; *In re Yates*, 663 F.2d 1054, 1056 (C.C.P.A. 1981)

(rejecting a routine optimization argument because the allegedly optimized parameter "was not recognized to be a result-effective variable."); *cf. In re Urbanksi*, 809 F.3d 1237, 1242 (Fed. Cir. 2016), ("[R]eaction time and degree of hydrolysis are result-effective variables that can be varied in order to adjust the properties of the hydrolyzed fiber *in a predictable manner*.") (emphasis added). Indeed, the words "result-effective" appear nowhere in Celltrion's papers.

Third, the evidence must show that the experimentation needed to optimize the variable also was known in the art. *In re Fay*, 347 F.2d 597, 602 (C.C.P.A. 1965) ("To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes *within the teachings of the art*.") (emphasis in original). Celltrion fails to provide any evidence describing the experimentation process that allegedly would have been needed to arrive at the claimed dosage, much less evidence that such experimentation was known in the art.

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) (internal quotes omitted). Celltrion identifies no such suggestions in the art.

Fifth, the experimentation required to arrive at the claimed optimum must, as the label "routine optimization" implies, be no more than routine. *Id.* ("The evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine."). Celltrion fails to submit evidence establishing that any such experimentation would have been merely routine.

There is therefore no evidence that a PHOSITA would have arrived at the claimed dosing through routine optimization and Celltrion's argument fails.

Celltrion's "routine optimization" argument also fails because the claimed dosing regimen produced unexpectedly good results. *Merck*, 874 F.2d at 809 ("Patentability may be imparted, however, if the results achieved at the designated concentrations are 'unexpectedly good.'"). Here, the evidence shows that a significant number of patients who received the claimed dosing regimen had no erosive progression at 24 weeks and beyond—and even after 2 years, *see, supra,* Section II.B., whereas prior art from before the effective filing date reported that erosive progression continued despite treatment with rituximab. *See, supra,* Section V.B.2.b)(i). Given these unexpectedly good results produced by the claimed regimen, [3] Celltrion's "routine optimization" argument would fail even if

[3] Celltrion claims that the results are not unexpected because "the prior art specifically taught that rituximab at doses both above and below the claimed doses

Celltrion satisfied the five requirements discussed above. *Merck*, 874 F.2d at 809; *In re Saether*, 492 F.2d 849, 854 (C.C.P.A. 1974) ("[F]urther evidence of unobviousness is shown by the improvements and unexpected results obtained by the claimed invention.").

In short, Celltrion simply mouths the words "routine optimization" without any analysis under the case law. *Ex parte Whalen*, 89 U.S.P.Q.2d 1078, 1084 (B.P.A.I. 2008) (holding that "the Examiner has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that a PHOSITA would have considered it obvious to 'optimize' the prior art compositions").

Even taken at face value, Celltrion's "routine optimization" arguments wither under scrutiny because Celltrion is actually relying on hindsight reconstruction, not routine optimization, as further discussed in the sections below.

b) Celltrion's "routine optimization" arguments rely on hindsight reconstruction, which is impermissible.

The claimed dosing of two intravenous infusions of 1000 mg each reflects choices with respect to at least four different dosing variables:

---

successfully treated inadequate responders." Pet. 61. But even assuming this were true, the art nowhere discloses achieving no erosive progression in such patients.

First, there would be a choice amongst dose-sizing options of at least (i) size-based dosing based on patient mass or BSA, like the 375 mg/m^2 infusions taught by De Vita, Ex. 1051; (ii) fixed dosing for all patients regardless of their size, as claimed in the '838 patent; or (iii) a combination of fixed and size-based dosing, as disclosed in Tuscano. Ex. 1034.

Second, the total dose of anti-B cell antibody would have to be chosen. The claimed amount is 2000 mg. Celltrion concedes that none of the cited references discloses this total dose. Pet. 52.

Third, the number of infusions over which to divide the total dose would have to be selected. The cited references all taught using at least four infusions. Ex. 1038 at 23(Example 5); Ex. 1031 at 27(Example 1); Ex. 1051. In contrast, all of the claims require two infusions.

Fourth, the amounts of each infusion would have to be chosen. The cited references uniformly taught starting with a first infusion no greater than 375 mg/m^2 (~640 mg on average), Ex. 1038 at 23; Ex. 1031 at 27; Ex. 1051, and taught increasing the size of subsequent infusions relative to the first. *See, e.g.,* 1031 at 27. In contrast, the '838 patent claims require both a first infusion substantially larger than 375 mg/m^2 and equal infusion sizes.

Celltrion completely ignores the first and fourth variables, and relies on erroneous characterizations of the art, or ignores the art altogether, in its arguments relating to the second and third variables.

(i) Celltrion ignores the variable requiring a choice between size-based dosing, fixed dosing, or a combination of both.

Celltrion does not even attempt to show that a PHOSITA would have arrived at fixed dosing, as claimed in the '838 patent, by routine optimization (or otherwise). Without any discussion or analysis, Celltrion's "routine optimization" argument silently assumes that a PHOSITA would have chosen fixed dosing instead of the size-based dosing that both De Vita and Curd teach, or a combination of fixed and size-based dosing like Tuscano teaches, to administer an anti-CD20 antibody to a TNFα-inadequate-responder. This is hindsight, not "routine optimization."

(ii) Celltrion's argument concerning the total dose variable relies on erroneous characterizations of the prior art.

Even assuming that a PHOSITA would have chosen fixed dosing, Celltrion fails to show that the PHOSITA would have chosen a total fixed dose of 2000 mg. Celltrion argues that "Goldenberg discloses successful treatment of RA with a total dose of 1500 mg (Ex. 1038 at 22) and De Vita discloses successful treatment of RA with a total dose of 2550 mg" and "[t]he claimed dose, 2000 mg, falls squarely between these two successful doses." Pet. 53. This is factually incorrect:

First, Goldenberg and De Vita do not disclose a range of total doses within which the claimed total dose of 2000 mg falls. Indeed, Celltrion mischaracterizes the total doses of both Goldenberg and De Vita. Celltrion asserts that "Goldenberg discloses successful treatment of RA with a total dose of 1500 mg." Pet. 53. But in fact, Goldenberg describes treatment "with 300 mg ***each*** of hLL2 and Rituximab, intravenously each week, for a period of 5 weeks." Ex. 1038 at 23 (emphasis added). Goldenberg explains that hLL2, like rituximab, is an anti-B cell antibody. Ex. 1038 at 1-2, 9, 20 (describing "hLL2" as a humanized version of LL2, an "anti-CD22 monoclonal antibody," where CD22 is a B-cell surface marker like CD20). Thus, Goldenberg discloses administering a total of 3000 mg, not 1500 mg, of anti-B cell antibody. Assuming that the treatment in Goldenberg's prophetic example could have been viewed as "successful," Goldenberg cannot accurately be characterized as disclosing "successful treatment of RA with a total dose of 1500 mg," as Celltrion represents.

Celltrion also mischaracterizes the total dose of De Vita. Celltrion asserts that "De Vita discloses successful treatment of RA with a total dose of 2550 mg." Pet. 53. But De Vita does not disclose a fixed dose of any amount. Rather, De Vita discloses a size-based dose of "four weekly infusions of 375 mg/m^2 each" based on the BSA of each patient. Ex. 1051. De Vita does not report the BSAs of the patients in the study or the absolute sizes of the doses given. The number 2550

appears nowhere in the reference. Without disclosing that it was doing so, Celltrion seems to have converted the size-based dose of De Vita into a fixed total dose by multiplying it by an average BSA of 1.7 m^2.

Second, neither Goldenberg nor De Vita demonstrates "successful" treatment of a TNFα-inadequate-responder as Celltrion asserts. Goldenberg reports only ***prophetic*** or ***paper*** results written in the present tense. Ex. 1038 at 23 (Example 5). "Prophetic examples are set forth in the present tense to indicate that they were not carried out." *See Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1376 n.1 (Fed. Cir. 2003). Because a prophetic example is not based on "work actually conducted or results actually achieved," it has no capacity to demonstrate successful or unsuccessful results. MPEP § 2164.02.

De Vita also does not demonstrate "successful" treatment of TNFα-inadequate-responders. De Vita reports internally contradictory results with respect to the one TNFα-inadequate-responder it addresses, stating that "patient 4 did not respond to treatment" and that "Patient 4 obtained an ACR20 response at month +5." Ex. 1051. Both statements cannot be true. Even if De Vita reported that it was Patient 3 who achieved an ACR20 response, the disclosed treatment would not have been considered "successful" in TNFα-inadequate-responders by a PHOSITA because prior art taught that such a low-level response, in an uncontrolled open-label study like De Vita, "is not clinically significant." Ex. 1017

at 2. Moreover, at best only one of the two TNFα-inadequate-responders had any response to the treatment, and that response paled in comparison to the ACR70 and ACR50 results achieved by the two patients (1 and 2) who were not TNFα-inadequate-responders. Ex. 1051. If anything, De Vita teaches that TNFα-inadequate-responders *cannot* be expected to successfully respond to rituximab.

Indulging Celltrion's erroneous characterizations of both De Vita and Goldenberg as demonstrating "successful" treatments, and accepting Celltrion's unannounced conversion of De Vita's size-based dosing into a fixed dose, De Vita and Goldenberg at best disclose dosing anti-B cell antibodies in total amounts of 2550 mg and 3000 mg, respectively. Even if those amounts could be described as endpoints of a range, that range would *exclude* the 2000 mg total dose claimed. Thus, "determining where in a disclosed" range an optimum total dose lies could not possibly have led a PHOSITA to the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (citing *In re Peterson*, 315 F.3d at 1330).

(iii) Celltrion's argument concerning the number of rituximab infusions fails.

Celltrion also fails to prove that a PHOSITA would have administered the total dose of rituximab as two infusions.

Celltrion argues that a PHOSITA would "have been motivated to administer rituximab in as few doses as possible to increase patient compliance and

convenience because rituximab is administered intravenously in a doctor's office or infusion center." Pet. 53. But Celltrion offers no evidence of any patient compliance or convenience problem with rituximab, or with any drug in RA patients generally, much less in patients who have run out of treatment options because they are TNFα-inadequate-responders. Nor is there reason to believe that there would be any such problem. Many TNFα-inadequate-responder patients were accustomed to frequent medical visits to receive infusion therapy. The anti TNFα drug infliximab (Remicade®), for example, required three infusions over six weeks followed by additional infusions every eight weeks thereafter. Ex. 2059 at 21.

Celltrion's "as few doses as possible" argument also ignores the reality that *decreasing* the number of infusions over which a total dose of rituximab is administered will necessarily *increase* the duration of an individual infusion. Unlike oral drugs that can be self-administered in an instant (e.g., by swallowing), infused therapies like rituximab are administered slowly, with the duration of the infusion dependent on the amount administered. Ex. 1027 at 4 (describing an initial infusion rate of 50 mg/hr, increasing over time absent infusion reactions). Thus, a larger infusion requires a patient to spend more time in a clinic, tethered to an infusion chair with an IV needle inserted in her arm. One article reports that the average time required for a first infusion of 375 mg/m^2 (~640 mg on average) of rituximab in cancer patients was 5.2 hours. Ex. 2063 at 4-5. Celltrion never

explains why patient compliance and convenience allegedly would have dictated fewer-but-longer visits over shorter-but-more-frequent visits, much less provides evidence that the claimed approach is an "optimum" for patient compliance.

Assuming, without explanation, that patient compliance and convenience would have dictated fewer but longer visits, Dr. Boers states in his declaration that "[a] person of skill in the art would have been concerned that giving a single, high dose of rituximab to patients may result in toxic reactions, and therefore, would have reached the dosing schedule of 2 doses." Ex. 1002 at ¶136. But Dr. Boers never articulates any reason why a PHOSITA supposedly *would* have been concerned about a single infusion of 2000 mg but supposedly *would not* have been concerned about two infusions of 1000 mg each. A 1000 mg infusion is still more than 150%, on average,[4] of the 375 mg/m^2 infusion amount (administered four times) that had been approved by the FDA as safe and effective for other indications. Dr. Boers's unprincipled distinction between toxicity concerns for two infusions versus toxicity concerns for one infusion betrays another instance of hindsight bias. *St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) ("[W]e must guard against hindsight bias and *ex post* reasoning.") (internal quotes and cites omitted).

[4] Assuming, for present purposes, an average BSA of 1.7 m^2, like Dr. Boers. Ex. 1002 at ¶ 74 n.2.

(iv) Celltrion's "routine optimization" argument ignores the variable of infusion amounts.

Celltrion's "routine optimization" argument would fail even assuming that a PHOSITA would have navigated all the other dosing variables to arrive at a total dose of 2000 mg of rituximab administered as two infusions because Celltrion fails to show that a PHOSITA also would have made the two infusions equal in size. And Celltrion's own admissions establish precisely the opposite, as discussed in Section c) below.

c) Celltrion admits that safety concerns would have led a PHOSITA away from using a dosing regimen as claimed here.

(i) Celltrion admits that a PHOSITA would not have made the infusion sizes equal.

According to Celltrion, a PHOSITA administering multiple infusions of rituximab would have made the first infusion smaller than the second. Acknowledging that the Rituxan® label approved in 1997 warned that "'Rituxan® is associated with hypersensitivity reactions'" and that "[t]hese hypersensitivity reactions occur in approximately 80% of patients upon the first infusion," Pet. 14, Celltrion admits in its companion IPR petition against U.S. Patent No. 7,820,161 that "[a] POSA would have been motivated to administer an initial dose of rituximab that is lower than a subsequent dose of rituximab in accordance with the general medical principle that patients should be titrated up slowly on medications to minimize unwanted side effects." Ex. 2068 at 38-39. According to Celltrion,

"[r]eal-world evidence confirms that a POSA would have titrated up the amount of rituximab when beginning treatment." *Id.* at 39. Thus, by Celltrion's own admission, a PHOSITA would not have arrived at the equal, 1000 mg infusions claimed in the '838 patent by routine optimization.

(ii) Celltrion admits that the prior art warned against a first infusion as high as 1000 mg

Each Ground 3 reference teaches using an initial infusion of rituximab equal to or lower than the FDA-approved infusion of 375 mg/m^2 (~640 mg on average):

- Curd taught three different rituximab dosing regimens with initial infusions of 50 mg/m^2, 150 mg/m^2, and 375 mg/m^2 respectively. Ex. 1031 at 27.
- Goldenberg taught an initial infusion of anti-B cell antibody totaling 600 mg. Ex. 1038 at 23.
- De Vita taught an initial infusion of 375 mg/m^2. Ex. 1051.

Thus, the alleged prior art uniformly taught an initial infusion size equal to, or lower than, 375 mg/m^2 or 600 mg fixed.

Celltrion elsewhere admits that because of the significant adverse events that had been observed with the FDA-approved 375 mg/m^2 infusions, the art "warn[ed] the skilled person against increasing the *first* dose." Ex. 2066 at 31; Ex. 2090 ¶4. "Thus," Celltrion writes, "in order not to increase the infusion-related side effects the skilled person would leave the dosage for the first dose the same" as the FDA-

approved dose. Ex. 2066 at 31; *see also* Ex. 2077 (reporting eight fatal infusion reactions from rituximab, stating that "[d]octors are warned that [the reaction] manifests within one-to-two hours of rituximab administration, and reminded of the recommended intravenous dosage of 375 mg/sqm body surface area per week for four weeks"); Ex. 2079 ("Approximately 80% of fatal infusions reactions occurred in association with the first infusion [of rituximab]."). In contrast, the '838 patent claims two larger, 1000 mg infusions. Celltrion's "routine optimization" argument therefore fails for this reason as well.

Thus, Celltrion is unable to show that it would have been obvious to administer two 1000 mg infusions of an anti-CD20 antibody to TNFα-inadequate-responders, as required by all claims.

2. None of the Ground 3 references discloses achieving the clinical responses required by claims 2-7 and 10-14.

The claimed clinical-response limitations also are missing from the prior art. Goldenberg does not even mention ACR scores or erosive progression. Ex. 1038. Nor does Curd. Ex. 1031. De Vita likewise is silent on erosive progression, and although it addresses both patients who were and were not TNFα-inadequate-responders, it reports achieving ACR50 and ACR70 scores only in patients that *were not* TNFα-inadequate-responders. Ex. 1051. Celltrion does not contend that Goldenberg, Curd, or De Vita discloses the clinical-response limitations of the claims.

B. Celltrion Fails To Establish A Motivation To Combine The Cited References To Arrive At The Claimed Invention.

The Ground 3 references do not disclose or suggest each limitation of the claims, as discussed above, but even if they did, "obviousness requires the additional showing that a PHOSITA at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Here, Goldenberg actually teaches away from at least the invention of claim 7, and in any event, Celltrion's motivation-to-combine arguments for claims 1-14 do not withstand scrutiny.

1. Goldenberg teaches away from at least the invention of claim 7.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). As a general rule, "a reference that 'teaches away' can not serve to create a *prima facie* case of obviousness." *Id.*; *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006) (finding no prima facie case of obviousness where prior art taught away from the claimed invention).

Claim 7 depends from claim 2 and requires that "the CD20 antibody is the only B-cell surface marker antibody administered to the patient." Ex. 1001. But

Goldenberg's sole (prophetic) example of using rituximab to treat RA—upon which Celltrion's Ground 3 combination depends—teaches a method where the CD20 antibody is *not* the only B-cell surface marker antibody administered to the patient. Ex. 1038 at 23. Rather, Goldenberg's example teaches administration of two B cell surface marker antibodies—rituximab and hLL2—as discussed in Section VI.A.1.b)(ii) above. *Id.* Because Goldenberg requires administering a B cell surface marker antibody in addition to a CD20 antibody, contrary to claim 7, a PHOSITA would not have been motivated to arrive at the claimed invention by combining Goldenberg with the other Ground 3 references.

2. Celltrion's motivation-to-combine arguments with respect to claims 1-14 do not withstand scrutiny.

Celltrion argues that "[a] POSA would have been motivated to treat RA patients who had previously failed TNFα-inhibitor treatment with rituximab with a reasonable expectation of success because the prior art, e.g, Goldenberg and De Vita, taught that such patients may be successfully treated with rituximab." Pet. 52. But neither Goldenberg nor De Vita demonstrate any such successful treatment, as discussed in Section VI.A.1.b)(ii) above. Celltrion therefore fails to establish the required motivation to combine for claims 1-14.

Regarding claims 4, 9 and 10-14, reciting combination with methotrexate, Celltrion argues that "[a] POSA would have further been motivated to include concomitant treatment with methotrexate because the prior art, e.g., Curd and

Goldenberg, taught exactly that combination of agents." *Id.* But Curd contains no mention of TNFα-inadequate-responders. Ex. 1031. And in any event, Curd simply included methotrexate in a long list of possible additional agents, while stating that "[p]referably however, the patient is only treated with RITUXAN®." *Id.* at 27. As for Goldenberg, only in prophetic Example 5 does it disclose treating a patient who was previously treated with a TNFα-inhibitor, and Example 5 contains no mention of methotrexate.

Celltrion argues that "the prior art as a whole taught that combination therapy including methotrexate is commonly used to treat patients with 'refractory' or 'hard-to-treat' RA" and "that new biologic treatments should be used in combination with methotrexate," Pet. at 52, but neither reference on which Celltrion relies for allegedly disclosing "successful" treatment of TNFα-inadequate-responders with rituximab—De Vita and Goldenberg—included methotrexate in their treatments. Ex. 1051; Ex. 1038.

C. Celltrion Fails To Establish A Reasonable Expectation Of Success In Achieving What Is Claimed.

As discussed above, a claim is not obvious unless a PHOSITA would have had "a motivation to combine accompanied by a reasonable expectation of ***achieving what is claimed*** in the patent-at-issue." *Intelligent Bio-Systems*, 821 F.3d at 1367 (emphasis added).

1. De Vita and Goldenberg would not have inspired in a PHOSITA a reasonable expectation of success in treating the patients of claims 1-14.

Celltrion argues that "[a] POSA would have had a reasonable expectation of success because the prior art teaches the successful treatment of RA with rituximab for patients who had previously failed TNFα-inhibitor treatment with rituximab [sic], and the prior art also teaches that refractory patients are often successfully treated with combination therapy that includes methotrexate." Pet. 54. But once again, neither reference on which Celltrion relies for allegedly disclosing "successful" treatment of TNFα-inadequate-responders—De Vita and Goldenberg—demonstrate any such success, as discussed in Section VI.A.1.b)(ii) above.

2. Celltrion fails to establish a reasonable expectation of success in specifically achieving the clinical responses required by claims 2-7 and 10-14.

None of Goldenberg, Curd, or De Vita discloses achieving an ACR50 response at 24 weeks, ACR70 response at 24 weeks, or no erosive progression at weeks 24 and beyond, in a TNFα-inadequate-responder, as discussed in Section VI.A.2 above. Celltrion fails to point to any teaching in the prior art suggesting that rituximab therapy can produce those claimed responses in such a patient.

Celltrion argues that "a POSA would have understood that treatment with rituximab would results [sic] in clinical improvement of RA symptoms, as was disclosed in De Vita and Goldenberg." Pet. 55. But claims 2-7 and 10-14 do not require mere "clinical improvement," they require specific clinical responses: ACR50, ACR70, or "no erosive progression at weeks 24 and beyond."

Moreover, De Vita 2002 taught that while ACR50 and ACR70 results were achievable in certain easier-to-treat RA patients, such results were **not** achieved in the harder-to-treat TNFα-inadequate-responders. Ex. 1032. And De Vita 2002 showed that erosive progression continues in TNFα-inadequate-responders despite treatment with rituximab, as discussed in Section V.B.2.b)(i) above. Thus, the only teaching in the prior art regarding ACR50, ACR70, and no erosive progression after rituximab therapy in TNFα-inadequate-responders indicated that such responses would *not* reasonably be expected. Celltrion's Ground 3 challenge to claims 2-7 and 10-14 therefore fails for want of the required reasonable expectation of success.

VII. CONCLUSION

For the foregoing reasons, the Board should decline to institute.

Dated: December 6, 2016

Respectfully submitted,

/s/*Michael R. Fleming*

Michael R. Fleming, Reg. No. 67,933 (Lead)
David I. Gindler (pro hac vice pending)
Gary N. Frischling, Reg. No. 35,515
Keith A. Orso, Reg. No. 52,084
Yite John Lu, Reg. No. 63,158
Irell & Manella LLP

Attorneys for Patent Owner
Genentech, Inc.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24(d), I certify that the present paper contains 13,973 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, signature blocks, certificate of service, or this certificate of word count.

Dated: December 6, 2016

Respectfully submitted,

/s/Susan Langworthy
Susan Langworthy

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on December 6, 2016, a copy of the foregoing document **GENENTECH INC.'S PATENT OWNER PRELIMINARY RESPONSE and EXHIBITS 2001 – 2099** have been served in their entireties via e-mail on counsel of record for petitioners at the following addresses:

Elizabeth J. Holland
Huiya Wu
Cynthia Lambert Hardman
Elaine H. Blais
Robert V. Cerwinski
GOODWIN PROCTER LLP
eholland@goodwinlaw.com
hwu@goodwinlaw.com
chardman@goodwinlaw.com
eblais@goodwinlaw.com
rcerwinski@goodwinlaw.com

Dated: December 6, 2016

Respectfully submitted,

/s/Susan Langworthy
Susan Langworthy