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Paper 15
Entered: August 30, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

IPR2019-00739
Patent 9,725,504 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Amgen Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–10 of U.S. Patent No. 9,725,504 B2 ("the '504 patent," Ex. 1001). Paper 2 ("Pet."). Alexion Pharmaceuticals ("Patent Owner" or "Alexion") timely filed a Preliminary Response. Paper 10 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 13 ("Reply"); Paper 14 ("Sur-Reply").

We review the Petition, Preliminary Response, Reply, Sur-Reply, and accompanying evidence under 35 U.S.C. § 314. An *inter partes* review may not be instituted unless "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Further, a decision to institute may not institute on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

After considering the evidence and arguments presented in the Petition and Preliminary Response, Reply, and Sur-Reply, we determine that Petitioner demonstrates a reasonable likelihood of prevailing in showing that at least one of the challenged claims of the '504 patent is unpatentable. Accordingly, we institute an *inter partes* review as to all the challenged claims of the '504 patent on all the grounds of unpatentability set forth in the Petition.

A. Real Parties-in-Interest

Petitioner identifies only itself as the real party-in-interest. Pet. 73. Patent Owner, likewise, identifies only itself as the real party-in-interest. Paper 3, 2.

B. Related Proceedings

The ’504 patent shares essentially the same specification with U.S. Patent Nos. 9,718,880 B2 (“the ’880 patent) and 9,732,149 (“the ’149 patent”). Amgen has filed Petitions for *Inter Partes* Review of the ’504, ’880, and ’149 patents in IPR2019-00739, IPR2019-00740, and IPR2019-00741, respectively. Pet. 73–74; Paper 3, 2.

The ’504, ’880, and ’149 patents are related as follows: The ’149 patent issued from application No. 15,284,015, filed January 19, 2017, which is a continuation of application No. 15/260,888 (now the ’504 patent), filed on September 9, 2016, which is a continuation of application No. 15/148,839 (now the ’888 patent), filed on May 6, 2016, which is a continuation of application No. 13/426,973, filed on March 22, 2012, which is a continuation of application No. 12/225,040, filed as application No. PCT/US2007/006606 on March 15, 2007. The parties do not dispute that March 15, 2007, is the relevant priority date of the challenged patent.

C. The ’504 patent and Relevant Background

The ’504 patent relates to the use of a humanized anti-C5 antibody (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria. *See* Ex. 1001, Abstract. For reference, we reproduce Figure 1 from the

Balthasar Declaration,[1] illustrating the basic structure of an antibody, such as eculizumab:

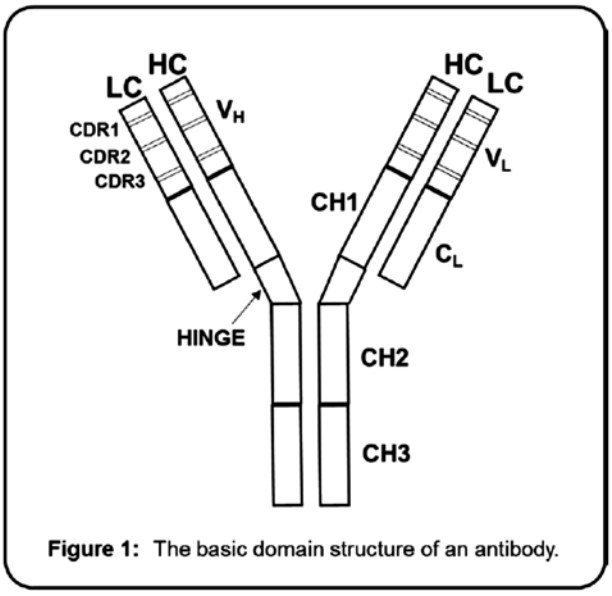


Figure 1: The basic domain structure of an antibody.

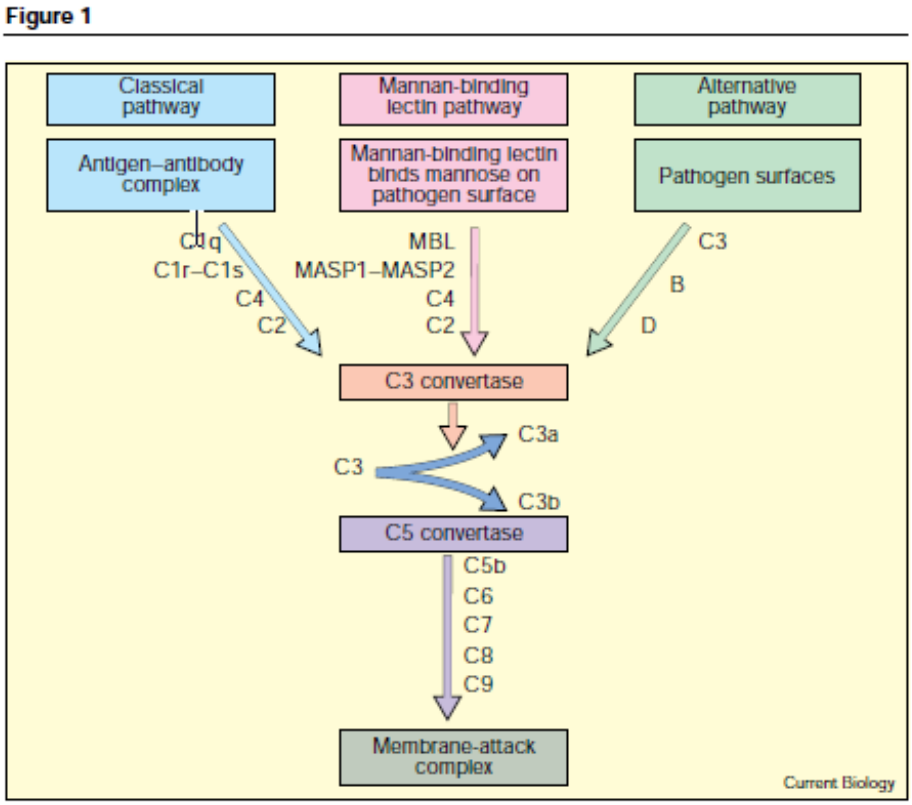
The figure above shows a basic antibody structure having hinged heavy chains (HC) and accompanying light chains (LC), each having constant regions (C_H and C_L) and variable regions (V_H and V_L), all arranged in a general "Y" shaped structure, as the variable regions and portions of the constant heavy chain regions are hinged away from one another. Ex. 1002 ¶¶ 23–24. The variable regions of each chain also include three complementarity determining regions (CDR), which provide the antibody with antigen-binding specificity. *Id*.

[1] Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1002, "Balthasar Declaration").

Paroxysmal nocturnal hemoglobinuria or PNH is an acquired hemolytic disease resulting from loss of function in certain cytoprotective proteins. Ex. 1001, 1:27–35; Ex. 1002 ¶ 31. This loss of function renders red blood cells, platelets, and other blood cells highly sensitive to attack via activated complement proteins (explained in detail below). Ex. 1002 ¶ 31. The resultant complement-mediated lysis of blood cells results in anemia, hemoglobinuria, and related symptoms, which impair a patient's quality of life to the extent that "[m]any PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels." Ex. 1001, 1:42–53. As further explained by Petitioner's expert, Dr. Balthasar, "[a]s a result of the destruction of RBCs and the resultant release of free hemoglobin into the blood, 'PNH is characterized by hemolytic anemia (a decreased number of red blood cells), hemoglobinuria (the presence of hemoglobin in the urine particularly evident after sleeping), and hemoglobinemia (the presence of hemoglobin in the bloodstream.')" Ex. 1002 ¶ 32 (quoting Ex. 1005 ¶ 7).

"Complement" is a "system of plasma proteins . . . so-named because it complements the activity of antibody in the lysis of bacteria." Ex. 1022 R259; *see generally* Ex. 1001, 7:6–8:56. As part of the immune system, complement "has a central role in host defense against many micro-organisms and in the modulation of inflammatory reactions.'" *Id.*; *see*

Ex. 1002 ¶ 28. The figure below shows "the main pathways and components of the complement activation system." Ex. 1022, R259.



The above figure illustrates how various complement proteins are organized into the "classical," "mannan-binding," and "alternative" activation pathways. Ex. 1022, R259; *see* Ex. 1001, 7:17–19. All three pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase into C5a and C5b. Ex. 1022, Fig. 1; *see* Ex. 1002 ¶ 29. As summarized in paragraph 29 of the Balthasar Declaration (Ex. 1002), cleavage of C5 initiates the terminal complement cascade. Conversely, blocking the cleavage of C5 prevents complement activation. *See, e.g.*, Ex. 1001, 10:65–

11:6 ("U.S. Pat. No. 6,353,245 [Evans][2] teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components."); 12:21–29.

According to the Specification, eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5 convertase and, is thus, intended to suppress the terminal activation cascade and resultant complement activation. Ex. 1001, Abstract, 1:56–57 (citing Thomas C. Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1023, "Thomas")). More specifically, "eculizumab" refers to humanized antibodies derived from mouse antibody 5G1.1, sometimes referred to as "murine 5G1.1" or "m5G1.1". *See* Prelim. Resp. 12–13. The term "humanized" refers to an antibody having a human framework, into which CDR regions from a non-human monoclonal antibody (e.g., mouse) are inserted. Ex. 1007, 5:57–67; Ex. 1002 ¶¶ 22–26. Accordingly, humanized versions of non-human antibodies may be indicated by the prefix "h" or "hu" as in "h5G1.1" and "hu5G1.1." *See e.g.*, Pet. 17, n.11, 19; Prelim. Resp. 12; Ex. 1002 ¶ 48.

Claim 1 refers to SEQ ID NO: 2 and SEQ ID NO: 4, which together comprise an eculizumab antibody. *See generally* Prelim. Resp. 1–2. Thus, for example, the '504 patent identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab Heavy Chain" and "Eculizumab Light Chain,"

[2] US 6,355,245 B1, issued Mar. 12, 2002 (Ex. 1007).

respectively. Ex. 1001, 30:22–31, 38–44. It is undisputed that SEQ ID NO: 2 encodes a hybrid IgG2/IgG4 heavy chain (i.e., having a genetically engineered heavy chain constant region derived from portions of IgG2 and IgG4 isotype antibodies). *See, e.g.*, Pet. 3; Prelim. Resp. 14; Ex. 1033, 1258 (Figure 2). Eculizumab is the non-proprietary name for Patent Owner's SOLIRIS product, which was approved by the FDA "for treatment of patients with PNH." *See, e.g.*, Prelim. Resp. 1–2, 5–6 (citing Ex. 1033, 1256;[3] Ex. 2005, 1[4]); Pet. 2 (citing Ex. 1009, 2); *see also* Prelim. Resp. 16 ("The '504 patent claims recite the complete amino acid sequence for SOLIRIS® . . . the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31–33, 35.).").

The '504 patent also discusses the conduct and results of the TRIUMPH trial in which 88 red blood cell transfusion dependent PNH patients were randomly assigned "to receive either placebo or Eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.)." Ex. 1001, 19:51–28:38.

> Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

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[3] Rother et al., *"Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria,"* 25(11) NATURE BIOTECHNOLOGY 1256–1264 (2007).
[4] SOLIRIS Product Label (rev. 3/2007).

Id. at 20:43–50. The Specification concludes that "[t]he results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency." *Id.* at 28:33–38. "[E]culizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis." *Id.* at Abstract.

D. Challenged Claims

Petitioner challenges claims 1–10 of the '504 patent, of which claim 1 is independent; claim 1 reads as follows:

> 1. A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Ex. 1001, 39:2–7. Among the dependent claims, claim 2 requires administration of the compound by intravenous infusion, claims 3 and 8 relate to dosage and dosing protocol, claims 4–6 relate to single unit dosage forms, claim 7 requires that the patient is anemic, and claim 9 and its dependent claim, claim 10, require that "administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)."

E. Asserted Grounds of Unpatentability

Petitioner asserts the following seven grounds for unpatentability (Pet. 23):

Ground	Claim(s)	Basis	Asserted Reference(s)
1	1–3, 7–10	102(b)[5]	Hillmen[6]
2	4, 5	103(a)	Hillmen and Bell[7]
3	6	103(a)	Hillmen, Bell, and Wang[8]
4	1–5, 7–10	103(a)	Bell, Bowdish,[9] and Evans[10]
5	6	103(a)	Bell, Bowdish, Evans, and Wang
6	1–5, 7–10	103(a)	Bell, Evans, and Mueller[11]
7	6	103(a)	Bell, Evans, Mueller, and Wang

[5] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '504 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 throughout this Decision.
[6] Hillmen et al., "*Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*," 350(6) N. Engl. J. Med. 552–59 (2004). (Ex. 1004).
[7] Bell et al., US 2005/0191298 A1, published Sept. 1, 2005 (Ex. 1005).
[8] Wang, US 2005/0271660 Al, published Dec. 8, 2005 (Ex. 1028)
[9] Bowdish et al., US 2003/0232972 A1, published Dec. 18, 2003 (Ex. 1006).
[10] Evans et al., US 6,355,245 B1, issued March 12, 2002 (Ex. 1007).
[11] Mueller et al., WO 97/11971, published April 3, 1997 (Ex. 1008).

In support of its patentability challenges, Petitioner relies on, *inter alia*, the Declaration of Joseph P. Balthasar, Ph.D. Ex. 1002.

F. Overview of Asserted References

1. Overview of Hillmen (Ex. 1004)

Hillmen discloses that "[p]aroxysmal nocturnal hemoglobinuria (PNH) arises from a somatic mutation of the PIG-A gene in a hematopoietic stem cell and the subsequent production of blood cells with a deficiency of surface proteins that protect cells from attack by the complement system." Ex. 1004, 552.

> Patients with PNH have chronic, often disabling symptoms of fatigue and intermittent episodes of dysphagia, abdominal pain, and hemoglobinuria. These symptoms are thought to be related to the intravascular destruction of PNH type III erythrocytes, which are deficient in complement inhibitors, by autologous complement. The hemolytic anemia frequently renders the patients transfusion-dependent. In addition, patients have an extremely high risk of potentially life-threatening thrombosis, particularly thrombosis of the hepatic and cerebral veins. Approximately 50 percent of patients with PNH die of the disease; the median duration of survival after diagnosis is 10 years.

Id. at 557.

Hillmen reports on the efficacy of eculizumab for "reduc[ing] the incidence of intravascular hemolysis, hemoglobinuria, and transfusion requirements in patients with PNH." *Id.* at 553. "Eleven transfusion-dependent patients with PNH received infusions of eculizumab (600mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12" *Id.* at Abstract, *see id.*

at 554. Based on this treatment, Hillmen concludes:

> Eculizumab is safe and well tolerated in patients with PNH. This antibody against terminal complement protein C5 reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion, with an associated improvement in the quality of life in patients with PNH.

Id. at Abstract.

Hillmen characterizes eculizumab as "a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." *Id.* (citing, e.g., Thomas (Ex. 1023)). According to Hillmen, the antibody "binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b, thereby preventing the release of the inflammatory mediator C5a and the formation of the cytolyticpore C5b-C9." *Id.* Because eculizumab "specifically prevents cleavage of C5, which is necessary for assembly of the membrane-attack complex," the treatment "presumably prolongs the survival of type III erythrocytes . . . which are highly sensitive to lysis by complement." *Id.* at 557.

2. Overview of Bell (Ex. 1005)

Bell discloses the treatment of PNH "using a compound which binds to or otherwise blocks the generation and/or activity of one or more complement components. . . . In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional fragments of hSGl.l." *Id.* ¶ 12; *see also id.* ¶ 52 ("The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename

eculizumab."). Bell further discloses: "Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in [Evans] and [Thomas] . . . the disclosures of which are incorporated herein in their entirety." *Id.* ¶ 52.

As noted by Dr. Balthasar, the data disclosed in Bell overlaps with that in Hillmen, but further includes data on extension studies in which patients continued treatment for paroxysmal nocturnal hemoglobinuria for a total of two additional years. *See* Ex. 1002 ¶ 39 (citations omitted).[12] Briefly, eleven transfusion-dependent PNH patients received weekly 600 mg doses of eculizumab by infusion for four weeks, followed by "900 mg of eculizumab 1 week later[,] then 900 mg on a bi-weekly basis." Ex. 1005 ¶¶ 81–82. Bell characterizes the first twelve weeks of treatment as a "pilot study." *Id.* ¶ 82. "Following completion of the initial acute phase twelve week study, all patients participated in an extension study conducted to a total of 64 weeks. Ten of the eleven patients participated in an extension study conducted to a total of two years." *Id.* Bell concludes that "[p]atients in the two year study experienced a reduction in adverse symptoms associated with PNH. *Id.* ¶¶ 82, 96.

[12] Page 38, footnote 17, of the Petition states: "Because the clinical study taught in Bell is the same C02-001 study disclosed in Hillmen, which discloses the eculizumab amino acid sequences of SEQ ID NOs: 2 and 4, Bell, too, therefore anticipates claims 1–4 and 7–10 for the same reasons discussed above for Hillmen." Despite this assertion, Petitioner's sole anticipation-based Ground in this IPR relies on Hillmen. *See* Pet. 23.

3. Overview of Wang (Ex. 1028)

Wang discloses formulations of eculizumab suitable for nebulization and pulmonary delivery. *See, e.g.*, ¶¶ 25, 62, 67. Wang discloses formulations comprising from 1 to 30 mg/ml eculizumab, and provides evidence that a formulation having 30 mg/ml eculizumab can be effectively and efficiently delivered using a conventional nebulizer. *Id.* ¶¶ 171–173, Fig. 10.

4. Overview of Bowdish (Ex. 1006)

Bowdish discloses "[i]mmunoglobulins or fragments thereof hav[ing] a peptide of interest inserted into a complementarity determining region (CDR) of an antibody molecule," whereupon, "[t]he antibody molecule serves as a scaffold for presentation of the peptide and confers upon the peptide enhanced stability." Ex. 1006 ¶ 6. In certain "embodiments, the peptide replacing the amino acids of a CDR is an agonist TPO [thrombopoeitin] peptide." *Id.* ¶ 17.

In Example 4, Bowdish describes a TPO mimetic peptide graft into the heavy chain CDR3 of antibody framework 5G1.1, described in Evans, which Bowdish incorporates by reference. *Id.* ¶¶ 191–193. According to Bowdish:

> Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated herein by reference.[13] The sequence was cloned into 5G1.1 in such a fashion as to replace the native CDR3 . . . [wherein t]he peptide graft translated into amino acids is Leu Pro Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Arg Ala

[13] U.S. Application Ser. No. 08/487,283 matured into U.S. Patent No. 6,355,245 B1, referenced herein as Evans (Ex. 1007).

> Pro Val (SEQ. ID. NO: 66). The 5G1+peptide was produced as a whole IgG antibody (See FIGS. 13A and 13B).

Id. ¶ 191. "Purified 5G1.1+peptide antibody as well as the parental 5G1.1 were analyzed for their ability to bind to cMpl receptor by FACS analysis." *Id.* ¶ 192.

In SEQ ID NOs: 69 and 70, respectively, Bowdish discloses the amino acid and nucleotide sequences for the "5G1.1 Light Chain." In SEQ ID NO: 67, Bowdish discloses the amino acid sequence of the "5G1.1–TPO Heavy Chain," with the substituted TPO mimetic sequence marked in bold. An excerpt of that sequence showing the amino acids of the TPO substitution in bold reads: DTAVYYCAR**LPIEGPTLRQWLAARAPV** WGQGTLVTVSS. Bowdish discloses the corresponding nucleotide sequence in SEQ ID NO: 68.

5. Overview of Evans (Ex. 1007)

Evans discloses anti-C5 antibodies useful in the treatment of glomerulonephritis (GN). Ex. 1007, Abstract. Evans' Example 7 describes the isolation anti-C5 monoclonal antibodies from mouse hybridoma designated 5G1.1. *Id.* at 37:34–39:30. In Figures 18 and 19, respectively, Evans discloses the amino acid sequence of the light and heavy chain variable regions of mouse antibody 5G1.1, with "[t]he complementarity determining region (CDR) residues according to the sequence variability definition or according to the structural variability definition . . . [bolded] and [underlined], respectively." *Id.* at 9:65–10:20. A representation of an excerpt of the heavy chain sequence showing the amino acids of CDR3 so marked reads: DSAVYYCAR**Y<u>FFGSSPNWYFD</u>V**WGAGTTVTVSS.

See id. at Fig. 19.

Evans describes making a series of different humanized 5G1.1 scFv[14] and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. AMG1007, 37:35-39:30, 42:59-45:33. With respect to the former, Evans discloses that "[p]articularly preferred constant regions . . . are IgG constant regions, which may be unaltered, or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG4." *Id.* at 45:29–33.

In Example 11, Evans discloses steps in the humanization of mouse antibody 5G1.1, including the construction of recombinant antibody, 5G1.1 scFv CO12. *Id.* at 42:59–45:33. According to Dr. Balthasar, the construct "'5G1.1 scFv CO12" contains all six 5G1.1 CDR regions and its sequence aligns perfectly with the eculizumab variable regions claimed by the '504 patent." Ex. 1002 ¶ 55 (comparing portions of SEQ ID NO: 2 of the '504 patent with portions of Evans' SEQ ID NO. 2). Dr. Balthasar's Figure 6, for example, shows that both sequences contain the larger of the two overlapping amino acid sequences Evans identifies as CDR3, YFFGSSPNWYFDV. *Id.*

6. Overview of Mueller (Ex. 1008)

Mueller discloses "[a]ntibodies to porcine P-selecting protein, porcine VCAM protein and porcine CD86 protein are useful for diagnosing human

[14] As Dr. Balthasar notes, "a scFv comprises an antibody's light and heavy chain variable domains connected by a linker." Ex. 1002 ¶ 54, n.4 (citing Ex. 1007, 6:39-41).

rejection of porcine xenotransplants and for improving xenotransplantation of porcine, cells, tissues and organs into human recipients." Ex. 1008, Abstract. According to Mueller, one object of the invention is to provide antibody molecules that neither activate complement nor bind to the FC receptor. *Id.* at 7:28–31. To achieve these and other goals, Mueller points to "[r]ecombinant (chimeric and/or humanized) antibody molecules comprising the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4, such antibodies being referred to hereinafter as 'HuG2/G4 mAb.'" *Id.* at 8:23–26. Mueller developed and tested "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4." *Id.* at 12:19–33. As controls for these experiments, Mueller used "a humanized antibody directed against human C5 (h5G1.1 C012 HuG4 mAb)." *Id.* at 11:34–12:4, 12:34–13:2, Figures 11, 12, 15. On pages 58–61, Mueller discloses the cDNA and amino acid sequence of "Human G2/G4."

II. ANALYSIS

A. Principles of Law

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics,*

Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). This "single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). "Under the principles of inherency, if the prior art necessarily . . . includes[ ] the claimed limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Similarly, "[a] reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (internal citation and emphasis omitted). Moreover, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968); *see Eli Lilly v. Los Angeles Biomedical Res. Inst.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that

subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

B. Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the

technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner contends that a person of ordinary skill in the art as of the relevant date would have "had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in the field." Pet. 21. Patent Owner does not dispute this definition, but suggests that we interpret the relevant field as directed to "engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry." *See* Prelim. Resp. 45 (emphasis omitted).

Petitioner's proposed definition is not inconsistent with the cited prior art. Patent Owner responds, however, that it "does not dispute Amgen's POSA definition, except to clarify that the POSA would have at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry." Prelim. Resp. 45 (emphasis omitted); *see also id.* (arguing that Petitioner cannot prove unpatentability of the challenged claims under either definition).

Considering that each of the asserted references (discussed *infra*) is substantially directed to the development of monoclonal antibodies for the treatment or diagnosis of human disease, Patent Owner's proposed clarification provides useful context. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art)

(quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)). Accordingly, we define one of ordinary skill in the art as a person with an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. Our decision whether to institute, however, does not turn on which party's definition of the skilled artisan is used, and our determinations would be unchanged if we applied Petitioner's definition.

C. Claim Construction

Based on the filing date of the Petition (Feb. 28, 2019), the Board interprets claim terms in an *inter partes* review ("IPR") using the same claim construction standard that is used to construe claims in a civil action in federal district court. *See* 83 Fed. Reg. 51,340 (Nov. 13, 2018) (to be codified at 37 C.F.R. pt. 42).

In construing claims, district courts give claims their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Sources for claim interpretation include "the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves [may] provide substantial

guidance as to the meaning of particular claim terms." *Id.* However, the claims "do not stand alone," but are part of "'a fully integrated written instrument,' consisting principally of a specification that concludes with the claims," and, therefore, the claims are "read in view of the specification." *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995)).

At this stage in the proceeding, we need only construe the claims to the extent necessary to determine whether to institute *inter partes* review. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

Although at this stage of the proceeding no claim term requires express construction, for the sake of clarity, we address Petitioner's unopposed position that "immediate," as used in claim 9, encompasses events occurring within one week after administering eculizumab:

> Claim 9 recites that the claimed method "results in an *immediate* and sustained decrease in mean levels of lactate dehydrogenase (LDH)." AMG1001, claim 9. The '504 patent specification teaches "[t]he impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an *immediate (one week)* and sustained decrease in mean levels of LDH." AMG1001, 22:22-25. Claim 10 depends from claim 9 and further requires that "the immediate decrease occurs *within one week* of administration of the antibody." AMG1001, claim 10. Thus, as Dr. Balthasar explains, a POSA would have understood the term "immediate"

> to include a decrease beginning "within one week" after administering the eculizumab. AMG1002, ¶¶64-65.

Pet. 22. Considering the above-cited portion of the Specification and the dependency of claim 10 noted in the Petition, we agree with Petitioner's assertion that "immediate" as used in claim 9 encompasses within its scope events occurring within one week after administering eculizumab.

D. Anticipation by Hillmen (Ground 1)

In Ground 1, Petitioner challenges claims 1–3 and 7–10 as anticipated by Hillmen. Pet. 25–37. Patent Owner opposes. Prelim. Resp. 45–51. For this Ground, here we focus on claim 1.

1. The Parties' Contentions

Petitioner contends "Hillmen discloses all the limitations of claim 1, either expressly or inherently, and is enabling." Pet. 25 (citing Ex. 1002 ¶¶ 75–84). In particular, Petitioner argues that Hillmen *explicitly* discloses every element of claim 1, except for eculizumab's amino acid sequence. *Id.* at 26. With respect to that amino acid sequence, Petitioner contends "Hillmen's antibody necessarily 'comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' because Alexion admitted that Hillmen's eculizumab possesses those very amino acid sequences." *Id.* at 26–27 (citing Ex. 1014, 765, 767 (Boone Declaration ¶¶ 5–6)[15]; Ex. 1024, 109; Ex. 1025, 2 (these exhibits identify a trial "CO2-

[15] Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, dated May 11, 2017 (submitted during the prosecution of U.S. Application No. 15/148,839, which became the '149 patent) (Ex. 1014, 763–70, "Boone Declaration").

001" as testing SOLIRIS). The Boone Declaration, cited by Petitioner, in relevant portion, states first that study C02-001 was a study of the effect of eculizumab (h5G1.1-mAb) on patients with PNH, that Dr. Boone had reviewed the eculizumab antibody used in that study and its amino acid sequence, and that Dr. Boone "concluded that the antibody (eculizumab) used in each of the studies . . . contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4." Ex. 1014, 764–67 (¶¶ 5–6).

Although Petitioner does not argue that Hillmen literally and expressly disclosed the claimed antibody structure with SEQ ID NOs: 2 and 4 (which, we note, it does not), Petitioner's position is that, because Hillmen disclosed a trial of the SOLIRIS eculizumab antibody, and because Patent Owner conceded that the eculizumab antibody used is the claimed anti-C5 antibody, that Hillmen inherently discloses the claimed sequences. Pet. 27–29 (citing *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004)).

Petitioner's inherency rationale, based on "the general knowledge in the relevant field" (*id.* at 31), is summarized as follows. Contemporaneous with Hillmen's disclosure, the skilled artisan would have known that Bowdish disclosed the entire amino acid sequence of eculizumab, but for a heavy chain CDR3 region, which Bowdish disclosed as substituted with a TPO (thrombopoietin) amino acid sequence; the skilled artisan, however, would have known that Evans disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, including heavy chain CDR3 region absent from Bowdish; alternatively, the skilled artisan would have understood that Mueller disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab, whereas Evans disclosed

the respective variable domains. Pet. 29–31 (citing Ex. 1004, 553–554; Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex 1007, 44:4–13; Ex. 1008, 52–53, 58–61; Ex. 1002 ¶¶ 60, 81–84). With this knowledge in hand, the skilled artisan would have known that Hillman discloses a method of treatment using eculizumab—which was necessarily the claimed anti-C5 antibody with the claimed SEQ ID NOs: 2 and 4. *Id.*

Petitioner also appears to argue that Hillmen inherently discloses the hybrid IgG2/IgG4 heavy chain portion of SEQ ID. NO: 2, because one of ordinary skill in the art would have known that eculizumab contains this structure. Pet. 17 (citing Ex. 1034, 1279; Ex. 1049, 838–839; Ex. 1002 ¶¶ 46–49). Petitioner argues, for example, that Tacken explicitly describes eculizumab as containing an IgG2/IgG4 constant region. *Id.* (quoting Ex. 1034, 1279); *see, e.g.*, Ex. 1002 ¶ 46 ("Tacken confirms that eculizumab contains a hybrid IgG2/IgG4 constant region. AMG1034, 1278-1279. Tacken describes using 'h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)' containing an 'IgG2/IgG4 constant region.' AMG1034, 1279.").

Petitioner also relies on statements made by Patent Owner on the record during the prosecution of U.S. Patent Application Ser. No. 11/127,438, where, in arguing that disclosures upon which the applicant relied for priority were supportive of the then-pending claims, Alexion stated:

> Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-

> scFv and functional fragments of h5G1.1 are *described in U.S. Patent No. 6,355,245* [Evans], the disclosures of which are incorporated herein in their entirely [*sic*] by this reference . . . Applicant submits that h5G1.1 . . . [was] *well-known to one of ordinary skill in the art as eculizumab* . . . at the time of filing of priority applications.

See Pet. 10 (quoting Ex. 1049, 838–39 (emphasis Petitioner's)). Thus, Petitioner argues, Alexion represented to the Patent Office that the antibody structure disclosed in Evans was well-known to the skilled artisan so that such a person of skill would have considered this structure to be the eculizumab in Hillmen, and which was publically disclosed before the March 15, 2007 priority date of the '504 patent.

Patent Owner takes the position that, "[p]rior to March 15, 2007, the priority date of the '504 patent, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art." Prelim. Resp. 1.

> If a POSA were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the '504 patent claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed a POSA to the 1996 "Thomas" publication (AMG1023) for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring "IgG4" heavy chain constant region. The claimed antibody of the '504 patent has a very different, uniquely engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

Id. at 2–3 (emphasis omitted).

It is Patent Owner's position that, reading Hillmen's disclosure of "eculizumab" and Hillmen's reference to Thomas, the skilled artisan would not have been directed to the version of eculizumab encompassed by claim 1 of the '504 patent, but would have understood Hillmen to refer to Thomas's disclosed eculizumab, which is an IgG4 isotype antibody, which does not have the hybrid IgG2/IgG4 heavy chain sequence as described in SEQ ID NO: 2. *Id.* at 3, 11–13 (referencing Ex. 1023). In particular, Patent Owner notes that Hillmen cites Thomas as *the* reference for eculizumab. *Id.* at 3, 12 (citing Ex. 1004, 533 (which cites Ex. 1023 as reference "15")).

> Thomas . . . described the design and testing of a humanized anti-C5 antibody (termed "humanized 5G1.1" or "h5G1.1") featuring an "IgG4" heavy chain constant region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (AMG1023 at 1396, 1399.) Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed "murine 5G1.1" or "m5G1.1") in an *in vitro* assay showing activity blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (AMG1023 at 1396.)

Id. at 12–13 (emphasis omitted).

Patent Owner states that "[t]oday, but not prior to the March 15, 2007 priority date for the '504 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in the claims of the '504 patent, namely, 'a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" *Id*. at 15 (emphasis omitted). Patent Owner argues that, as of the critical date, Hillmen did not

> enable[ ] a POSA to make and use the specific antibody recited in claims 1-3 and 7-10 without undue experimentation, because

> Hillmen guided a POSA as of March 15, 2007 to make and use a very different antibody – the ***IgG4*** isotype antibody of Thomas. *See, e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation").

Id. at 46–47. Patent Owner further argues that

> [t]he mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date.

Id. at 48–49 (citing *Endo Pharm. Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378–83 (Fed. Cir. 2018)).

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of claim 1 of the '504 patent under Ground 1.

Petitioner concedes Hillmen does not expressly disclose the claimed antibody; instead, Petitioner relies on the doctrine of inherency and a post-priority-date admission by Patent Owner that the pharmaceutical (eculizumab) referenced in Hillmen was actually the claimed antibody.

Hillmen "tested the clinical efficacy of eculizumab, a humanized antibody that inhibits the activation of terminal complement components, in patients with PNH." Ex. 1004, 552. Hillmen teaches that "[e]culizumab is a recombinant humanized monoclonal antibody that was designed to block the

activation of terminal complement components.[14,15] It binds specifically to the terminal complement protein C5." *Id.* at 553. Citation "14" of Hillmen refers to Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 NATURE 323–27 (1988). This reference is not an exhibit in this proceeding and Petitioner does not suggest that it mentions eculizumab. Citation "15" of Hillmen refers to Thomas (Ex. 1023), which discloses a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, which was shown to effectively block C5 cleavage. *See* Ex. 1023, 1389.

Thomas discloses the process of developing a humanized antibody (h5G1.1 HuG4) for human C5. Thomas summarizes this work in a section titled "*Construction of a humanized h5G1.1 antibody*":

> Having demonstrated the effective humanization of the 5G1.1 variable regions, an intact humanized antibody (IgG4 isotype) was constructed and produced in 293-EBNA cells. The avidity of this humanized antibody (h5G1.1 HuG4) for human C5, was compared to the murine 5G1.1 mAb by determining the ability of each to compete binding of biotinylated 5G1.1 mAb to C5 (Fig. 9). The humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody. However, the humanized h5G1.1 HuG4 antibody was equipotent with the murine antibody at protecting PAEC from lysis by human serum, with a 0.5-fold molar ratio of antibody to C5 (1:1 ratio of antibody binding sites to C5) completely inhibiting lysis of the PAEC (Fig. 10).

Id. at 1396.[16] We find nothing in Thomas that expressly discloses or alludes

[16] Patent Owner argues that as of the '504 patent's priority date, many other references cited Thomas when referring to eculizumab. *See* Prelim. Resp. 24–29, Table 1. Without going into detail, we find Patent Owner has accurately shown how other, contemporaneous prior art references cited Thomas for this purpose.

to a hybrid IgG2/IgG4 antibody. *See generally* Ex. 1023.

We also consider Dr. Balthasar's assertion that one of ordinary skill in the art "would have known that eculizumab contains a hybrid IgG2/IgG4 heavy chain constant region" because Tacken "describes using 'h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)' containing an 'IgG2/IgG4 constant region.'" Ex. 1002 ¶ 46 (citing Ex. 1034, 1279).

In seeking to address this assertion, Patent Owner takes the position that Tacken (also addressed in the context of Petitioner's obviousness challenges) is non-analogous art because it "does not involve the same field as the '504 patent, and would not have been reasonably pertinent to the particular problem addressed by the '504 patent." Prelim. Resp. 37; Sur-Reply 2–3. On the present record, we do not find Patent Owner's argument persuasive. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (mere lawyer's arguments and conclusory statements that are unsupported by factual evidence are entitled to little probative value).

"Prior art is analogous if it is from the same field of endeavor or if it is reasonably pertinent to the particular problem the inventor is trying to solve." *Circuit Check Inc. v. QXQ Inc*., 795 F.3d 1331, 1335 (Fed. Cir. 2015). In the present case, Tacken discloses the development of "a humanized antibody, hD1V1G2/G4 (hD1), directed against the C-type lectin DC-specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN) to explore its capacity to serve as a target receptor for vaccination purposes." Ex. 1034, Abstract. Given Patent Owner's position that the relevant field of the '504 patent encompasses the "engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry"

(*see* Section II(B), above), Tacken's development of the monoclonal antibody hD1V1G2/G4 (hD1) "for vaccination purposes" would appear to be in the same field of endeavor. Moreover, because Tacken's antibodies employ the same IgG2/IgG4 constant region as SEQ ID NO. 2 of claim 1, we disagree that Tacken is not reasonably pertinent to the '504 patent.

With reference to its hD1V1G2/G4 (hD1) antibody, Tacken discloses that, "[a]n isotype control antibody, h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5." Ex. 1034, 1279. Although, as Patent Owner points out, Tacken then cites to Thomas, Patent Owner does not address why Tacken would use an eculizumab having the IgG4 constant region as set forth in Thomas as "[a]n isotype control antibody" for one having an IgG2/IgG4 constant region. Dr. Balthasar, however, testifies that Tacken also cites Mueller II[17] "as providing information about the hybrid IgG2/IgG4 constant region portion of eculizumab." Ex. 1002 ¶ 56 (citations omitted); *see* Ex. 1034, 1279 (indicating that in the construction of hD1V1G2/G4 (hD1), "humanized variable heavy and variable light regions were [ ] genetically fused with a human hybrid IgG2/IgG4 constant domain," as set forth in Mueller II (reference 17)). On the present record, we read Tacken as disclosing that humanized monoclonal antibody 5G1.1, known as eculizumab, encompasses

[17] John P. Mueller et al., *Humanized porcine VCAM-specific monoclonal antibodies with chimeric IgG2/G4 constant regions block human leukocyte binding to porcine endothelial cells*, 34 Mol. Immunol. 441–52 (1997) (Ex. 1031).

a molecule having a hybrid IgG2/IgG4 constant domain.

That Tacken, Bowdish, and Mueller suggest that eculizumab may include an IgG2/IgG4 constant domain, however, does not necessarily lead to the conclusion that Hillmen discloses the same molecule. Rather, the present record indicates that "eculizumab" is not a single, fixed chemical entity. To the contrary, the art identified as "eculizumab" at least two such compounds that differed in the heavy chain constant region: one having the IgG4 isotype (as evidenced in Thomas), and a second having a hybrid IgG2/IgG4 isotype (as evidenced by, e.g., Tacken).

Patent Owner made the above dichotomy explicit in an official representation to the Patent Office. During Alexion's prosecution of Application No. 11/127,438, an application outside of the chain of priority of the '504 patent, but claiming the use of eculizumab for the treatment of pulmonary conditions, the Examiner took the position that "the description of 'eculizumab or pexelizumab' as well as 'the mutated Fc portions' in the priority documents is not readily apparent." Ex. 1049, 741, 830–834 (representative claim amendments). In response, Alexion asserted that

> **eculizumab was first constructed in the IgG4 isotype**, see, e.g., the bridging paragraph of the left and right columns of page 1396 of Thomas et al. (1996) [Ex. 1023], . . . **and then into the G2/G4 format**, see Mueller et al. (1997) *Molecular Immunology*, Vol. 34, No.6, pages 441-452 [Ex. 1031], . . . while **in either form** the h5G1.1 antibody was well known to be incapable to activate human complement, see, e.g., the right column, lines 27-28, of page 1399 of Thomas et al., 1996, *Id.*, and the bridging paragraphs of pages 446 to 448 and 450 to 451 of Mueller et al, 1997, *Id.* Thus, Applicant submits that it was well-known to one of ordinary skill in the art at the time of filing

> of priority applications that eculizumab has a G2/G4 Fc portion, i.e., a mutated Fe portion.

Id. at 838–839 (bolding added). Alexion's statement, above, supports both Thomas's disclosure of eculizumab in the IgG4 isotype as the first construction of eculizumab, as well as an understanding that "eculizumab" referred to and refers to a genus of antibodies, including one with the hybrid IgG2/IgG4 isotype of the challenged claims. Accordingly, in view of the record before us, we conclude that "eculizumab" referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs.

Upon considering the facts here in view of Petitioner's reliance on *Crish*, 393 F.3d 1253, and Patent Owner's reliance on *Endo Pharms.*, 894 F.3d 1374, we find the latter case analogous here. In *Crish*, the Federal Circuit found that a claim to the nucleotide sequence of the hINV gene promoter region was inherently disclosed by prior art that "specifically identified [the promoter region] by size and location" because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Crish*, 393 F.3d at 1257–59. Here, however, Hillmen does not "specifically identify" an eculizumab antibody containing the hybrid IgG2/IgG4 sequence of SEQ ID NO: 2, as required by claim 1.

Endo Pharms. compels a different result under the facts here. In *Endo Pharms*., the issue was again inherency (in the context of obviousness) where prior art scientific articles described clinical trials for a testosterone undecanoate composition, but did not disclose its specific, and later claimed, formulation including a particular mixture of castor oil and benzyl benzoate. *Endo Pharms*., 894 F.3d at 1278. It was later confirmed that the

composition of the clinical trials described in the prior art articles did, indeed, have the claimed mixture of castor oil and benzyl benzoate. *Id.* The Federal Circuit held that because it was not demonstrated that a skilled artisan could extrapolate the vehicle formulation (a mixture of castor oil and benzyl benzoate) used in the prior art articles based on reported pharmacokinetic performance data, such performance could not have only been attributed to the claimed formulation and the generic disclosure of the pharmaceutical formulation in the prior art did not inherently disclose the claimed formulation. *Id.* at 1281–83. Furthermore, *Endo Pharms.* distinguished *Crish* because it was about the inherent properties of a known prior art product rather than a product that was named but not known or determinable based on the prior art disclosure of its performance characteristics. *Id.* at 1383.

In Ground 1, the prior art reference, Hillmen, discloses a clinical trial of "eculizumab" but does not otherwise identify the structure of the antibody tested, other than by referencing Thomas. Ex. 1004, 552, 553 (citing Ex. 1023). Thomas discloses a version of eculizumab different from that claimed (an IgG4 isotype rather than a hybrid IgG2/IgG4 antibody). Even accepting that a skilled artisan would have known of a hybrid IgG2/IgG4 antibody, as claimed (*see, e.g.*, Ex. 1002 ¶ 13), Hillmen's mere reference to "eculizumab" would have at least invoked a molecule having the IgG4 isotype taught in Thomas. Thus, Hillmen's disclosure of "eculizumab" would not have necessarily led the skilled artisan to the claimed antibody with "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Moreover, none of the references teaching or suggesting

an IgG2/IgG4 isotype (e.g., Bowdish, Evans, Tacken, Mueller, or Mueller II) is cited in Hillmen. *See id.* at 559. We disagree with Petitioner's position that such references' teaching would have somehow overridden Hillmen's direct invocation of Thomas's disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure.[18] Accordingly, under *Endo Pharms.*, as discussed above, there is no inherent anticipation of claim 1 over Hillmen.

To summarize, as we presently understand the art as of the filing date of the '504 patent, one of ordinary skill understood that eculizumab encompassed molecules by both IgG4 isotypes and IgG2/IgG4 hybrid structures, whereas a plain reading of Hillmen suggests that it specifies the former. Accordingly, one of ordinary skill in the art would not have necessarily understood Hillmen to disclose a version of eculizumab having the IgG2/IgG4 heavy chain constant region of SEQ ID No. 2. For the above reasons, Petitioner has not demonstrated a reasonable likelihood that claim 1, the sole independent claim of the '504 patent, is unpatentable under Ground 1.

E. Obviousness in view of Hillmen, Bell, and Wang (Grounds 2 and 3)

In Grounds 2 and 3, Petitioner challenges claims 4 and 5 as obvious in view of Hillmen and Bell, and claim 6 further in view of Wang. Pet. 37–45.

[18] We need not address here Patent Owner's non-trivial argument that Petitioner "has improperly attempted to shoehorn" the obviousness arguments of Grounds 4–7 into its anticipation contentions. Prelim. Resp. 47.

Patent Owner opposes. Prelim. Resp. 52–55. Pertinent to each of Grounds 2–7, we address Patent Owner's secondary considerations evidence in section II(H), below.

For Grounds 2 and 3, Petitioner states: "Bell disclosed a Phase 2 Pilot Study involving 11 PNH patients treated with eculizumab over a period of 12 weeks—identical to that disclosed in Hillmen. . . . Given the substantial overlap, a POSA would have had ample reason to combine Hillmen and Bell, with a reasonable expectation of success at achieving the claimed subject matter." Pet. 37–38 (citations omitted). Responding to these contentions, Patent Owner notes that, "Grounds 2 and 3 rely upon Hillmen as the sole prior art allegedly disclosing the claimed element of an antibody comprising 'a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' . . . . [but] Hillmen did not disclose the claimed antibody sequence either expressly or inherently." Prelim. Resp. 52–53. Patent Owner's point is well taken.

As discussed in Section II(D)(2), above, Petitioner has not established that Hillmen inherently discloses the IgG2/IgG4 heavy chain constant region of SEQ ID NO: 2, and the Petition sets forth no additional argument on that subject in support of Grounds 2 and 3. Petitioner also does not argue, nor do we discern, where the required sequence is taught in Bell or Wang. Accordingly, Petitioner has not demonstrated a reasonable likelihood that claims 4–6 are unpatentable over the combinations of Hillmen, Bell, and Wang set forth in Grounds 2 and 3.

F. Obviousness in view of Bell, Bowdish, Evans, and Wang (Grounds 4 and 5)

Petitioner challenges claims 1–5 and 7–10 as obvious in view of Bell, Bowdish, and Evans (Ground 4), and claim 6 further in view of Wang (Ground 5). Pet. 45–60. Patent Owner opposes. Prelim. Resp. 56–61; *see also id*. at 55. For the purpose of institution, we focus on claim 1.

1. The Parties' Contentions

With respect to Ground 4, Petitioner contends that Bell taught all limitations of claim 1 but for eculizumab's amino acid sequence. Pet. 45–47. Petitioner points, for example, to Bell's disclosure that preferred treatments for PNH included "'an *anti-C5 antibody* selected from the group consisting of *h5G1.1-mAb (eculizumab)* . . .' suitable for treating PNH, and also that the antibody 'h5G1.1-mAb' was 'undergoing clinical trials under the tradename *eculizumab*.'" *Id.* at 46 (citing Ex. 1005 ¶¶ 12, 52). Petitioner then argues that one of ordinary skill in the art would have looked to Bowdish and Evans to obtain the amino acid sequence of eculizumab. *See* Pet. 47–54.

Petitioner contends that the skilled artisan would have looked to Bowdish for the light and most of the heavy chain sequence of eculizumab in light of Bowdish's use of an "anti-C5 antibody as the starter 'scaffold' antibody sequence for creating a recombinant TPO-mimetic" antibody. Pet. 47; Ex. 1002 ¶¶ 130–135. According to Petitioner, Bowdish disclosed "the full antibody amino acid sequence for such a 5G1.1 antibody [i.e., an anti-C5 antibody] except for the heavy chain CDR3 (HCDR3) sequence, which Bowdish replaced with the TPO-mimetic peptide sequence,

LPIEGPTLRQWLAARAPV." *Id.* (citing Ex. 1006 ¶¶ 191–193, Figs. 13A (SEQ ID NO: 67; "5G1.1 – TPO Heavy Chain (Bold Denotes TPO mimetic) Amino acid sequence"), 13B (SEQ ID NO: 69; "5G1.1 Light Chain Amino Acid Sequence"). In particular, Petitioner argues:

> A POSA . . . would have understood that the only portion of the "scaffold" 5G1.1 antibody sequence not expressly disclosed in Bowdish is the HCDR3 sequence because Bowdish taught that "[t]he TPO mimetic peptide graft in Fab clone X4b has been *transplanted into the heavy chain CDR3* of another antibody framework, *5G1.1* . . . The sequence was *cloned into 5G1.1* in such a fashion as to *replace the native CDR3*."

Pet. 50 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶ 137 (emphasis Petitioner's)).

Petitioner further argues that to obtain the CDR3 sequence missing from Bowdish, one of ordinary skill in the art would have looked to Evans "because both Bell and Bowdish explicitly direct the artisan there for information on how the h5G1.1 antibody was originally created." *Id.* at 53 (citing Ex. 1002 ¶ 142; Ex. 1006 ¶ 191). Alternatively, Petitioner argues, one of ordinary skill in the art would have readily identified the entire IgG2/IgG4 heavy chain sequence from Bowdish alone, because Bowdish incorporates Evans by reference. *Id.* at 5, 18 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 54–55).

According to Petitioner, "a POSA would have understood that *each* of the 5G1.1 antibody heavy chain variable regions in Evans contain *the same CDR3 sequence*: YFFGSSPNWYFDV. Thus, regardless of which 'version' of Evans' humanized 5G1.1 the POSA selected to combine with Bowdish, that heavy chain would contain the YFFGSSPNWYFDV CDR3 sequence." *Id.* at 51 (internal citations omitted) (*citing e.g.*, Ex. 1002 ¶ 136). In sum,

the "prior art would have led a POSA to make a simple substitution of one known element for another—i.e., replace the TPO-mimetic peptide sequence in Bowdish's antibody with the HCDR3 sequence from Evans—to yield predictable results: a humanized anti-C5 antibody." Pet. 53–54.

Petitioner relies on the Balthasar Declaration as support and further explanation as to how one of ordinary skill in the art would derive the claimed antibody based on the asserted art. *See* Pet. 47–51. Dr. Balthasar provides a number of illustrations useful to understanding Petitioner's argument.

Figure 4 from Dr. Balthasar's report, relating to the eculizumab light chain sequence, is reproduced below.

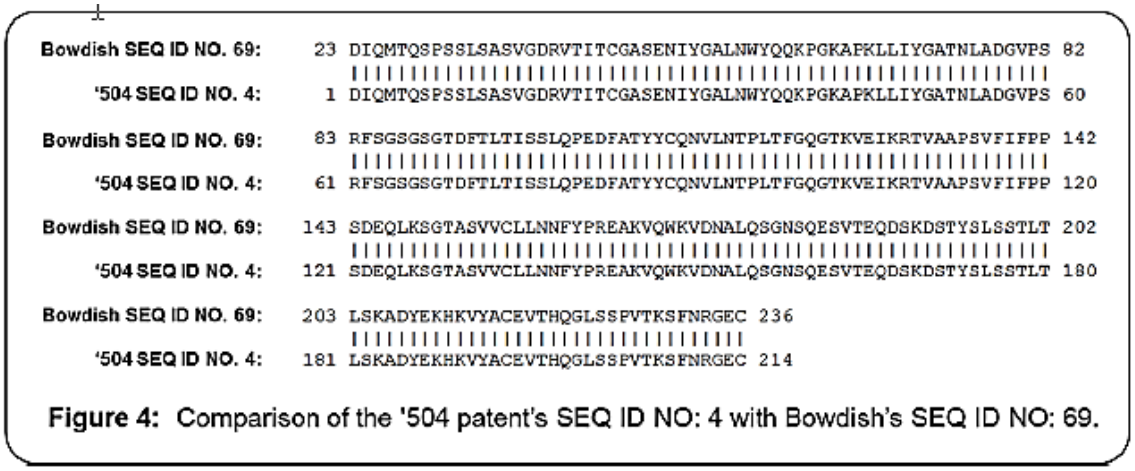

Figure 4: Comparison of the '504 patent's SEQ ID NO: 4 with Bowdish's SEQ ID NO: 69.

Ex. 1002 ¶ 52. Figure 4 purports to show identity between the mature peptide sequence[19] of the eculizumab light chain disclosed in Bowdish and

[19] Dr. Balthasar notes that Bowdish's Figures 13A and 13B identify leader sequences, not included in the comparisons of Figures 4 and 5 because one of ordinary skill in the art "would have understood that leader sequences are cleaved off as a standard part of the maturation of an antibody." *Id.*

SEQ ID NO. 4 of the ’504 patent. *Id.*

Figure 5 from Dr. Balthasar’s report, relating to the heavy chain sequence of eculizumab, is reproduced below.

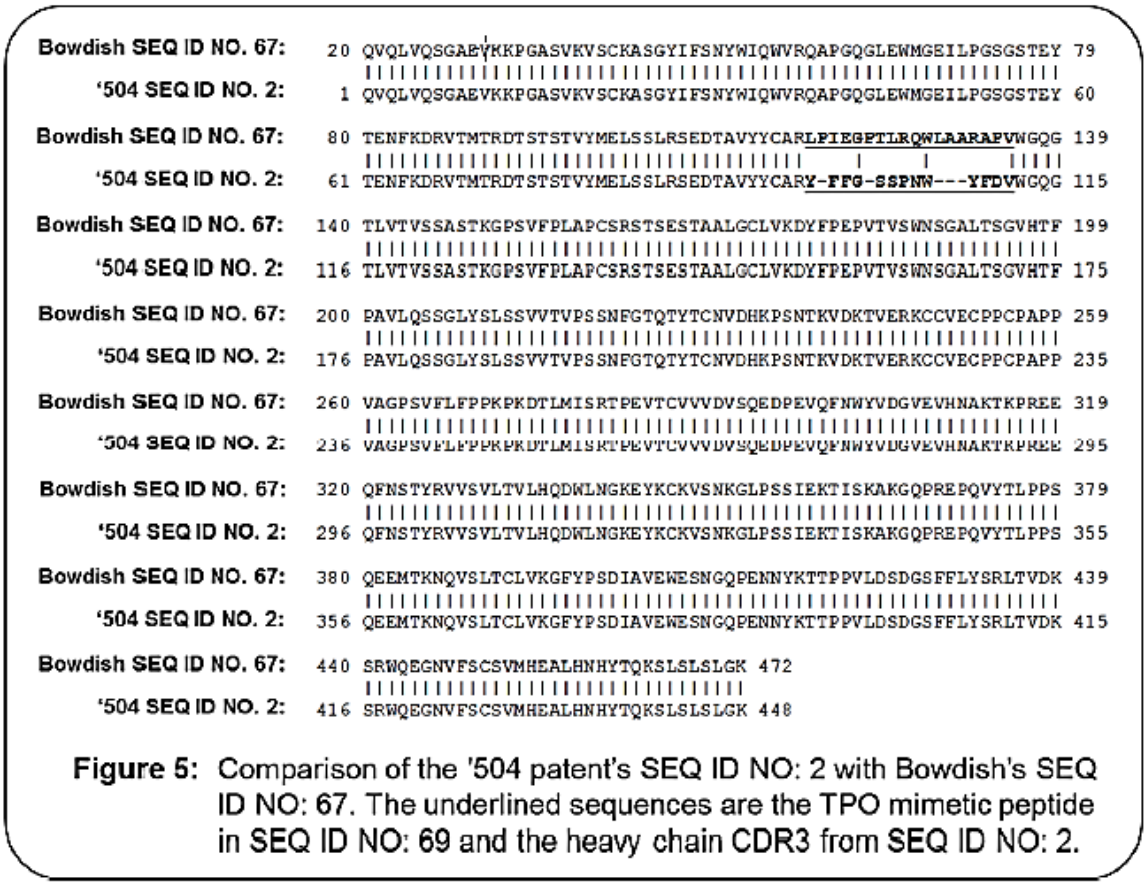

Figure 5: Comparison of the '504 patent's SEQ ID NO: 2 with Bowdish's SEQ ID NO: 67. The underlined sequences are the TPO mimetic peptide in SEQ ID NO: 69 and the heavy chain CDR3 from SEQ ID NO: 2.

Id. ¶ 55. According to Dr. Balthasar, “Figure 5 shows that the mature portion of SEQ ID NO: 67 from Bowdish (*i.e.*, amino acids 20 to 472) aligns perfectly with SEQ ID NO: 2 from the ‘504 patent outside of the heavy chain CDR3 region.” *Id.*

Figure 6 of Dr. Balthasar's declaration, relating to the heavy chain CDRs of eculizumab, is reproduced below.

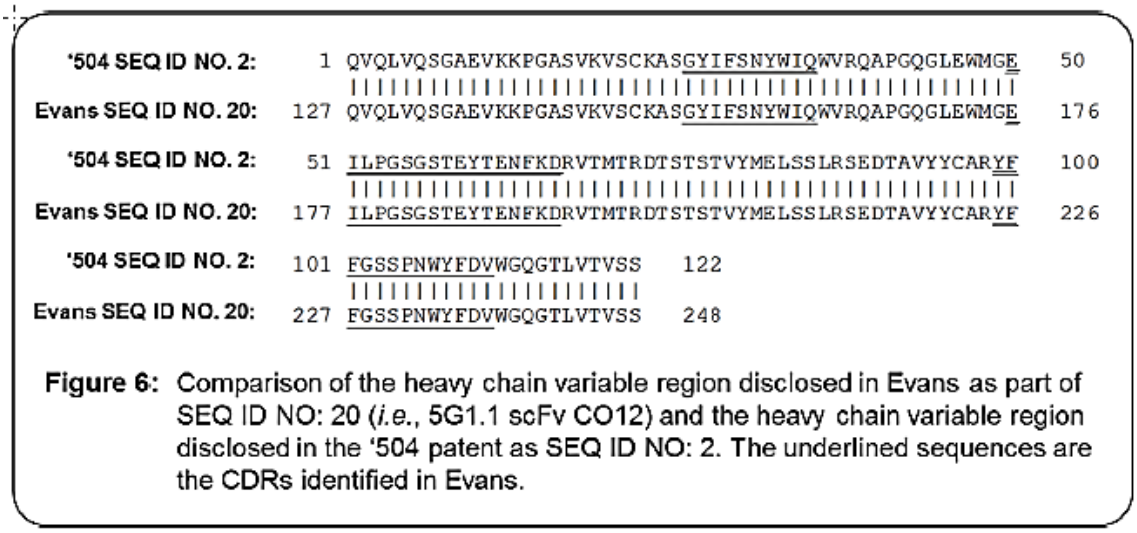

Figure 6: Comparison of the heavy chain variable region disclosed in Evans as part of SEQ ID NO: 20 (*i.e.*, 5G1.1 scFv CO12) and the heavy chain variable region disclosed in the '504 patent as SEQ ID NO: 2. The underlined sequences are the CDRs identified in Evans.

Ex. 1002 ¶ 53. According to Dr. Balthasar, Figure 6 shows an alignment of SEQ ID NO: 2 of the '504 patent with the heavy chain CDRs identified in Evans underlined, including the YFFGSSPNWYFDV sequence of CDR3. *Id.* ¶¶ 55, 136.

Figure 11 of Dr. Balthasar's declaration, relating to the relationship between the heavy chain CDR3 and Bowdish's TPO peptide, is reproduced below.

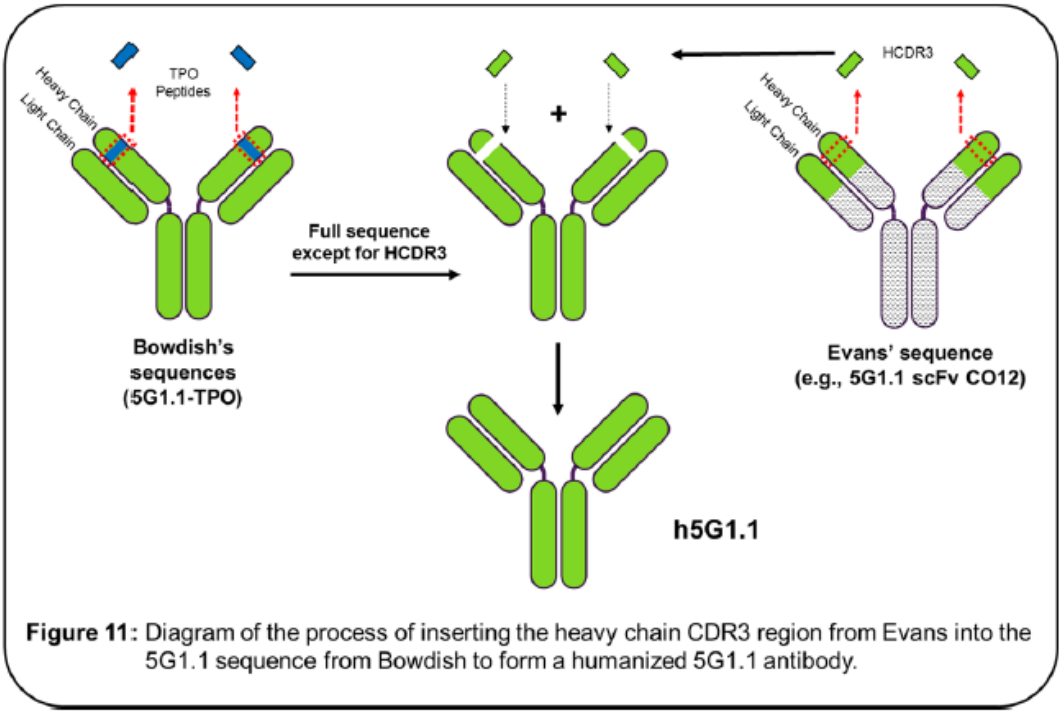

Figure 11: Diagram of the process of inserting the heavy chain CDR3 region from Evans into the 5G1.1 sequence from Bowdish to form a humanized 5G1.1 antibody.

Ex. 1002 ¶ 120. Figure 11 shows the original Bowdish scaffold antibody, including the location of eculizumab heavy chain CDR3; the use of Evans as a source of the HCDR3; and the replacement of Bowdish's TPO peptide with Evan's HCDR3. *Id.* According to Dr. Balthazar, Figure 11 "illustrate[s] how a POSA would have arrived at the claimed sequence (*i.e.*, eculizumab) by placing the heavy chain CDR3 disclosed in Evans into the 5G1.1 antibody sequence disclosed in Bowdish." *Id.*

With respect to reason to combine, Petitioner appears to argue that, because the combination of Bowdish and Bell taught the use of eculizumab for the treatment of PNH, the skilled artisan would have looked to Evans to recreate the molecule used in those successful studies. *See* Pet. 53; Ex. 1002 ¶¶ 122, 139–142. Moreover, with respect to the specific sequence of SEQ ID NO: 2, Petitioner asserts that, as of the filing date of the '504 patent, it

was well known "that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system." Pet. 17 (citing Ex. 1032, 11, 19, 28; Ex. 1031, 451; Ex. 1002 ¶¶ 47, 57). As noted by Dr. Balthasar, for example:

> A POSA would have been aware that "the HuG2/G4 antibody design should prove useful in humanization of other antibodies intended for human use where elimination of FcR binding and C [*i.e.*, complement] activation may be desirable." AMG1031, 451; *see also*, AMG1034, 1280. Because the goal of using eculizumab in treating PNH is to reduce the level of complement activation, using a heavy chain constant region that avoids a counter-productive activation of complement by the therapeutic antibody aligns well with the desired outcome. AMG1005, ¶¶[0003], [0012].

Ex. 1002 ¶ 47.

Patent Owner argues that, absent impermissible hindsight, the skilled artisan would not have combined, or reasonably expected success in combining the asserted references. Prelim. Resp. 4–5, 56–61. Patent Owner argues that Bell, like Hillmen, taught eculizumab was the antibody of Thomas and nothing in the other references would point the skilled artisan toward a different antibody, e.g., the IgG2/IgG4 hybrid covered by the claim. *Id.* Patent Owner also argues Thomas taught away from the claimed invention because Thomas described an "eculizumab" with an IgG4 constant region. *Id.* at 57.

Patent Owner argues that even assuming one of ordinary skill did combine Bowdish and Evans to obtain eculizumab having the claimed sequence, "a POSA would not have reasonably expected the resulting

compound to work in a pharmaceutical composition for preventing C5 cleavage and safely and effectively treating PNH . . . . [because] even small changes to the amino acid sequence could have a substantial impact on the binding properties and the safety and efficacy of an antibody intended for human administration." *Id.* at 60 (citing *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019). Patent Owner thus contends that, in view of this complexity and unpredictability, the skilled artisan would not have ventured away from Thomas's known antibody; i.e., would not have looked to Bowdish and Evans for an isotype variant of that antibody. *Id.* at 41.

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood that claims 1 and 6 of the '504 patent would have been obvious under Grounds 4 and 5, respectively.

Regarding Patent Owner's argument that the combination of Bell, Bowdish, and Evans involves improper hindsight and that the combination fails to render the challenged claims obvious because Bell's disclosed antibody would necessarily be that of Thomas's disclosure, we are not convinced. As summarized in Section I(F)(2), above, Bell extols the virtues of eculizumab for the treatment of PNH, but does not identify the antibody's amino acid sequence. Bell does cite to and incorporates by reference both Evans and Thomas. *See* Ex. 1005 ¶ 52. Accordingly, Thomas's IgG4 isotype antibody would be one type of eculizumab contemplated by Bell. But, as discussed in section II(D)(2), one of ordinary skill in the art would

have understood that "eculizumab" encompassed multiple isotypes, including one having the hybrid IgG2/IgG4 isotype noted in Tacken and Bowdish. Here, Bowdish discloses a substantial portion of the anti-C5 antibody 5G1.1 and points to Evans as evidencing the remaining amino acid sequence. And with respect to Patent Owner's argument that neither Bowdish nor Evans uses the term "eculizumab" (Prelim. Resp. 58–59), on the present record, we accept from Dr. Balthasar's Declaration that one of ordinary skill in the art would have looked to those references for the structure of eculizumab, particularly given that Bowdish incorporates Evans by reference for the construction of 5G1.1. *See*, *e.g.*, Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 43–46, 51, 54, 56, 122; *see also* Ex. 1001, 39:1–32 (the '504 patent's claims also do not use the term "eculizumab"). Accordingly, Petitioner's arguments rely on the disclosures of the prior art and no improper hindsight is necessarily invoked under Petitioner's rationale.

As for Patent Owner's contention that Thomas taught away from the claimed invention (or, somehow taught away from the prior art combination), we disagree. A "teaching away" requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* at 1200 (citation and emphasis omitted). "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . .

alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *Id.* at 1201. Thomas does not criticize, discredit, or discourage the claimed invention or the prior art combination. Thomas, at most, teaches the original eculizumab construction, an alternative to the version as taught by Bowdish and Evans.

On the present record, we are not persuaded by Patent Owner's argument that "[e]ven if Bowdish and Evans were combined . . . , a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating PNH" because even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration, we disagree. *See* Prelim. Resp. 60.

As an initial matter, it is not clear whether claim 1 requires any showing of safety and efficacy as these are standards for FDA approval of new drugs rather than of patent law. *Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1372–73 (Fed. Cir. 2017), *cert. granted*, 138 S. Ct. 2678 (2018), and *aff'd*, 139 S. Ct. 628 (2019) ("Approval of a new drug by FDA, however, is a more demanding standard than that involved in the patents-in-suit. The patents here make no reference to FDA standards and broadly claim a palonosetron formulation for reducing the likelihood of emesis and CINV.").

Further, Bell teaches that a variety of compounds containing the variable regions of a humanized 5G1.1 are useful to the treatment of PNH, stating: "In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional fragments of h5Gl.l."

Ex. 1005 ¶ 12. Moreover, Bell touts the benefits of "eculizumab" in a long-term clinical trial, indicating that the treatment is suitable for treatment of patients suffering from PNH, as set forth in claim 1. As noted above, one of ordinary skill in the art understood eculizumab to encompass a humanized 5G1.1 antibody having the IgG2/IgG4 isotype indicated in SEQ ID NO: 2.

Although we recognize Patent Owner's argument that "sequence changes outside of the antigen-binding site, *e.g.*, in the heavy chain constant region" may influence antibody affinity, specificity, and immunogenicity, this is counterbalanced by Petitioner's citation to eculizumab of the IgG2/IgG4 isotype and its reasoned argument that the skilled artisan would look to the hybrid sequence because it was known "that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system." *See* Prelim. Resp. 11; Pet. 17 (citing Ex. 1032, 11, 19, 28; Ex. 1031, 451; Ex. 1002 ¶¶ 47, 57).

On balance, the present record suggests that a person of ordinary skill in the art would have reasonably expected a version of eculizumab having a heavy chain consisting of SEQ ID NO: 2 to work for the purpose set forth in claim 1 ("treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH)"). The parties are invited to further address this issue during trial.

We take note of Patent Owner's arguments relating to and evidence of objective indicia of non-obviousness, discussed above at Section II(E). Although we noted that there was some evidence to support Petitioner's contentions of commercial success, long-felt but unmet need, and industry

praise, we also noted some potential shortcomings in Patent Owner's presentation, including the rebutability of the presumption of a nexus between their evidence and the claimed and novel subject matter. We expect this issue will be further developed at trial.[20]

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is a reasonable likelihood that claim 1 of the '504 patent would have been obvious over Bell, Bowdish, and Evans under Ground 4. With respect to Ground 5, which challenges only dependent claim 6, we await further development of the parties' positions in the Patent Owner Response and Petitioner's Reply.

G. Obviousness in view of Bell, Evans, Mueller, and Wang (Grounds 6 and 7)

Petitioner challenges claims 1–5 and 7–10 as obvious in view of Bell, Evans, and Mueller (Ground 6), and claim 6 further in view of Wang (Ground 7). Pet. 61–73. Patent Owner opposes. Prelim. Resp. 61–63; *see also id.* at 55. For the purpose of institution, we focus on claim 1.

1. The Parties' Contentions

In sum, Petitioner asserts, "the only element of claim 1 not expressly taught in Bell is that its humanized anti-C5 antibody 'comprises a heavy

[20] In addition to challenging Petitioner's positions with respect to claim 1, Patent Owner also raises non-trivial arguments in response to Petitioner's contentions specific to dependent claims 5 and 6, which we need not address at this stage of the proceeding. *See* Pet. 39–45 (citing e.g., Ex. 1005 ¶ 58, 89–96; Ex. 1002 ¶¶ 104–109), 60–61 (citing Ex. 1027, 1638 (¶ 3.5), Ex. 1004 (¶ 5.3.9); Ex. 1028, Fig. 10, ¶ 67; Ex. 1029, Table 1; Ex. 1030, Table 1; Ex. 1002 ¶¶ 168; Prelim. Resp. 55, 60–61.

chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" Pet. 62. According to Petitioner, "Evans disclosed the complete amino acid sequences of the heavy and light chain variable domains of a humanized anti-C5 antibody," whereas "Mueller disclosed the amino acid sequence of a light chain constant region and the hybrid IgG2/IgG4 heavy chain constant region." *Id.* at 62–63 (citing Ex. 1007, 44:4–13, SEQ ID NO: 20; Ex. 1002, ¶¶172–173, 183–185; Ex. 1008, 58–61). Petitioner further argues:

> Knowing that chimeric IgG2/IgG4 constant regions that were known not to activate the complement system (AMG1008, 7:28-31, 8:23-26, 12:27-32), a POSA reading Bell and Evans also would have looked to Mueller for "h5G1.1" sequence information. Mueller taught methods for making "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 . . . (HuG2/G4 mAb)." AMG1008, 12:27-30; *see also, id.*, 8:23-26. In particular, Mueller described a control antibody "h5G1.1 CO12 HuG2/G4 mAb," which a POSA would have readily identified as a humanized anti-C5 antibody because of the "h5G1.1" nomenclature coupled with the hybrid IgG2/IgG4 constant region ("HuG2/G4"). AMG1008, 12:37, FIG. 15; AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶190.

Id. at 64.

Figure 14 from the Balthasar Declaration is reproduced below.

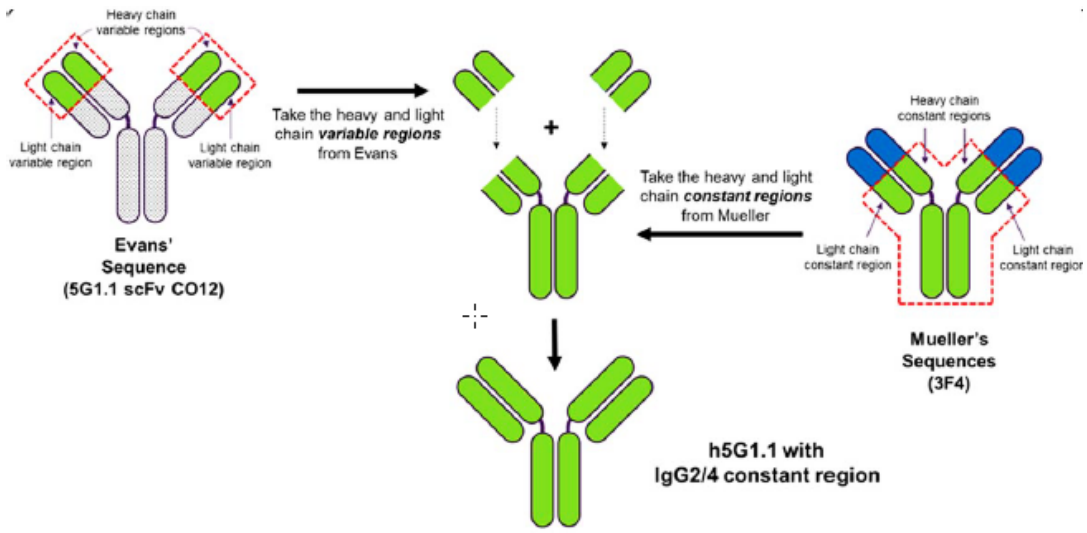

Figure 14.

Ex. 1002 ¶ 173. According to Petitioner, the above figure presents an overview of how one of ordinary skill in the art would have combined the teachings of Evans and Mueller to arrive at the eculizumab antibody described in claim 1. *Id.*

Relying on Dr. Balthasar's testimony, Petitioner argues that "Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant domain when Mueller disclosed the sequence of the chimeric anti-VCAM '3F4' antibody." Pet. 64 (citing Ex. 1002 ¶ 186; Ex. 1008, 58–61). According to Petitioner, one of ordinary skill in the art would have aligned Mueller's chimeric 3F4 HuG2/G4 heavy chain and mature 3F4 heavy and light chain variable regions such that a skilled artisan aligning the two would identify the 3F4 variable regions (at Figure 9) as amino acids 20–137 of the 3F4 HuG2/G4 heavy chain and amino acids 20–131 of the 3F4 light chain. *Id.* at 65 (citing Ex. 1008, 51–53, 58–61, Figure 9; Ex. 1002 ¶ 186).

Petitioner contends that the skilled artisan "would have immediately known that the remainder of the 3F4 HuG2/G4 heavy chain (amino acids 138-463 is the hybrid IgG2/IgG4 constant region of that antibody, and that the remainder of the 3F4 chain (amino acids 132–238) is the light chain constant region of that antibody." *Id.* at 65–66 (citing Ex. 1002 ¶¶ 179, 186, Figure 15; Ex. 1008, 52–53, 56–57). With this understanding of the heavy and light chain constant domain sequences in mind, Petitioner contends the skilled artisan would have looked to Evans to complete the whole antibody using Evans's variable regions identified from its SEQ ID NO: 20, particularly because Evans uses the same "CO12" nomenclature to refer to its 5G1.1 scFv as Mueller does in referring to h5G1.1. *Id.* at 66–67 (citing Ex. 1002 ¶¶ 173, 180–182).

Petitioner's argued rationale for combining Mueller and Evans is that Mueller taught antibodies with lower immune response and identified an antibody as h5G1.1 CO12 HuG2/G4 mAb, which the skilled artisan would have known is eculizumab. Further, Petitioner argued, Evans taught the complementary parts of this anti-C5 antibody, so, by combining the elements of the two references, a complete antibody would have been created having the SEQ ID NO: 2 and SEQ ID NO: 4 of the claim. *Id.* at 64; *see also id.* at 69–70 (further discussing why one of ordinary skill in the art would have combined the cited references with a reasonable expectation of success).

Patent Owner argues "[a] POSA would have understood that Mueller could have used ***any*** antibody with an IgG4 or IgG2/G4 isotype as a 'negative control' for its *in vitro* experiments, as long as it did not bind to

VCAM," meaning, there would be no reason to incorporate the variable regions taught by Evans. *Id.* at 62–63. And, without improper hindsight, Mueller and Evans would not have been combined by the skilled artisan. Prelim. Resp. 61. Patent Owner argues "[a] POSA as of March 15, 2007 considering the problem addressed by the '504 patent – developing an antibody that prevents cleavage of C5 and can safely and effectively treat patients suffering from PNH– would have had no reason to look at Mueller, which had nothing to do with that problem." *Id.* (citing *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013) ("While a prior art reference may support any finding apparent to a person of ordinary skill in the art, prior art references that address different problems may not, depending on the art and circumstances, support an inference that the skilled artisan would consult both of them simultaneously.").

2. Analysis

In contrast to Grounds 4 and 5, where Bowdish expressly incorporated Evans by reference, thereby rendering the combination unquestionable, in Grounds 6 and 7 we find no express link between the teachings of Mueller and Evans. Although such a combination is possible, the mere fact that prior art can be combined does not establish that one of ordinary skill would have done so. *See, e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (The "mere fact that the prior art may be modified in the manner suggested . . . does not make the modification obvious unless the prior art suggested the desirability of the modification.").

Grounds 6 and 7 present a close question on whether there would have been motivation to combine Mueller and Evans in the manner argued by Petitioner. Upon review of the Balthasar Declaration, it is apparent that Mueller's 3F4 heavy chain provides a match for part of the claimed SEQ ID NO: 2. *See* Ex. 1002 ¶ 58, Figure 8. Further, Mueller's 3F4 light chain provides a match for part of the claims SEQ ID NO: 4. *Id.* ¶ 59, Figure 9. The Balthasar Declaration provides an illustration as its Figure 10, reproduced below, showing the extent that each of Evans and Mueller (and Bowdish, per Grounds 4 and 5) discloses the claimed SEQ ID NOs: 2 and 4.

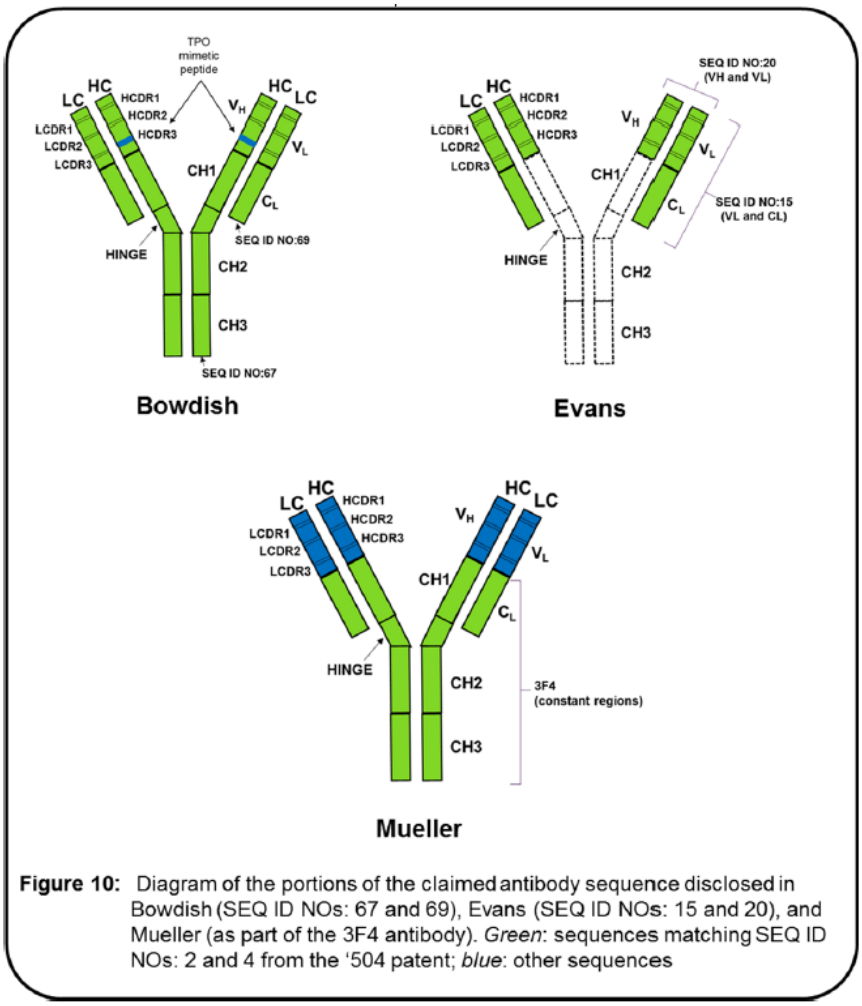

Figure 10: Diagram of the portions of the claimed antibody sequence disclosed in Bowdish (SEQ ID NOs: 67 and 69), Evans (SEQ ID NOs: 15 and 20), and Mueller (as part of the 3F4 antibody). *Green*: sequences matching SEQ ID NOs: 2 and 4 from the '504 patent; *blue*: other sequences

Ex. 1002 ¶ 60. Dr. Balthasar's Figure 10 shows three antibody structures: Bowdish top-left, Evans top-right, and Mueller bottom center. The Figure shows identity with SEQ ID NOs: 2 and 4 of the '504 patent in green and differences in blue.

Based on the above figure, Petitioner's rationale for combining the teachings of Mueller and Evans is somewhat tenuous. In particular, we are concerned with the proposed reasons one of ordinary skill in the art would have paired Evans with Mueller, choosing precisely those portions of Evans's and Mueller's constructs to create an antibody having exactly the sequences set forth SEQ ID NOs: 2 and 4. At this stage in the proceedings, based on the evidence before us, the answer is not entirely clear and Patent Owner's argument regarding improper hindsight makes some sense. True, Mueller discloses "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)," but little else regarding its structure. *See* Ex. 1008, 12. It is not apparent that the skilled artisan, knowing of Evans, would have looked to Mueller, or vice versa.

Based on our understanding of the evidence presented at this stage in the proceedings, Petitioner has not sufficiently demonstrated a reasonable likelihood that claim 1 of the '504 patent would have been obvious over the combinations set forth in Grounds 6 and 7.

H. Objective Evidence of Non-Obviousness

Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any

relevant secondary considerations. *See Graham*, 383 U.S. at 17–18. Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406, (2007). Although evidence pertaining to secondary considerations must be taken into account whenever present, it does not necessarily control the obviousness conclusion. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Petitioner contends no objective indicia of nonobviousness support patentability of the challenged claims. Pet. 37, 38, 45, 60–62, 71–73. In particular, Petitioner notes that during the prosecution of the '504 patent, Alexion argued that the claimed heavy chain of eculizumab, i.e., the hybrid IgG2/IgG4 constant domain, provided surprising and unpredictable results, such as decreased effector function, reduced immunogenicity, and increased half-life. Pet. 72 (citing Ex. 1014, 588, 593 (¶ 8)). However, Petitioner contends, because eculizumab's hybrid IgG2/IgG4 constant region was well known in the art (as evidenced by Tacken), the allegedly surprising and unpredictable features of the antibody have no nexus to the challenged claims. *Id.* (citing Ex. 1034, 1279).

Petitioner further contends that one of ordinary skill in the art would not have found surprising the alleged beneficial results of using the hybrid constant region because, in view of Mueller II, antibodies with the claimed hybrid IgG2/IgG4 heavy chain were known not to bind FcR and to be less immunogenic, whereas it was well known that antibodies with this claimed hybrid heavy chain would have an increased half-life. *Id.* (citing Ex. 1031,

488, 451; Ex. 1032 ("Rother"), 5, 19[21]; Ex. 1002 ¶ 210–212); *see*, *e.g.*, Ex. 1032, 5–6 (disclosing that antibodies having "an engineered constant region that includes an IgG2-derived portion and an IgG4-derived portion . . . maintain the function of the non-Fc component and/or have increased half-life compared to the non-Fc component alone and/or lack unwanted antibody Fc-mediated cell activating and inflammatory properties including events resulting from Fc-receptor antibody engagement and complement activation").

Patent Owner contends that evidence of commercial success, long-felt, but unmet need, and industry praise support the non-obviousness of the challenged claim. Prelim. Resp. 63. Patent Owner argues that SOLIRIS, the product embodying the claimed antibody, is a commercial success, having annual net product sales in excess of $1 billion in 2018. *Id.* at 64. (citing Ex. 2018, 70). Patent Owner further contends that this commercial success "has a direct nexus to the patented features of the '504 patent, which claims the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH, as well as complement-mediated hemolytic condition aHUS." *Id.*

At this stage in the proceedings, based on the evidence presented by Patent Owner, it is apparent that SOLIRIS is a successful product. "[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product "is the invention disclosed and claimed in the patent." *WBIP*,

[21] Rother et al., WO 2005/007809 A2, published Jan. 27, 2005 (Ex. 1032).

LLC v. Kohler Co., 829 F.3d 1317, 1329 (Fed. Cir. 2016). This "presumption of nexus is rebuttable: a patent challenger may respond by presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *Id.* Here, the parties appear to agree that the claim of the '149 patent is directed to the commercial product SOLIRIS. However, commercial success "is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention – as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

Patent Owner argues that because SOLIRIS is "the first FDA-approved treatment to reduce hemolysis in patents with PNH," there is evidence that the claimed antibody fulfilled a long-felt, unmet need in the market. Prelim. Resp. 64 (citing Ex. 2019, 1270).

At this stage in the proceeding, the available evidence supports that anti-C5 antibodies were considered potential therapeutic options for "many years" before 2007, and that Alexion's eculizumab product "is currently the only complement-specific antibody on the market" and is the "first and only approved therapy for PNH." Ex. 2019, 1270. Again, it may be presumed that there is a nexus between the claimed and novel elements of the SOLIRIS product and the meeting of the long-felt need. However, "[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner also contends "SOLIRIS® also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade . . . ." Prelim. Resp. 64--65 (citing Ex. 2020; Ex. 2021).

As with the other two contended bases for indicia of non-obviousness, while it is apparent there was high praise for the SOLIRIS product from the relevant industry, there is a rebuttable presumption that this praise has a nexus with the claimed subject matter. *Cf. In re Kao*, 639 F.3d at 1068.

Given the early stage of these proceedings, we decline to accord much weight to Patent Owner's substantially untested evidence of objective indicia of nonobviousness. The parties will have the opportunity to further develop these facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

I. The Board's Discretion to Deny Institution under 35 U.S.C. §§ 325(d) and 314(a)

1. The Parties' Positions

Patent Owner argues the "Petition should also be denied institution under 35 U.S.C. §§ 325(d) and 314(a), because Amgen's Grounds rely on the 'same or substantially the same prior art or arguments' previously presented to the PTO" "[i]n the course of patent prosecution leading to issuance of the '504 patent, as well as prosecution of related U.S. Patent Nos. 9,719,880 ('the '880 patent') and 9,732,149 ('the '149 patent'). Prelim. Resp. 17, 65–66; *see id.* at 65–66 (asserting that the Examiner considered Hillmen, Evans, and Wang; and further reviewed Bell ("cumulative of Bowdish"), and Mueller II ("cumulative of Mueller").

Patent Owner argues that in the course of prosecution leading to the issuance of the '504 patent, the Examiner:

> • Expressly discussed Amgen's asserted references Hillmen 2004 (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection, before ultimately finding the claims to be allowable over the art (*see, e.g.*, AMG1014 at 557-561, 623-628, 738-743);
>
> • Considered Amgen's asserted reference Bell (AMG1005), which Alexion submitted to the PTO (*see, e.g.*, AMG1014 at 566);
>
> • Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here (*see, e.g.*, AMG1014 at 565); and
>
> • Considered the "Mueller II" article (AMG1031), which is cumulative of Amgen's asserted "Mueller" reference (AMG1008) because, as Amgen's declarant recognized, it "discloses the same antibodies" as Mueller. (*See, e.g.*, AMG1014 at 499; AMG1002 ¶ 182 & n.14.)

Prelim. Resp. 18.

Petitioner's position on this issue is that "[t]he arguments and evidence presented herein were not before the examiner during prosecution and, therefore, do not constitute 'the same or substantially the same prior art or arguments' under 35 U.S.C. §325(d).'" Pet. 24. In particular, Petitioner argues that

> the examiner rejected Alexion's claims as (i) anticipated by Hillmen in view of Thomas; (ii) obvious over Hillmen, Thomas and Evans; and (iii) obvious over Hillmen, Thomas, Evans, and Wang. AMG1014, 557-561. Those rejections rested solely on disclosures in Thomas and Evans for eculizumab sequence information. *Id.* The examiner later allowed the '504 patent

> claims mistakenly believing—because of Alexion's mischaracterization of the art—that the sequence and structure of eculizumab were not already known.
>
> Though Hillmen, Evans, and Wang were referenced by the examiner during prosecution, this Petition presents them in a different light, along with new references—Bell, Bowdish, and Mueller, which teach the IgG2/IgG4 constant region missing from the art combination raised during prosecution.
>
> Bell and a parent application to Bowdish (US 2003/0049683 A1) was cited but not relied upon during prosecution, and Mueller was not cited at all. The art combinations here, which were not raised by the examiner during prosecution, provide the complete sequence of eculizumab, thereby teaching the very thing the examiner mistakenly concluded was missing from the prior art. Consequently, this Petition is not the same/substantially the same as or cumulative of any previous arguments and § 325(d) does not preclude instituting this Petition.

Id. at 24–25.

2. Analysis

Regarding the Board's discretion under 35 U.S.C. § 325(d), in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, the Board enumerated non-exhaustive factors to be considered in exercising discretion under 35 U.S.C. § 325(d) on whether to institute *inter partes* review. Case IPR2017-01586, slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (precedential as to § III.C.5, first paragraph). The non-exhaustive *Becton* factors are:

> 1. the similarities and material differences between the asserted art and the prior art involved during examination;
>
> 2. the cumulative nature of the asserted art and the prior art evaluated during examination;

> 3. the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> 4. the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> 5. whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> 6. the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Id. (numbering added). The *Becton* factors are not dispositive, but are part of a balanced assessment of the relevant circumstances in a particular case and we do not simply default to a tally of each factor to determine whether or not an IPR should be instituted.

Here, Patent Owner has not clearly identified how its arguments fall under the above-noted factors, but has generally argued that the prior art before us now was considered by the prosecuting Examiner either directly or as being cumulative of references that were so considered, and has further argued that the unpatentability issues presented in the Petition are the same as those at issue before the Examiner. Upon review of this evidence, we note that the Examiner considered Hillmen in rejecting a claim for obviousness-type double patenting and for anticipation. *See* Ex. 1014, 482, 557–561. As discussed above, at this stage in the proceedings, the anticipation Ground 1 over Hillmen, on its own, is not considered sufficient to institute IPR; therefore, Hillmen's consideration during prosecution is not determinative here. Rather, we focus on the Bell, Bowdish, and Evans—the references of Ground 4, upon which we base our institution decision.

As an initial matter, Alexion did address the substance of Evans during prosecution. *See* Ex. 1014, 588. But, according to Patent Owner, the Examiner "[c]onsidered" Bell and "U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here." Prelim. Resp. 18. Both of these citations, however, are to an Information Disclosure Statement signed by the Examiner. *See id.* (citing Ex. 1014, 565, 566). Patent Owner does not direct us to, nor do we discern, where either Bell or some version of Bowdish was substantively considered during prosecution. The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution. *See, e.g.*, *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, slip op. at 40 (PTAB Nov. 7, 2018) (Paper 8) (declining to deny institution based on Section 325(d) where the reference was listed on the face of the patent, but Patent Owner provided no evidence "about the extent to which the Examiner evaluated" the reference during prosecution); *Digital Check Corp. d/b/a ST Imaging v. E-Imagedata Corp.*, IPR2017-00178, slip op. at 12–13 (PTAB Apr. 25, 2017) (Paper 6) (acknowledging that a prior art reference was cited in an IDS, but granting institution because there was no indication that the claims were rejected based on those references or that the Examiner substantively discussed those references during prosecution); *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, slip op. at 7–9 (PTAB Apr. 3, 2017) (Paper 8) (refusing to deny institution based on Section 325(d) for grounds based on a prior art reference that was simply cited in an IDS and

not considered at any length); *Praxair Distribution, Inc. v. INO Therapeutics LLC*, IPR2015-00893, slip op. at 8 (PTAB Sept. 22, 2015) (Paper 14) (granting institution even though the references were previously cited in an IDS because patent owner failed to identify with specificity where the references were considered); *HyperBranch Medical Technology, Inc. v. Confluent Surgical, Inc*., IPR2018-01099, slip op. at 17 (PTAB Nov. 27, 2018) (Paper 14) (instituting IPR because, *inter alia*, "[t]he Examiner does not appear to have considered the combined teachings of Spero and Haber during examination of the '021 patent.").

Based on the evidence presented by Patent Owner, *Becton* factors 1–6 weigh in favor of not exercising our discretion not to institute here. Therefore, based on the evidence cited by Patent Owner and for the reasons above, we decline to exercise our discretion under section 325(d) to deny institution here.

Other than the heading of Section VI of the Preliminary Response and that section's first sentence invoking the statute, Patent Owner presents no arguments or evidence directed to the Board's discretion under 35 U.S.C. § 314(a). *See* Prelim. Resp. 65–66. *Therefore*, we also decline to exercise our discretion under Section 314(a) to deny institution.

III. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of prevailing on Ground 4 in showing that claim 1 of the '504 patent is obvious over the combination of Bell, Bowdish, and Evans. Given this determination, we institute trial on all

challenged claims raised in the Petition.[22] *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

Our decision at this stage derives from our preliminary review of the challenged claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration. We emphasize that at this stage of the proceeding, we have not made a final determination as to the construction of any claim term or the patentability of the instituted claims. Our final decision will be based on the full record developed during trial.

IV. ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claims 1–10 of U.S. Patent No. 9,725,504 B2, in accordance with each ground on which the challenge to each claim is based in the Petition, is hereby *instituted*; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '504 patent will commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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[22] In view of the complexity of the art and arguments presented, the parties are, nevertheless, invited to negotiate an agreement to focus on some subset of the asserted claims and Grounds.

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