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Paper 9
Entered: December 8, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00999
Patent 9,725,504 B2

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

POLLOCK, *Administrative Patent Judge.*

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

I. INTRODUCTION

Samsung Bioepis Co., Ltd. ("Petitioner" or "Samsung Bioepis") filed a Petition for an *inter partes* review of claims 1–10 (all claims) 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 6 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 7 ("Reply"); Paper 8 ("Sur-reply").

We reviewed 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 do so 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. We note that there are disputed issues in this proceeding under 35 U.S.C. § 325(d) and § 314(a) concerning discretionary denial; however, we

decline to exercise our discretion to deny institution. *See* Pet. 65–78; Prelim. Resp. 17–32; Reply; Sur-Reply.

A. Real Parties-in-Interest

Petitioner identifies only itself as the real party-in-interest. Pet. 2. Patent Owner, likewise, identifies only itself as the real party-in-interest, but also notes that it is wholly owned by AstraZeneca PLC. Paper 4, 1.

B. Related Proceedings

In February of 2019, Amgen, Inc. filed Petitions for *Inter Partes* Review of the '504 patent and U.S. Patent Nos. 9,718,880 B2 ("the '880 patent) and 9,732,149 B2 ("the '149 patent") in IPR2019-00739 ("the 00739 IPR"), IPR2019-00740 ("the 00740 IPR"), and IPR2019-00741 ("the 00741 IPR"), respectively (collectively, "the Amgen IPRs"). *See* Pet. 2 (citing Ex. 1024), Paper 4, 1; Prelim. Resp. 1 n.2. We instituted *Inter Partes* Review in each of the 00740 IPR, 00739 IPR, and 00741 IPR. *See, e.g.*, Ex. 1024. In June of 2020, and following settlement between the parties, we terminated each of the Amgen IPRs without issuing a final written decision. *See* Ex. 1026. Before the filing of the instant IPR, Patent Owner submitted the records of the three terminated IPRs in the prosecution of related applications, which issued as U.S. Patent Nos. 10,590,189 B1 ("the '189 patent" Ex. 3002) and 10,703,809 B2 ("the '809 patent" (Ex. 3003)) (collectively, "the child patents"). *See* Ex. 3002, code [56]; Ex. 3003, code [56].

According to Petitioner, "[t]he '504 patent has never been asserted in any litigation." Pet. 65.

The '504 patent shares essentially the same specification with the '880 patent, the '149 patent, and more recently issued '189 and '809 patents. Samsung Bioepis filed Petitions for *Inter Partes* Review of the '880, '504, '149, '189, and '809 patents in IPR2023-00998, IPR2023-00999, IPR2023-00933, IPR2023-01069, and IPR2023-01070, respectively. Pet. 2; Paper 4, 1.

The '504, '880,'149, '189, and '809 patents are related as follows: The '809 patent issued from application No. 16/804,567, filed on February 28, 2020, which is a continuation of application No. 16/750,978, filed on January 23, 2020, which is a continuation of application No. 15/642,096 (now the '189 patent), filed on July 5, 2017, which is a continuation of application No. 15/284,015 (now the '149 patent), filed October 3, 2016, 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 '880 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. Pet. 17; Prelim. Resp. 2.

C. The '504 patent and Relevant Background

The '504 patent, listing Leonard Bell, Russell P. Rother, and Mark J. Evans as inventors, relates to the use of a humanized anti-C5 antibody (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). *See* Ex. 1001, code (72), Abstract.

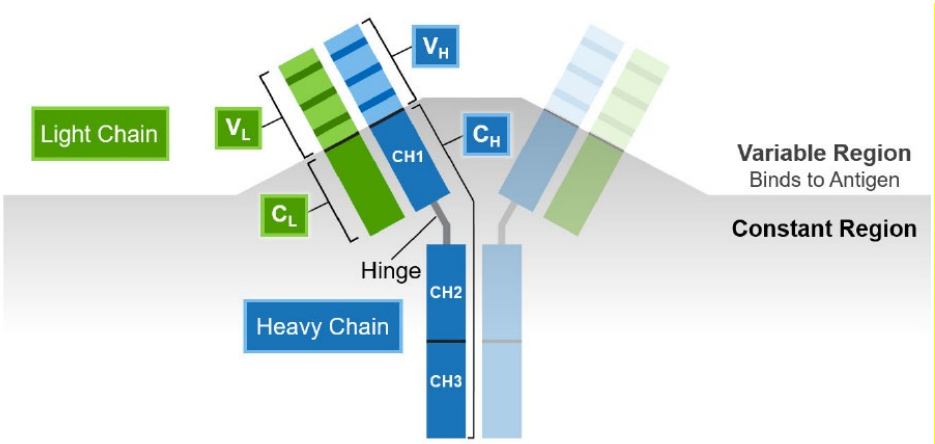
PNH is an acquired hemolytic disease resulting from loss of function in certain cytoprotective proteins. Ex. 1001, 1:27–37. This loss of function renders red blood cells, platelets and other blood cells highly sensitive to attack via activated complement proteins (explained in detail below). *Id.* The resultant complement-mediated lysis of blood cells results in several 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 declarant, Dr. Ravetch, "[p]atients who suffer from PNH have sudden attacks in the night ('paroxysmal nocturnal') and have hemoglobin in the urine, causing dark coloring ('hemoglobinuria')" and "other known clinical symptoms, such as anemia, fatigue, thrombosis and pain." Ex. 1003 ¶ 56. [1]

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. *See generally* Ex. 1001, 7:11–8:56. As part of the immune system, "[c]omplement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions." *Id.*, 7:17–22. The complement cascade progresses through the classical or alternative pathways, which "differ in their initial steps," yet "converge and share the same 'terminal complement' components (C5 through C9) responsible for the activation and destruction of target cells."

[1] Declaration of Jeffrey V. Ravetch, M.D., Ph.D. ("Ravetch Declaration").

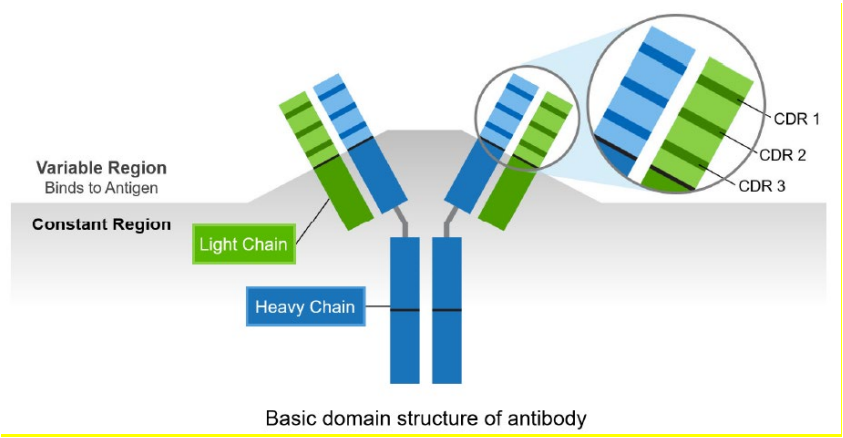
Id., 7:23–28. Before converging in terminal complement components, complement component "C3 is . . . regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways." *Id.*, 7:53–56. All pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase into C5a and C5b. *Id.*, 7:51–53.

Blocking the cleavage of C5 with specific antibodies, however, is known to prevent complement activation. *See, e.g.*, Ex. 1001, 10:57–65 ("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."); 12:6–10. For reference, we reproduce figures from paragraphs 37 and 38 of the Ravetch Declaration, illustrating the basic structure of an antibody such as eculizumab:



Basic domain structure of antibody

[2] US 6,355,245 B1, issued Mar. 12, 2002 (Ex. 1005).



The figures above show a basic antibody structure having hinged heavy chains (colored blue) and accompanying light chains (colored green), with each chain having constant regions (C_{H1}, C_{H2}, C_{H3}, 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 angled away from one another via a hinge region between CH1 and CH2. Ex. 1003 ¶¶ 37, 44. The above figures also illustrate that the variable regions of each chain also include three complementarity determining regions (CDR 1, CDR 2, and CDR 3), which provide the antibody with antigen-binding specificity. *Id.* ¶ 38.

There are five classes of antibodies, with IgG being the most abundant class in humans and represented by the illustration above. *Id.* ¶¶ 43–44. IgG has been characterized as having subclass constant domains, for example, IgG1, IgG2, IgG3, and IgG4, defined by their amino acid combinations. *Id.* Each displays unique properties based on affinity for specific receptors. *Id.*

According to the '504 patent "[a] preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. . . . Such antibodies which are

specific to human complement are known . . . [and] include a preferred whole antibody (now named eculizumab). Ex. 1001, 12:23–31 (citing Evans). The Specification further discloses that 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. *Id.* at Abstract, 1:56–57 (citing as endnote 11, 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. 1010, "Thomas")). More specifically, "eculizumab" refers to a specific humanized antibody derived from mouse antibody 5G1.1, sometimes referred to as "murine 5G1.1" or "m5G1.1." *See* Prelim. Resp. 7–8. 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. 1005, 5:57–67; Ex. 1003 ¶ 53. 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. 9, 10, 11; Prelim. Resp. 20, fn.9; Ex. 1003 ¶ 61; *but see* Ex. 2022 ¶ 121 (Dr. Casadevall noting that "'5G1.1' or 'h5G1.1' could potentially refer to multiple different antibody structures (when not further limited or clarified by additional context)"); Ex. 1003 ¶ 66 (Dr. Ravetch noting the use of "5G1.1 and h5G1.1 as 'synonyms'").

The sole independent claim of the '504 patent, claim 1, recites the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, which together comprise an eculizumab antibody. *See generally* Prelim. Resp. 13. Thus, the '504 patent identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab

Heavy Chain" and "Eculizumab Light Chain," respectively. Ex. 1001, 30:14–31, 39–46 (subject to Certificate of Correction dated October 24, 2017, which changed the first amino acid of SEQ ID NO: 2 from "A" to "E")). 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. 9–10; Prelim. Resp. 9–10; Ex. 2100, 1258 (Figure 2). Eculizumab is the non-proprietary name for Alexion's Soliris product, which was approved by the FDA "to reduce hemolysis in patients with PNH." *See, e.g.*, Prelim. Resp. 4 (citing Ex. 2100, 1256;[3] Ex. 2005, 1[4]); Pet. 10; *see also* Prelim. Resp. 8–9 ("SOLIRIS® has the amino acid sequence recited in the '504 patent's claims, namely, 'a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'").[5]

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, 19:41–28:31.

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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 1256–64 (2007).

[4] SOLIRIS Product Label (rev. 3/2007).

[5] The parties agree that "eculizumab," marketed as Soliris, refers to one specific antibody having the primary amino acid sequence of SEQ ID NO: 2 and SEQ ID NO:4. *See*, *e.g.*, Prelim. Resp. 9–10, 14, 39; Pet. 10–11; Ex. 2022 ¶¶ 98–103, 133; Ex. 1003 ¶ 165.

> 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.

Id. at 20:29–40. 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 28:26–31. "[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 only claim 1, reproduced below, is independent:

> 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)." *Id.* at 39:8–32.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following five grounds for unpatentability (Pet. 4, 26–29):

Ground	Claim(s)	Basis	Asserted Reference(s)
1	1–5, 7–10	103(a)[6]	Bell,[7] Bowdish,[8] Evans,[9] Tacken,[10] and Mueller PCT[11]
2	6	103(a)	Bell, Bowdish, Evans, Tacken, Mueller PCT, and Wang[12]
3	1–5, 7–10	103(a)	Bell, Evans, Tacken, and Muller PCT

[6] 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.

[7] Bell et al., US 2005/0191298 A1, published Sept. 1, 2005 (Ex. 1007).

[8] Bowdish et al., US 2003/0232972 A1, published Dec. 18, 2003 (Ex. 1004).

[9] Evans et al., US 6,355,245 B1, issued March 12, 2002 (Ex. 1005).

[10] Paul J. Tacken et al., *Effective induction of naive and recall T-Cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody*, 106 BLOOD 1278–85 (2005) (Ex. 1008).

[11] Mueller et al., WO 97/11971, published April 3, 1997 (Ex. 1009).

[12] Wang, US 2005/0271660 Al, published Dec. 8, 2005 (Ex. 1044)

Ground	Claim(s)	Basis	Asserted Reference(s)
4	6	103(a)	Bell, Evans, Tacken, Mueller PCT, and Wang
5	1–5, 7–10	102(b)	Bell

In support of its patentability challenges, Petitioner relies on, *inter alia*, the Declaration of Jeffrey V. Ravetch, M.D., Ph.D. and the Declaration of Cindy Ippoliti, Pharm.D. Ex. 1003, Ex. 1062. For the purpose of the Preliminary Response, Patent Owner relies on the Declarations of Drs. Arturo Casadevall (Ex. 2022), Bernhardt Trout (Ex. 2024), and Michel Nussenzweig (Ex. 2026), previously submitted in the 00740 IPR. *See* Prelim. Resp. 3, n.5, 54, n.12, 50 n.11.

F. Overview of Asserted References

Petitioner asserts that "[e]ach reference in Grounds 1-5 . . . qualifies as prior art under 35 U.S.C. § 102(b)." Pet. 19. Patent Owner does not presently dispute that any of the asserted references qualifies as prior art. *See generally* Prelim. Resp.; *but see id.* at 56, 58 (Patent Owner's contention that Bowdish is not analogous art, which we address below).

1. Overview of Bowdish (Ex. 1004)

Bowdish is a U.S. Patent Application published on December 18, 2003,[13] and listing Alexion as the official correspondence address. Ex. 1004 code [76].

[13] According to Office records, Bowdish eventually issued as US Patent 7,396,917 B2.

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." *Id.* ¶ 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 it 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.[14] 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 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 cMp1 receptor by FACS analysis." *Id.* ¶ 192. "The FACS staining was performed essentially as described previously herein, with the exception that the detection was done using PE conjugated F(ab')2 fragment of goat anti-human IgG (H+L). *Id.*

[14] US Application. Ser. No. 08/487,283 matured into U.S. Patent No. 6,355,245 B1, referenced herein as Evans (Ex. 1005).

In SEQ ID NOs: 69 and 70, respectively, Bowdish discloses the amino acid and nucleotide sequences for the "5G1.1 Light Chain." *Id.* ¶ 50. 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. *Id.* ¶ 49. Bowdish discloses the corresponding nucleotide sequence in SEQ ID NO: 68. *Id.*

2. Overview of Evans (Ex. 1005)

Evans is a U.S. patent, issued March 12, 2002, and assigned on its face to Alexion. Ex. 1005 code (73). Among its listed inventors are Mark J. Evans, Russell P. Rother, and Thomas C. Thomas. *Id.* at code (75).

Evans is cited in the '504 patent, as well as by other evidence of record, as teaching a "[s]uitable anti-C5 antibod[y] known to those of skill in the art" and the "antibod[y] . . . specific to human complement[,] . . . whole antibody (now named eculizumab)," as well as "methods of engineering such antibodies." Ex. 1001, 10:57–65, 12:13–21, 12:42–55; *see also* Ex. 1004 ¶ 191 (Bowdish incorporating Evans by reference for teaching "[c]onstruction of 5G1.1); Ex. 1007 ¶ 52 (Bell incorporating Evans by reference for teaching "[p]articularly useful anti-C5 antibod[y] . . . h5G1.1-mAb [or] h5G1.1-scFv," and identifying that "[t]he antibody h5G1.1-Mab is currently undergoing clinical trials under the tradename eculizumab.").

Evans discloses anti-C5 antibodies useful in the treatment of glomerulonephritis (GN). Ex. 1005, Abstract. Evans's Example 7 describes the isolation of 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 acid sequence of CDR3 so marked reads: DSAVYYCAR**Y<u>FFGSSPNWYFD</u>V-**WGAGTTVTVSS.

Evans describes making a series of different humanized 5G1.1 scFv[15] and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. Ex. 1005, 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 eighteen constructs "encoding . . . recombinant mAbs comprising the 5G1.1 CDRs." *Id.* at 42:56–45:33. One of these constructs, designated 5G1.1 scFv CO12, "encodes a humanized (CDR grafted and framework sequence altered) scFv" which, according to Petitioner's declarant, Dr. Ravetch, "includes all six CDR sequences and variable regions of SEQ ID NOS: 2 and 4 of claims 1–3." Ex. 1003 ¶ 90 (citing Ex. 1005, Example 11 (12)).

[15] As Dr. Ravetch notes, "[a]n scFv fragment corresponds to V_L and V_H domains of an antibody joined by a short peptide linker." Ex. 1003 ¶ 39.

Evans also teaches that its anti-C5 antibodies can be administered "in a variety of unit dosage forms," and that doses are generally between 1 to 100 mg per kg and preferably between about 5 to 50 mg per kg of patient weight. Ex. 1005, 17:60–18:11. Evans discloses that its antibodies will generally be administered intravenously in a formulation that "must be sterile" and which "may" contain preservatives. *Id.* at 18:29–43.

3. Overview of Bell (Ex. 1007)

Bell is a published U.S. Patent Application listing Leonard Bell and Russell P. Rother as inventors. Ex. 1007, code 76. Both Bell and Rother are listed as inventors of the '504 patent; Russell P. Rother is also listed as an inventor on the face of Evans. *See* Ex. 1005, code (75).

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 h5G1.1." *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. According to Bell, formulations of its anti-C5 antibodies "suitable for injection" "must be sterile" and may or may not contain preservatives. ¶ 62.

The data disclosed in Bell includes data on studies in which 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. 1007 ¶¶ 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.

4. Overview of Tacken (Ex. 1008)

Tacken, an article published in 2005, notes the disclosed research was supported by "funding from Alexion Pharmaceuticals" to the lead author, and that three of the paper's other authors "are employed by Alexion Pharmaceuticals, whose potential product was studied in the present work." *Id.* at 1278. One of these authors, Russell P. Rother, is also an author of Thomas (Ex. 1010), a named inventor on Evans (Ex. 1005, code (75)), and cited as an inventor of the '504 patent (Ex. 1001, code 75).

Tacken describes "a humanized antibody, hD1V1G2/G4 (hD1), directed against the C-type lectin DC-specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN)," and its use as a dendritic cell-based vaccine. Ex. 1008, Abstr. 1278. In the section describing "Recombinant antibodies," Tacken describes the DC-SIGN construct as comprising a humanized variable heavy chain region "genetically fused with

a human hybrid IgG2/IgG4 constant domain" previously shown to "prevent[] antibodies from binding to Fc receptors. [citing Mueller 1997[16]]." *Id.* at 1279. Tacken used mouse IgG1 and 5G1.1 antibodies as isotype controls in binding and internalization assays. *Id.* at 1280. With respect to the latter, Tacken states: "An isotype control antibody, h5G1.1-mAb (5G1.1, "eculizamab [*sic*]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5. [citing Thomas (Ex. 1010)]." *Id.* at 1279.

5. Overview of Mueller PCT (Ex. 1009)

Mueller PCT is an international patent publication listing Alexion as applicant. Ex. 1009, code (71). Among the listed inventors of Mueller PCT are two of the listed inventors of the '504 patent: Mark J. Evans and Russell P. Rother. *Id.* at code (75).

Mueller PCT discloses "[a]ntibodies to porcine P-selecting protein, porcine VCAM protein and porcine CD86 protein are useful for diagnosing human rejection of porcine xenotransplants and for improving xenotransplantation of porcine, cells, tissues and organs into human recipients." *Id.* at Abstract. According to Mueller PCT, 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.

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[16] 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(6) MOL. IMMUNOL. 441–452 (1997). Ex. 1006.

To achieve these and other goals, Mueller PCT 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 PCT discloses the development and testing of "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 . . . (HuG2/G4 mAb)." *Id.* at 12:19–33. As controls for these experiments, Mueller PCT used "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)." *Id.* at 11:34–12:4. 12:34–13:2, Figures 11, 12, 15.

On pages 52–61 of the reference, Mueller PCT discloses the amino acid sequence of the hybrid IgG2/G4 anti-VCAM antibody, 3F4. According to Dr. Ravetch, "an alignment of the amino acid sequence of Mueller PCT's hybrid IgG2/G4 heavy chain constant region of the 3F4 (chimeric) human G2/G4 antibody with the heavy chain constant region of '504 patent's SEQ ID NO:2 shows that Mueller PCT discloses the same IgG2/G4 heavy chain constant region as described in SEQ ID NO:2" of the '504 patent, whereas alignment of "the light chain in 3F4 is identical to the constant region of the light chain disclosed in SEQ ID NO:4." Ex. 1003 ¶¶ 103–104.

6. Overview of Wang (Ex. 1044)

Wang is a U.S. Patent Application Publication assigned on its face to Alexion. Ex. 1044, code (73). Wang discloses formulations of eculizumab suitable for nebulization and pulmonary delivery. *See, e.g.*, *id.* ¶¶ 25, 60, 67. According to Wang, eculizumab formulations "may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." *Id.*

¶ 67. Wang further discloses inhalable 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.

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 ordinary 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:

> A person of ordinary skill in the art ("POSA") would have knowledge of the scientific literature and have skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007. (EX1003, ¶¶16-20; EX1062. ¶¶ 15–19.) A POSA also would have knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same. (*Id.*, ¶19; EX1062, ¶18.) Typically, a POSA 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 discovery, development, and design of therapeutic antibodies for use as potential treatments in human disease. (*Id.*) Also, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others on the team, *e.g.*, to solve a given problem; for example, a clinician, a doctor of pharmacy, and a formulation chemist may have been part of a team. (*Id.*)

Pet. 15–16.

Patent Owner does not presently dispute this 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. 51 (further arguing that Petitioner cannot prove unpatentability of the challenged claims under either party's definition).

At this stage in the proceeding, we accept and use Petitioner's proposed definition of the skilled artisan, as being both unopposed by Patent Owner and inclusive of Patent Owner's additional qualification. In this respect, it appears that Petitioner's language "at least two years of experience in the discovery, development, and design of therapeutic antibodies for use as potential treatments in human disease" encompasses Patent Owner's proposed modification, and is consistent with the level of skill in the art reflected in the prior art of record. *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)).

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 Patent Owner's supplemented definition. Further, we note that evidence may be presented as the case progresses to support some other proposed definition of the skilled artisan, which may influence our determination of this issue.

C. Claim Construction

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* 37 C.F.R. § 42.100(b)).

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) (en banc)).

Neither party requests the construction of any claim term. *See, e.g.*, Pet. 18. 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))). At this stage in the proceeding we find it unnecessary to construe the language of any challenged claim because the claim language is readily understandable on its face, within the context of the claims.

With this understanding, as well as the legal principles and our understanding of the definition of the skilled artisan as set forth above in mind, we address the parties' positions below.

D. Objective Evidence Indicating Non-Obviousness

Before addressing the specifics of Petitioner's obviousness grounds, we address Petitioner's contention that there are no objective indicia of nonobviousness that would outweigh the strong case of obviousness. Pet. 62–65, 76–77. "Objective indicia of nonobviousness can serve as an important check against hindsight bias and 'must always when present be considered.'" *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015) (internal quotation omitted). 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, or objective indicia, evidencing non-obviousness. *See Graham*, 383 U.S. at 17–18. Relevant objective indicia of nonobviousness 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 objective indicia of nonobviousness 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 notes that any objective evidence of nonobviousness must have a nexus to the claimed invention. Pet. 62–63 (citing *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Petitioner asserts that Patent Owner cannot argue commercial success of its drug Soliris, a long-felt and unrecognized need, or industry praise as objective evidence of nonobviousness, because the use of eculizumab as a treatment for PNH was expressly taught in the prior art and therefore not novel in the claim. *Id.* at 63–65 (citing Ex. 1003 ¶¶ 169–174). As for evidence of copying, Petitioner argues that its intent to develop a biosimilar of Soliris is inapposite, as biosimilar statutes and regulations require that any biosimilar of Soliris be "highly similar to the reference product." *Id.* at 65 (citing 42 U.S.C. § 262(i)(2); Ex. 1003 ¶ 173.

In response, Patent Owner asserts that commercial success, long-felt but unmet need, and industry praise all support the patentability of the challenged patent claims. Specifically, Patent Owner relies on the commercial success of Soliris, which Patent Owner asserts has generated substantial sales in the relevant market. Prelim. Resp. 71 (citing Ex. 2018,

70). Patent Owner also asserts that Soliris fulfilled a long-felt, unmet need as the first FDA-approved treatment to reduce hemolysis in PNH patients and has received industry praise as the recipient of several awards. *Id.* at 71–72 (citing Ex. 2019, 1270; Ex. 2020; Ex. 2021). Moreover, Patent Owner dismisses Petitioner's copying argument, as Patent Owner contends Petitioner could have chosen to develop biosimilars of other biologic products, but instead chose to copy Soliris. *Id.* at 72. Patent Owner argues that, contrary to Petitioner's assertions, the claimed sequences were novel and nonobvious at the time of the invention. *Id.* at 72–73.

At this stage of the proceeding, we find Petitioner has shown sufficiently that Patent Owner's objective evidence of nonobviousness carries little weight. "For objective indicia evidence to be accorded substantial weight, we require that a nexus must exist 'between the evidence and the merits of the claimed invention.'" *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330–31 (Fed. Cir. 2017) (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). If the patentee relies on the commercial embodiment of the claimed invention and that embodiment is the invention disclosed and claimed, a presumption of nexus exists. *See Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). That presumption is rebuttable and the evidence is not pertinent, however, "if the feature that creates the commercial success [or other secondary considerations] was known in the prior art." *See Ormco Corp. v. Align Tech.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

On this record, although there is a presumption of nexus between Soliris and the challenged claims, we find Petitioner has sufficiently rebutted

that presumption. In its Preliminary Response, Patent Owner relies heavily on Soliris and its treatment of PNH as evidence of commercial success, long-felt need, and industry praise. Prelim. Resp. 71–72. At this stage of the proceeding, however, we are persuaded that Bell, Hillmen 2004,[17] and Hill 2005[18] all disclosed that eculizumab was a useful treatment for PNH more than a year before the '504 patent was filed. *See* Pet. 7–8 (citing, e.g., Ex. 1007 ¶¶ 52; Ex. 1013, 9; Ex. 1011, 3), 58 (further citing Ex. 1003 ¶ 162). We also agree with Petitioner that the Federal Circuit's holding in *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354 (Fed. Cir. 2022) is instructive with respect to Patent Owner's evidence of copying. *See* Pet. 58. The Court noted that it has held that "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Adapt Pharma* at 1374 (quoting *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013)). Similarly, here, evidence of copying in the biosimilar context is not probative of nonobviousness because the "biological product [must be] highly similar to the reference product." *See* 42 U.S.C. § 262(k)(2)(A). That there may be "hundreds of other biologic products" that Petitioner could have developed, as Patent Owner asserts,

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[17] Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. ENG. J. MED. 552–59 (2004) (Ex. 1011).

[18] Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 BLOOD 2559–65 (2005) (Ex. 1013).

does not outweigh the strong evidence of obviousness regarding the sequence, composition, and use of eculizumab.

In light of the foregoing, we are not persuaded that Patent Owner's objective indicia evidence is sufficiently probative of nonobviousness at this stage of the proceeding. *See Ormco*, 463 F.3d at 1313 (finding patentee's evidence did not show commercial success where allegedly novel features were taught by the prior art); *see also Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017) (finding objective indicia evidence not probative of nonobviousness where prior art suggested the allegedly successful feature of the claimed invention). We recognize, however, that consideration of objective indicia of nonobviousness is highly fact dependent. We note that our determination here is preliminary, and we will re-evaluate the evidence on a full trial record in our Final Written Decision.

E. Obviousness in view of Bell, Bowdish, Evans, Tacken, and Mueller PCT (Ground 1) and further in view of Wang (Ground 2)

Under Ground 1, Petitioner challenges claims 1–5 and 7–10 as obvious over Bell, Bowdish, Evans, Tacken, and Mueller PCT. Pet. 26–27, 29–47. Under Ground 2, Petitioner challenges the remaining claim 6 as obvious over Bell, Bowdish, Evans, Tacken, Mueller (as argued under Ground 1), and further relies on Wang. Pet. 29, 48–51. Patent Owner opposes. Prelim. Resp. 51–60. We focus first on Ground 1 as applied to independent claim 1.

1. Claim 1

According to Petitioner, one of ordinary skill in the art would have been motivated to obtain the sequence of the anti-C5 antibody eculizumab

(also referred to as "h5G1.1") because Bell teaches that this molecule is "particularly useful" and effective in the treatment of PNH. *See* Pet. 22–23, 26, 29, 36–37 (citing, e.g., Ex. 1007 ¶¶ 12, 52, 81–97, Figs. 1a, 1b, 3, 6a, 6b, 7–10; Ex. 1003 ¶¶ 111, 123). With respect to the sequences of the claimed anti-C5 antibody, Petitioner admits that "Bell's disclosure does not include the exact amino sequence of eculizumab," but argues that the sequence is necessarily disclosed because "Bell teaches that the antibody h5G1.1 *is* eculizumab, and that 'methods for the preparation of' h5G1.1 'are described in' Evans (EX1005) and Thomas (EX1010), both of which are incorporated into Bell in their entirety." *Id.* at 29–30 (citing Ex. 1007 ¶ 52). Accordingly, Petitioner points to Bowdish, and its incorporation of Evans, as disclosing the entirety of eculizumab including SEQ ID NO: 2 and SEQ ID NO: 4 as a starter-scaffold-antibody for making a 5G1.1 antibody with a TPO mimetic peptide. *See* Pet. 30–37 (citing, *inter alia*, Ex. 1003 ¶¶ 39, 113–124; Ex. 1004, Figs. 13A, 13B, ¶ 191; Ex. 1005, page 1 (Title), Fig. 8, Figs. 18–19, 7:60–64, 9:44–45, 9:65–10:20, 42:56–45:33 (Example 11), 143:22–144:14, claim 19).

According to Petitioner, "Bowdish's SEQ ID NO:69 discloses the light chain sequence of SEQ ID NO:4 in claim 1 of the '504 patent." Pet. 30 (citing Ex. 1004, Fig 13B; Ex. 1003 ¶¶ 113–114). Petitioner contends that Bowdish, via its incorporation of Evans, also discloses SEQ ID NO:2, which is the sequence of eculizumab's heavy chain. *Id.* at 30–32. In particular, Petitioner points to Bowdish's SEQ ID NO:67 as disclosing all element of eculizumab's heavy chain "with the exception of the 13 amino acid 'native CDR3' of '5G1.1' within SEQ ID NO:2." *Id.* at 31 (citing Ex. 1004, ¶ 191,

Fig 13A; Ex. 1003 ¶ 115). Petitioner asserts that the remaining 13 amino acids of the SEQ ID NO: 2 are accounted for by Bowdish's replacing the native CDR3 portion of Evans's antibody with a TPO mimetic peptide where, Petitioner contends, Bowdish's incorporation of Evans's by reference discloses this native CDR3 sequence and, thus, the entirety of the antibody described in challenged claim 1. *Id.* at 31–32.

Petitioner's argument is illustrated by the following illustration from the Petition, incorporated from Dr. Ravetch's Declaration:

Id. at 33; *see also* Ex. 1003 ¶ 116. The figure above illustrates reverse engineering the Bowdish antibody based on its disclosure that Evans disclosed the "[c]onstruction of 5G1.1" antibody, into which Bowdish's TPO mimetic peptide graft was inserted (shown in in red) "to replace the native CDR3 (represented by the middle image above ["Evans h5G1.1 scFv C012"] with 5' ttg cca ATT GAA GGG CCG ACG CTG CGG CAA TGG CTG GCG GCG CGC GCG cct gtt 3' (SEQ. ID. NO: 65)." Ex. 1004 ¶ 1; Ex. 1003 ¶ 114; Ex. 1004 ¶ 116. Bowdish states that "[t]he 5G1+peptide was produced as a whole IgG antibody (See **FIGS. 13A and 13B**)." Ex. 1004 ¶ 191; *see also* Ex. 1003 ¶ 116–117. Thus, the figure above shows, left-to-right, Bowdish's final antibody having a grafted TPO mimetic peptide

colored red, then the substitution of that TPO mimetic peptide segment with the CDR3 segment from Evans that it replaced, and last, the starting full antibody having the amino acid sequence of Evans, which Petitioner asserts is eculizumab, i.e., the claimed antibody C5-specific antibody consisting of SEQ ID NO: 2 and SEQ ID NO: 4. *See generally* Ex. 1003 ¶¶ 113–124.

According to Petitioner, "A POSA following Bowdish's incorporation of Evans would have no difficulty immediately identifying the sequence Bowdish refers to as 'the native CDR3.'" Pet. 33. In this respect, Petitioner points to Evans's Example 11, which describes eighteen constructs of "recombinant mAb-encoding DNAs." Pet. 33–34 (citing Ex. 1005, 42:56–45:33; Ex. 1003 ¶¶ 39, 117–119). According to Evans, "one each of the various L1, L2, and L3 CDRs" and "one each of the various H1, H2, and H3 CDRs" disclosed in Example 11, assembled into "matched pairs of the variable regions (e.g. a VL and a VH region) . . . may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies of the invention." Ex. 1005, 45:5–33. Of the eighteen constructs of Example 11, Petitioner focuses on nine "humanized single-chain variable domain structures ("scFvs") which correspond to the VH and VL domains of an antibody joined by a short peptide linker and starting with the "MA" leader sequence. Pet. 34 (citing Ex. 1005, 42:56-45:33; Ex. 1003, ¶¶ 39, 117-119). "Importantly," Petitioner argues,

> the *identical* HCDR3 sequence is used in *every one* of these examples. (EX1005, 9:65-10:20, 42:56-45:33, 143:22-144:14, Figs. 18-19, Claim 19; EX1003, ¶120, Appendix A.) This is not surprising, since the CDR regions determine binding to target

> (here, C5), and are a fundamental component of the uniqueness of a particular antibody such as 5G1.1. (EX1003, ¶120.)

Pet. 34.

Thus, Petitioner contends, without naming any of such antibodies "eculizumab," Evans taught artisans how to build each of these humanized 5G1.1 antibodies and, in light of Bell, would have been motivated to try all nine sequences to arrive at the sequence for eculizumab. *Id.* at 52–53; (citing, *inter alia*, Ex. 1003 ¶¶ 153–154; *KSR*, 550 U.S. at 421).

Petitioner also points to Tacken as further confirmation that Bowdish discloses the hybrid IgG2/IgG4 heavy chain of eculizumab, as recited in challenged claim 2. Pet. 37–41. Petitioner contends that, like Bell, Tacken equates h5G1.1 with eculizumab and, moreover, teaches that eculizumab contains "the same" IgG2/IgG4 constant region disclosed in Mueller 1997 (Tacken's reference 17). *Id.* at 37–38 (citing Ex. 1008, 1279; Ex. 1003 ¶ 127). Noting that "Mueller PCT, the companion patent application for Mueller 1997, expressly discloses the full amino acid sequence for the IgG2/IgG4 constant domain heavy chain used in the 'h5G1.1 HuG2/G4' Antibody," Petitioner contends that "[a] routine alignment of the IgG2/G4 constant domain heavy chain from Mueller PCT and Bowdish would have immediately confirmed that the antibody disclosed in Bowdish has *precisely* the sequence of eculizumab" recited in claim 2. *Id.* at 38–39 (citing Ex. 1009, 14, 58–59, 97; Ex. 1003 ¶¶ 125–127 (showing comparison of heavy chain constant regions)).

Patent Owner argues that Petitioner uses impermissible hindsight and its present-day knowledge of the Soliris (eculizumab) antibody to

reconstruct the sequences of independent claim 1. *See generally, Prelim.* Resp. 51–60. Patent Owner argues, for example, that Bowdish is non-analogous art, and one of ordinary skill in the art seeking to develop an anti-C5 antibody composition for treating PNH would never have started with Bowdish" because it has "nothing to do with blocking C5 cleavage or treating PNH." *See* Prelim. Resp. 33, 43, 56, 58. Petitioner, supported by the testimony of Dr. Ravetch, contends that Bowdish is analogous art in the field of the '504 patent. Pet. 35–36 (citing Ex. 1003 ¶ 122). In this respect, Dr. Ravetch testifies:

> A POSA looking for the amino acid sequences encoding eculizumab would have easily found Bowdish, and considered it to be analogous art to Bell and Evans for at least three reasons: (1) it provides express disclosures about the structure of the antibody "5G1.1," (2) it identifies "Alexion Pharmaceuticals" as the inventors' addressee that is the same as the assignee for Evans, and (3) it cites to the same Evans patent as does Bell for the structure of 5G1.1. Thus, a POSA would have been motivated to combine the teachings of Bowdish and Evans in view of Bell to arrive at the claimed sequence.

Ex. 1003 ¶ 122.

"Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). On the record before us, it appears that Bowdish is both reasonably pertinent and within the same field of endeavor of the '540 patent for the reasons identified by Dr. Ravetch, because it is directed to the

construction of a humanized monoclonal antibody comprising a TPO mimetic peptide graft into the heavy chain CDR3 of antibody framework 5G1.1, and because it uses "the parental 5G1.1" sequence as a control for FACs analysis of the TPO mimetic antibody. *See* Ex. 1004 ¶¶ 191–193; Ex. 1003 ¶ 124.

Patent Owner further argues that one of ordinary skill in the art would not have been motivated to combine Bowdish and Evans because, in citing to the Evans's application, "Bowdish refer[s] to a ***mouse*** antibody in its reference to '[c]onstruction of 5G1.1,'" whereas "Evans disclos[es] only a mouse antibody plus humanized recombinant 'fragments' that are unusable as the 'scaffold' to make Bowdish's full-length TPO-mimetic compound." *Id.* at 52; *see also id.* at 57 (arguing that Bowdish's reference to "5G1.1" as the parental scaffold for its TPO-mimetic antibody potentially encompasses a wide variety of possible murine and humanized antibodies and fragments"). We do not agree with Patent Owner's assessment on the current record.

As Patent Owner correctly quotes from Bowdish's Example 4: "The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1. ***Construction of 5G1.1*** is described in U.S. Application Ser. No. 08/487,283, incorporated herein by reference." Prelim. Resp. 54 (emphasis added); Ex. 1006 ¶ 191. It is not disputed here that U.S. Application 08/487,283 issued as Evans. *See* Ex. 1005, code (21); *see generally* Prelim. Resp. The portion of Evans relating to "***Construction*** of 5G1.1" (Ex. 1004 ¶ 191) appears to be (or at least includes) Example 11, which is titled

"***Construction*** and Expression of Recombinant mAb." Ex. 1005, 42:55–58 (emphasis added). According to Dr. Ravetch, "Evans'[s] Example 11 teaches construction of . . . humanized 5G1.1 scFv constructs." Ex. 1003 ¶ 185. And none of the other Evans Examples addressing an anti-C5 antibody or a 5G1.1 antibody designate their respective disclosure as relating to "construction," as per the title of Example 11 and the sentence of Bowdish expressly incorporating Evans. *See* Ex. 1005, 33:1–42:54 (Examples 1–10); Ex. 1003 ¶ 185.

Thus, on this record, we find that Petitioner's pointing to the antibodies (or fragments) of Evans's Example 11 for use as a starting point for Bowdish's invention to be more reasonable than Patent Owner's arguments that antibodies would have been selected from some other Example.

With respect to Tacken's description of eculizumab as having an "IgG2/IgG4 constant region," Patent Owner contends that the prior art "consistently directed a POSA to read Thomas (EX1010)," which disclosed an IgG4 antibody. Prelim. Resp. 9–13. According to Patent Owner, "Tacken is the ***only*** document before March 15, 2007 that purportedly associated 'eculizumab' with a hybrid IgG2/IgG4 constant region." *Id.* at 11. "[N]othing in Tacken contradicted the consistent teaching of the prior art ***as a whole*** that 'eculizumab' had an IgG4 constant region." *Id.* And, considering the art as a whole, "the ***only*** plausible conclusion a POSA could have reached in view of the entire content of the art was that 'eculizumab' was Thomas's IgG4 antibody. *Id.* at 12–13 (citing Ex. 2022 ¶¶ 147, 151).

Dr. Ravetch, however, testifies that "Thomas does not refer to the word 'eculizumab' anywhere, indeed it is simply not true that the 'pertinent literature' 'said' that eculizumab was Thomas'[s] IgG4-isotype antibody" Ex. 1003 ¶ 182. Moreover,

> none of the prior art references teach that "eculizumab" has the IgG4 isotype, indeed Thomas does not refer to "eculizumab" at all. Tacken instead is the only reference that discloses any information regarding the constant domain structure of 'eculizumab,' and it unambiguously teaches that "eculizumab" has the hybrid IgG2/G4 constant domain.

Id. at ¶ 167.

As noted in Section I.F.4, above, Tacken describes a lectin-specific antibody comprising a humanized variable heavy chain region "genetically fused with a human hybrid IgG2/IgG4 constant domain. [citing Mueller 1997]." *Id.* at 1279. Tacken used mouse IgG1 and human 5G1.1 antibodies as isotype controls in binding and internalization assays. *Id.* at 1280. With respect to the latter, Tacken states: "An isotype control antibody, h5G1.1-mAb (5G1.1, "eculizamab [*sic*]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5 [citing Thomas (Ex. 1010)]." *Id.* at 1279. On its face, we find it plausible that Tacken suggests that eculizumab (h5G1.1) contained a "human hybrid IgG2/IgG4 constant region," making it suitable for use as an IgG2/IgG4 isotype control for the IgG2/IgG4–containing antibody under development. *See* Ex. 1003 ¶ 70 (citing Ex. 1029, 10–11 (Alexion's statement in unrelated patent prosecution that in light of Evans and Mueller 1997, it was well known as of 2002 "that eculizumab has a G2/G4 Fc portion").

Patent Owner, in contrast, contends that one of ordinary skill reading Tacken would understand it to "identify[] "eculizumab" and "SOLIRIS®" as Thomas's ***IgG4*** antibody," in the same manner as the other prior art it cites. *See* Prelim. Resp. 12; Sur-reply 3. Addressing the implication that Tacken instead teaches that eculizumab "contain[s] the same IgG2/IgG4 constant region" as Tacken's lectin-specific antibody (having "a human hybrid IgG2/IgG4 constant domain"), Patent Owner's declarant from the 00740 IPR downplays the disclosure as "a single sentence taken out of context from a single publication," and which the skilled artisan would have found "ambiguous," "confusing," and possibly a "mistake" to be disregarded in view of "the numerous clear statements in the key publications regarding 'eculizumab' that identify it as the IgG4 antibody of Thomas." *See* Ex. 2022 ¶¶ 141–148; Ex. 1008, 1279.

We do not favor this interpretation on the present record, and particularly in view of what appears to be a close association between Alexion and the authors of Tacken. *See* Ex. 1008, 1278 (footnote). Specifically, Tacken discloses that the lectin-specific antibody research was supported by "funding from Alexion Pharmaceuticals" to the lead author, and that three of the paper's other authors were "employed by Alexion Pharmaceuticals, whose potential product was studied in the present work." *Id.* at 1278. Notably, one of the Tacken authors, Russell P. Rother, is also an author of Thomas, published some nine years earlier. *See* Ex. 1010, 1389.

On the present record, we find it unlikely that the Mr. Rother (*a named inventor of the '504 patent*) and the other Tacken authors were mistaken in referring to eculizumab as having an IgG2/IgG4 constant region.

We find more plausible that Tacken cites to Thomas as describing eculizumab's C5-specific CDRs, and refers to Mueller 1997 for the IgG2/IgG4 heavy chain sequence common to both eculizumab and the anti-lectin antibody under development. We also find it plausible that other documents Patent Owner points to as citing to Thomas also do so in reference to the C5-specific variable domain, rather than to the constant region or other non-antigen binding features of the molecule. *See* Prelim. Resp. 13; Pet. 72–73; Ex. 1036, 6–8. We invite the parties to further address this issue at trial.

Finally, we note Patent Owner's argument that Petitioner ignores "the complexity and unpredictability of designing monoclonal antibodies for human clinical therapy," and, in particular, the "substantial risks and unpredictability associated with changing the constant region isotype of a known antibody." Prelim. Resp. 46–49 (capitalization normalized). While these factors may have relevance to the design of new monoclonal therapies, we do not find them relevant here. The thrust of Petitioner's argument appears not to entail creating a *new* antibody, but in how one of ordinary skill in the art would have been motivated to reconstruct the amino acid sequence eculizumab, an *existing* antibody, which, as evidenced by Bell (*see* Section I.F.3, above), was already shown to be safe and effective for the treatment of PNH. As such, Patent Owner's arguments regarding the risks of modifying the 5G1.1 antibody constant region to arrive at eculizumab are not pertinent to our analysis.

In light of the above, and on the record before us, Petitioner has shown sufficiently that, under Ground 2, one of ordinary skill in the art

would have been motivated with a reasonable expectation of success, to re-create eculizumab by replacing the CDR3 region of Bowdish's "5G1.1+peptide antibody" with Evans's CDR3 sequence to arrive at Bowdish's "parental 5G1.1," having the sequences set forth in claim 1. *See* Ex. 1004, ¶¶ 191–193. And in light of Bell's disclosure that pharmaceutical formulations containing this antibody are particularly useful in reducing the symptoms of PNH (*see*, *e.g.*, Section I.F.3, above), Petitioner has shown sufficiently that one of ordinary skill in the art would have been motivated to practice the method of claim 1 with a reasonable expectation of success.

2. Dependent Claims 2–10

The challenged dependent claims recite additional limitations relating to the method and composition administered in independent claim 1. Petitioner relies on Bell, Bowdish, Evans, and Wang with respect to these limitations. *See*, *e.g.*, Pet. 42–47 (Ground 1), 48–50 (Ground 2). Of these, Patent Owner briefly challenges Petitioner's support for the recited "300 mg single-use dosage form" of claims 5 and 6, and, in the context of claim 6 (challenged under Grounds 2 and 4), "30 ml of a 10 mg/ml antibody solution." Prelim. Resp. 49–50 (citing Ex. 1007 ¶¶ 82, 91; Ex. 2024 ¶¶ 69–90; Ex. 1044 ¶ 67). Although Patent Owner is welcome to expand its arguments at trial, on the record before us we find Petitioner's well-reasoned explanations regarding these limitations sufficient for the purpose of institution.

With respect to "300 mg single-use dosage form," recited in dependent claims 5 and 6, Petitioner notes that Bell suggests the administration of its antibodies "in a variety of unit dosage forms," and

discloses a dosage regime for the treatment of PNH involving the administration of 600 mg and 900 mg intravenous doses. Pet. 49 (citing Ex. 1007 ¶ 58); *see also*, *id.* at 43–44 (further citing Ex. 1007 ¶ 82; Ex. 1003 ¶ 138; Ex. 1062 ¶ 55). According to Petitioner's declarant, Dr. Ippoliti, "[a] POSA would have known that single-use dosage units are preferred for use in organized health care settings such as hospitals, and especially in contexts such as intravenous infusion in which sterility must be maintained." Ex. 1062 ¶ 53 (citations omitted). Moreover, "[a] pharmacy also would not prefer to stock (nor, presumably, would a drug company prefer to make), two different vial amounts of 600 and 900 mg each" because, among other things, "[t]his would unnecessarily complicate antibody supply services, inventory tracking." *Id.* at 55. Thus, reasons Petitioner,

> [g]iven Bell's express disclosure of a dosage regimen having 600 and 900 mg phases, a 300 mg unit dosage form would have been obvious. 300 is the highest common factor of 600 and 900, and thus the most convenient unit dose to use without the need to manufacture vials of differing quantities, and without causing unnecessary waste of costly antibody treatments.

Pet. 43–44 (citing Ex. 1003 ¶ 138; Ex. 1062 ¶ 55).

Addressing the "30 ml of a 10 mg/ml antibody solution" limitation of claim 6, Petitioner contends that this element would have been obvious in view of Wang and the understanding of one of ordinary skill in the art. Pet. 49–50. Petitioner points out that Wang discloses that eculizumab formulations could be successfully and stably formulated in an aqueous solution at concentrations in the range of 1 to 30 mg/ml, which includes the concentration of 10 mg/ml recited in claim 1. *Id.* (citing Ex. 1044 ¶¶ 25, 67, 170–173, Fig. 10; Ex. 1003 ¶ 148; Ex. 1062 ¶ 59). Dr. Ippoliti further

testifies that one of ordinary skill in the art "also would have known that 10 mg/ml was well within the known range of concentrations of several FDA-approved antibodies." Ex. 1062 ¶ 59 (citations omitted). With this background, Dr Ippoliti concludes that,

> given the desirability of supplying eculizumab as a 300 mg single-use dose amount as discussed above, and based on simple arithmetic, it would have been obvious for a POSA to use 30 ml of 10 mg/ml solution to administer the desired single-use dose of 300 mg. A POSA would also consider it advantageous to have the total supplied volume of the antibody drug substance be 30 ml – neither such a small volume that there would be concern about successfully drawing all the drug substance into a syringe, nor such a large volume as to be impractical to draw using a standard syringe or impractical to dilute into an IV solution for infusion into the patient.

Id.

In consideration of the above, and on the record before us, Petitioner has shown sufficiently that the dependent claims are unpatentable as obvious.

F. Obviousness in view of Bell, Evans, Tacken, and Muller (Ground 3) and further in view of Wang (Ground 4)

Under Ground 3, Petitioner challenges claims 1–5 and 7–10 as obvious over Bell, Evans, Muller, and Tacken. Pet. 27–28, 51–57. Under Ground 4, Petitioner challenges remaining claim 6 as obvious over Bell, Bowdish, Evans, Tacken, Mueller PCT (as argued under Ground 3), and further relies on Wang. Pet. 57. Patent Owner opposes. Prelim. Resp. 61–65. We focus first on Ground 3 as applied to independent claim 1.

1. The Parties' Contentions

Petitioner begins with Bell's disclosure, which it contends would have motivated an ordinarily skilled artisan to determine the amino acid sequence of its disclosed anti-C5 antibody eculizumab for use in the treatment of PNH as described in claim 1. *Id.* at 51. In this respect, Petitioner asserts that Bell points directly to Evans and Thomas, each being incorporated by reference. *Id.* (citing Ex. 1003 ¶ 136). According to Petitioner, such an artisan would have recognized in Evans the critical CDR sequences for the heavy and light chains of an original mouse antibody 5G1.1 that binds C5, as were variable domain sequences for humanized forms of 5G1.1. *Id.* at 51–52 (citing Ex. 1005, 1:1–3, 9:65–10:20, 42:56–45:23, 143:22–144:14, Figs. 18–19, Claim 19; Ex .1003 ¶¶ 151–152). Petitioner also points to Evans's Example 11, which provides nine humanized scFv structures corresponding to the V_H and V_L domains of an antibody joined by a short peptide linker. *Id.* at 52 (citing Ex. 1005, 42:56–45:33; Ex. 1003 ¶ 152). According to Petitioner,

> Evans then explains that "one each of the various L1, L2, and L3 CDRs" and "one each of the various H1, H2, and H3 CDRs" disclosed in Example 11, assembled into "matched pairs of the variable regions (e.g. a VL and a VH region) . . . may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies *of the invention*."

Id. at 52 (citing Ex. 1005, 45:5–33; Ex. 1003 ¶ 152). Thus, Petitioner contends, without naming any of such antibodies "eculizumab," Evans taught artisans how to build each of these humanized 5G1.1 antibodies and, in light of Bell, would have been motivated to try all nine sequences to arrive at its sequence. *Id.* at 52–53; Ex. 1003 ¶¶ 153–154.

In particular, Petitioner points to Bell as support for Evans teaching the structure of 5G1.1 antibodies, and eculizumab, specifically. *Id.* at 53. Petitioner asserts that a limited (finite) number of antibodies are taught in this scenario and that the artisan would have had good reason to pursue them (Bell says to do so, for example), meaning each was obvious to try; hence, producing eculizumab was obvious to try. *Id.* (citing, *inter alia*, *KSR*, 550 U.S. at 421).

Petitioner further points to Mueller PCT as focusing such an ordinarily skilled artisan upon an antibody construct identified as CO12, because Mueller PCT discusses an h5G1.1 *CO12* HuG2/G4 antibody, which would point to Evans's CO12 example, which would result in "a perfect match to SEQ ID NOS:2 and 4 recited in challenged claim 1." *Id.* at 53–55 (citing Ex. 1009, 14; Ex. 1003 ¶¶ 155–156).

Petitioner also points to Tacken as specifically teaching that eculizumab has an IgG2/IgG4 constant region (refers to Mueller 1997), and also would have motivated the ordinarily skilled artisan to create an antibody as in Evans with such a constant region (as discussed in both Mueller 1997 and Mueller PCT). *Id.* at 56–57 (citing Ex. 1003 ¶¶ 157).

Patent Owner argues that "Evans discloses only the 5G1.1 ***murine*** antibody," which is unrelated to the antibody of Mueller PCT. *See* Prelim. Resp. 62. Patent Owner argues there would have been no motivation for the skilled artisan to have combined sequences from Evans and Mueller PCT to arrive at the sequence of eculizumab and, even were one to attempt to make such an antibody, the prior art pointed toward Thomas's IgG4 sequence. *Id.* at 58–59. Patent Owner argues that only with hindsight would a person of

ordinary skill in the art have reasonably expected to successfully produce an antibody by combining a variable region of Evans with an IgG2/G4 heavy chain constant region of Mueller PCT, or would have expected it to cleave C5 and safely and effectively treat PNH. *Id* at 63–64.

2. Analysis

We find Petitioner has met its burden for institution and do not find Patent Owner's arguments persuasive on this record largely for the reasons discussed above over similar arguments relating to Grounds 1 and 2.

On the present record, we find compelling Petitioner's assertion that Bell and Tacken provide a starting point for an ordinarily skilled artisan to develop eculizumab as an h5G1.1-mAb, anti-C5 antibody, and also as to what eculizumab's structure would be – an h5G1.1-mAb with an IgG2/IgG4 constant region. *See* Ex. 1007 ¶¶ 12, 52; Ex. 1008, 1279. We similarly find compelling Petitioner's assertion that an ordinarily skilled artisan would have looked to Evans for a humanized variable domain of 5G1.1 (Bell tells one to do so to produce eculizumab for treating PNH in humans), and that, upon focusing on an antibody like that identified by Tacken (also identified as eculizumab, specific for the human terminal complement protein C5), such a skilled artisan would have produced one having SEQ ID NOS: 2 and 4, as recited in challenged independent claim 1. Mueller PCT discloses the amino acid sequence of such a human G2/G4 constant region, thus, a skilled artisan would have also found that combined isotype sequence useful in such an endeavor. Thus, at this stage of the proceeding, we find no fatal flaw to Petitioner's case under Ground 3.

In sum, based on the evidence presented at this stage in the proceeding, Petitioner has shown sufficiently that claim 1 would have been unpatentable as obvious over Evans, Bell, Tacken, and Mueller PCT as set forth in Ground 3. For the reasons discussed in Section II.K.2, above, Petitioner has also shown sufficiently that the dependent claims of the '504 patent would similarly be unpatentable under Ground 3 (claims 2–5 and 7–10) or Ground 4 (claim 6).

G. Anticipation by Bell (Ground 5)

In Ground 5, Petitioner challenges claims 1–5 and 7–10 as anticipated by Bell. Pet. 28–62. Patent Owner opposes. Prelim. Resp. 65–70. For the purpose of institution, we focus on independent claim 1.

1. The Parties' Contentions

According to Petitioner, in disclosing successful clinical studies involving eculizumab for the treatment of PNH, Bell inherently anticipates claim 1. *See* Pet. 28 (citing Ex. 1003 ¶¶ 1–14, 19–20, 162–168; Ex. 1062 ¶¶ 1–9, 19). More specifically, Petitioner contends that Bell (which incorporates Evans (Ex. 1005) and Thomas (Ex. 1010) by reference) discloses the eculizumab antibody by name, unambiguously refers to the h5G1.1 IgG2/IgG4 molecule described SEQ ID NOS: 2 and 4, and teaches its use as a treatment for PNH as required by the challenged claims. Pet. 58–62 (citing *e.g.*, Ex. 1003 ¶¶ 162–168).

Referencing its arguments with respect to Grounds 1 and 3, Petitioner asserts that an ordinarily skilled artisan would have known that eculizumab has the same sequence as the claimed SEQ ID NOS: 2 and 4 (based on Bowdish, Evans, Muller PCT, and Tacken (which disclose eculizumab's

IgG2/IgG4 structure)), and that Alexion itself stated to the Office that Bell's disclosed eculizumab contained the heavy and light chain sequences as claimed. *Id.* at 59 (citing; Ex. 1002, 1320–27 (¶¶ 5–6);[19] Ex. 1003 ¶¶ 163–164; Ex. 1025, 41).

> Petitioner asserts that
>
> > Bell inherently anticipates because (1) Alexion admits that the "eculizumab" disclosed in Bell was *necessarily* of the same sequence as recited by challenged claim 2; and (2) the prior art available to a POSA fully enabled the preparation of eculizumab as of no later than the 2005 (the publication date of Tacken).

Id. at 59 (citing Ex. 1003 ¶ 164); *see id.* at 28, 61–62; Ex. 1008, 1279–1280.

Patent Owner argues that Bell fails to expressly or inherently disclose the claim elements because it omits "the exact amino acid sequence of eculizumab." Prelim. Resp. 66–67. Patent Owner argues that "[w]hile Bell described administering 'eculizumab' for treating PNH, ***nothing*** in Bell taught the uniquely-engineered heavy chain reflected in 'SEQ ID NO: 2.'" *Id*. at 66. Patent Owner contends this is because Bell references Thomas's IgG4 antibody, which is not the amino sequence of SEQ ID NO: 2. *Id.* at 66–67.

Patent Owner contends that Bell's "mere naming of an investigational product (*e.g.*, 'eculizumab') . . . does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product" unless "a POSA could have ***necessarily*** determined that later claimed

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[19] Declaration of Laural S. Boone, J.D., PhD., submitted during the prosecution of the '504 patent.

structure/composition from the information publicly available as of the priority date." *Id.* at 68–69 (citing *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018) ("*Endo Pharms*.")). Patent Owner argues that eculizumab was not available to the public and its sequence was not disclosed as of Bell's date. *Id.* at 69–70 (citing Ex. 1002, 737–740).[20]

Patent Owner also argues that Bell fails to enable the invention of claim 2 because Petitioner's theory requires consideration of Bowdish, Evans, Mueller PCT, and Tacken, and such a combination is inappropriate for anticipation. *Id.* at 67–68 (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002)).

2. Analysis

On the present record we find Petitioner has met its burden of showing there is a reasonable likelihood that claim 1 is anticipated by Bell. We find the facts under Ground 5 largely in line with those under Grounds 1 and 3, discussed above.

Bell uses the word "eculizumab" at least 25 times throughout its disclosure, describing it as an anti-C5, h5G1.1-mAb, but without further expressly describing its structure. *See generally* Ex. 1007. The record suggests that one of ordinary skill in the art understood "eculizumab" to refer to a specific antibody. *See, e.g.*, Ex. 1008, 1279 ("An isotype control

[20] We understand Patent Owner to cite to the Declaration of Laural S. Boone, which, in the present IPR, is found on pages 1320–27 of Exhibit 1002.

antibody, h5G1.1-mAb (5G1.1, eculiz[u]mab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5," as discussed in Mueller 1997 and Thomas); Ex. 2022 ¶¶ 102–104 (Patent Owner's declarant testifying that as of the critical date, one of ordinary skill in the art "would have understood that the term 'eculizumab' referred to a single, unique antibody with a single defined structure and primary amino acid sequence"), 119 (similar).

Consistent with the above, Bell states that eculizumab is *the* "particularly useful . . . anti-C5 antibody . . . h5G1.1-mAb," discussed throughout its disclosure as a therapy for PNH patients, including, in its Examples, as a successful treatment of 11 specific PNH patients. Ex. 1007 ¶¶ 12, 21, 25, 26, 28, 30–35, 37, 52, 61, 81–96, Figs. 1A, 1B, 2, 3, 4, 5, 6a, 6b, 7, 8, 9, 10, claims 1–3, 8, 20–21, 109, 114, 119. Bell also identifies that Evans (and Thomas), which it incorporates by reference, discloses methods for eculizumab's preparation. *Id.* ¶ 52.

On the present record, we find the facts here to be highly analogous to those of both *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004) ("*Crish*"), and *Nichols Institute Diagnostics, Inc. v. Scantibodies Clinical Laboratory, Inc.*, 195 F. App'x 947 (Fed. Cir. 2006) ("*Nichols*"), each of which suggests claim 1 is anticipated.

In *Crish*, the claimed invention at issue was a "[a] purified oligonucleotide comprising at least . . . the nucleotide sequence from 521 to 2473 of SEQ ID NO:1, and wherein said portion . . . has promoter activity." *Crish*, 393 F.3d at 1254. So, similar to the presently claimed pair of amino acid sequences providing an antibody (eculizumab) that binds C5, the

invention of *Crish* was a sequence of oligonucleotides that had promoter activity, namely "the hINV promoter."

Further, the issue in *Crish* was whether a publication by inventor Crish disclosing the complete structure of hINV as a plasmid, but not the express sequence of the promoter region as claimed, anticipated the claim. *Id.* at 1255 *et seq*. Crish argued that those working in the relevant field had used the disclosed plasmid and sequenced it to obtain a different promoter sequence from the claimed sequence. *Id.* at 1255. Crish argued that those of ordinary skill in the art would not have then recognized the claimed sequence in view of such results obtained by other workers. *Id.*

The similarities to this case are apparent. Here, we also have prior art disclosing eculizumab, which Bell discloses as useful in the treatment PNH. Also here, Patent Owner argues that no one could have known the claimed amino acid sequences for eculizumab and, in fact, would have looked to the wrong antibody therefor (i.e., to Thomas's disclosure of an IgG4 antibody rather than the claimed IgG2/IgG4 antibody). Crish's claimed SEQ ID NO: 1 was obtained by sequencing the same plasmid disclosed in the prior art reference. *Id.* at 1256. Here, the '504 patent itself states that Evans teaches an antibody that binds to C5 and that it discloses a preferred whole antibody, which was later named eculizumab.

The Federal Circuit held in *Crish* that "[t]he sequence is the identity of the structure of the gene, not merely one of its properties." *Id.* at 1258. The Court further recognized that "one cannot establish novelty by claiming a known material," i.e., the sequence of nucleotides in *Crish's* gene/promoter. *Id.* The Court held that hINV was known and its promoter

region identified in the inventor's own prior art by size and location, if not by its sequence, and "[t]he only arguable contribution to the art that Crish's [claimed invention] makes is the identification of the nucleotide sequence of the promoter region of hINV." *Id.* The Court further held that "[t]he starting material plasmid necessarily contains the gene of interest including the promoter region," thus, "the claims necessarily encompass the gene incorporated in the starting material plasmid." *Id.* at 1259.

The Federal Circuit held that, in claiming SEQ ID NO: 1, "Crish [was] claiming what Crish earlier disclosed," and "Crish cannot rely upon the inability of another worker to correctly sequence the promoter region of the hINV gene from [the plasmid] . . . when he has sequenced it accurately himself." *Id.* Thus, the Federal Circuit concluded that the Crish-published prior art and its disclosed starting materials anticipated the claim. *Id.*

Here, like *Crish*, the asserted prior art, i.e., Bell (with its incorporation of Evans and Thomas), is Alexion's, and at least to some degree, the '504 patent inventor's own work.[21] Further, here, like *Crish*, the prior art discloses the claimed antibody, eculizumab, and how to construct it, even if

[21] We note that Bell, Evans, and Thomas are all associated with Alexion: Two of the named inventors of the '504 patent (Leonard Bell and Russell P. Rother) are also named inventors of Bell. *See* Ex. 1001, code (72); Ex. 1007, code (76)). Two of the named inventors of the '504 patent (Russell P. Rother and Mark J. Evans) are also named inventors of Evans *See* Ex. 1001, code (72); Ex. 1005, codes (73), (75); Ex. 1004, code (76) (correspondence address). And all of the named inventors of the '504 patent (Leonard Bell, Russell P. Rother, and Mark J. Evans) are also authors of Thomas. *See* Ex. 1001, code (72); Ex. 1010, 1389.

there may have been some confusion by those in the field over precisely the structure of the antibody's heavy chain (i.e., IgG4 or IgG2/IgG4). Therefore, it would appear that, here, the same conclusion as in *Crish* would be appropriate.

Nichols is very similar to *Crish*, and its facts are similar to those of the present record. In *Nichols*, the claimed invention was an antibody (or fragment) that selectively binds a peptide of hPTH that has one of six peptide sequences, i.e., SEQ ID Nos 1–6, which were hPTH 1–10, hPTH 1–9, hPTH 1–8, hPTH 1–7, hPTH 1–6, and hPTH 1–5. *Nichols*, 195 F. App'x at 949. The inventors, before their patent application, published an abstract disclosing that they developed a mixture of ten antibodies that bound to specific peptides of hPTH (i.e., hPTH 1–37); however, the true significance of the antibody mixture was not recognized at the abstract's publication.

There was no dispute in *Nichols* that the claimed antibody was present in the serum disclosed in the abstract. *Id.* at 950–51. Here, there is no dispute that the antibody Bell used to treat PNH is eculizumab. And here, as noted above, the '504 patent itself states that Evans discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See e.g.,* Ex. 1001, 12:28–57. Further, the inventor in *Nichols* testified that the claimed antibody was isolated from the serum disclosed in the abstract using known methods. *Nichols*, 195 F. App'x at 950–51. The *Nichols* patentee also argued that the abstract disclosed that the antibodies *predominantly* bound to the hPTH peptides, but that the claimed antibody required "selective" binding, and also that no one recognized the significance of the claimed antibody until after the abstract was published. *Id*.

The Federal Circuit in *Nichols* held that the abstract inherently anticipated the claimed antibody because, if it were isolated from the disclosed serum, using known methods, the isolated antibody would exhibit the claimed binding property, and recognition of the inherent disclosure by those of skill in the art was not needed. *Id.* Therefore, it would appear that, here, the same conclusion as in *Nichols* would be appropriate.

Thus, applying *Crish*, Bell's disclosure of eculizumab and its use in treating PNH is the disclosure of the identity of the antibody of claim 1, and its use in the recited method. Likewise, applying *Nichols*, disclosure of the existence of eculizumab, even as a generic reference to the antibody (like disclosing the preparation of sera of a mixture of unidentified antibodies), is an inherent disclosure of the claimed antibody, even if its precise sequence was unappreciated at the time.

We are unpersuaded by Patent Owner's citation to *Endo Pharms.*, which, on this record, we find distinguishable on its facts. In *Endo Pharms.*, the Federal Circuit found a claim to a formulation including (1) testosterone undecanoate in a certain mixture/ratio of (2) castor oil and (3) benzyl benzoate was not inherently disclosed by prior art articles reporting clinical studies—the prior art did not disclose the use of any co-solvent with castor oil—however, it was established that the actual formulation used in the reported studies had the claimed amounts of castor oil and benzyl benzoate. *Endo Pharms.*, 894 F.3d at 1377–78. In *Endo Pharms.*, the evidence asserted for the inherency of the unreported benzyl benzoate element was pharmacokinetic performance data, but such was not argued to be attributable only to the claimed vehicle formulation, and the "prior art was

replete with potential co-solvents" that could have been used in place of benzyl benzoate. *Id.* at 1382. Thus, benzyl benzoate and the claimed ratio of it to castor oil was not necessarily disclosed. *Id.*

The Federal Circuit held that this uncertainty in mixture composition and the possible variability in mixtures that could achieve the same reported results fell short of the holding in *Crish*, where the claim was to a specific oligonucleotide, which, but for its claimed promoter sequence, was disclosed in the prior art. *Id.* at 1383. We find the facts here more like those of *Crish* and less like those of *Endo Pharms.,* because there appears to be no dispute here that eculizumab, as disclosed by Bell, *is* the claimed antibody.

As for whether eculizumab (the antibody of claim 1) was enabled by Bell, we find that the present record supports that it was. Bell is explicit that Evans described "[m]ethods for the preparation of h5G1.1, h5G1.1-scFv and other functional fragments of h5G1.1." Ex. 1007 ¶ 52. Furthermore, Petitioner asserts, in addition to Bell's explicit reference to Evans, the knowledge of those of ordinary skill in the art included that eculizumab had a human hybrid IgG2/IgG4 constant domain. *See, e.g.*, Ex. 1008, 1279. Moreover, the '504 patent, itself, refers to Thomas (incorporated by Bell) as disclosing that eculizumab "is a humanized monoclonal antibody directed against the terminal complement protein C5," and states that Evans (also a part of Bell), discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001 1:56–57, 12:16–31. Therefore, on the present record, we are unpersuaded regarding Patent Owner's non-enablement argument.

Regarding Patent Owner's argument that Petitioner's citation to Bowdish, Evans, Mueller PCT, and Tacken implicates obviousness and is inappropriate for an anticipation ground, we understand that Petitioner cites these references as part of the background understanding of one of ordinary skill in the art. Petitioner states, "[t]he teachings of at least Bowdish and Evans, and Evans and Mueller PCT, all in view of Tacken, provided POSA with multiple direct routes to [the eculizumab amino] sequence." Pet. 58. Each of these references predates Bell, therefore, their teachings about eculizumab / 5G1.1 antibodies would have been a part of the general knowledge an ordinarily skilled artisan would have brought to their reading of Bell. *See* Ex. 1004; Ex. 1005; Ex. 1008; Ex. 1009. We understand Petitioner's point to be that when Bell mentions "eculizumab," it would invoke such an understanding of the antibody in the ordinarily skilled artisan reading the reference. Under Ground 5, Petitioner does not suggest combining with Bell any teachings from these references, other than Evans, which Bell incorporates by reference.

Again, to summarize, based on the evidence presented at this stage in the proceedings, Petitioner has shown that there is reasonable likelihood that at least claim 1 of the '504 patent is anticipated by Bell, for the reasons articulated under Ground 5.

III. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner contends that we should exercise our discretion to deny the Petition under 35 U.S.C § 325(d). Prelim. Resp. 1–2, 17–32; Sur-reply 1–6. According to Patent Owner, prior art asserted and arguments presented

in the Petition are the same as, or cumulative of, art and arguments previously presented to the Office. Prelim. Resp. 17–25. Patent Owner also argues that Petitioner has not shown the Office erred in a manner material to patentability of challenged claims. *Id.* at 25–32. Petitioner disagrees with both points. Pet. 65–78; Reply 1–6; Ex. 1003 ¶¶ 175–189.

A. Principles of Law

Institution of an *inter partes* review is discretionary. *See Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 273 (2016) (explaining that because § 314 includes no mandate to institute review, "the agency's decision to deny a petition is a matter committed to the Patent Office's discretion"); *see also Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (stating that under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding").

Under § 325(d), in determining whether to institute an *inter partes* review, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." One of the guideposts for our discretion is 35 U.S.C. § 325(d), which provides, in relevant part:

> MULTIPLE PROCEEDINGS -- . . . In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

Thus, 35 U.S.C. § 325(d) identifies two separate issues that the Director may consider in exercising discretion to deny institution of review:

whether the petition presents to the Office the same or substantially the same art previously presented to the Office; and whether the petition presents to the Office the same or substantially the same arguments previously presented to the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (designated precedential March 24, 2020) ("*Advanced Bionics*"). We consider multiple factors when determining whether to exercise our discretion under § 325(d), including:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (informative; precedential as to § III.C.5, first paragraph) (paragraphing added). These 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.

We integrate the above considerations into the *Advanced Bionics* two-part framework in deciding discretionary denial under § 325(d), first considering *Becton, Dickinson* factors (a), (b), and (d) to determine whether the same or substantially the same art or arguments were previously presented to the Office, and if so, evaluating *Becton, Dickinson* factors (c), (e), and (f) to determine whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, 7–11.

B. *Advanced Bionics* Part One

With respect to the first part of the *Advanced Bionics* analysis, we address "whether the same or substantially the same art . . . w[as] previously presented to the Office." *Advanced Bionics*, 7–8 (stating that "[p]reviously presented art includes . . . art provided to the Office, such as on an Information Disclosure Statement (IDS)").[22] Patent Owner contends that Evans, Wang, and a counterpart reference to Bell were disclosed in the prosecution leading to the issuance of the '504 patent. Prelim. Resp. 17–18,

[22] Although the parties also address the alternative question of whether the same or substantially the same *arguments* were previously presented to the Office, that analysis is not necessary here, but is subsumed, in relevant part, in our discussion of the second prong of *Advanced Bionics*.

20–22. Patent Owner further points to the '435 patent[23] and Mueller 1997 (Ex. 1006) as cumulative of Bowdish and Mueller PCT, respectively. *Id.*

In response, Petitioner characterizes the'435 patent as a "*counterpart*" and "parent of Bowdish," but fails to identify any relevant differences between the two references. *See* Reply 1–2. More substantively, Petitioner argues that Mueller PCT is not cumulative to Mueller 1997 because only the former "discloses the complete IgG2/G4 constant domain used in eculizumab." Reply 2 (citing Pet. 67–68, 68 n.6).[24] Petitioner further points out that Patent Owner identifies no citation to Tacken in the prosecution leading to the issuance of the '504 patent "despite Tacken's express teaching that eculizumab contains the IgG2/G4 constant domain." *Id.* at 2.[25]

Patent Owner also points to the prosecution history of the later-issued '189 and '809 child patents, wherein Patent Owner had

> submitted the entire history of each of Amgen's IPRs against the '880, '504, and '149 patents, including all the references cited in those IPRs including Bowdish, Evans, Bell, Tacken, and Mueller PCT as well as all briefs, expert reports, and testimony, early in the prosecution to be considered by [the Examiners].

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[23] Bowdish et al., US 7,482,435 B2, issued Jan. 27, 2009. (Ex. 2016).

[24] Petitioner's contention is undercut somewhat by "Dr. Ravetch's characterization of Mueller PCT as "a '***companion*** patent application describing the ***same work*** published in the Mueller 1997 article." *See* Sur-reply 4 (citing Ex. 1003 ¶¶ 62, 102).

[25] Although Petitioner further argues that mere citation of references in an IDS may not be sufficient to satisfy the first element of Advanced Bionics, that line of inquiry is not necessary here. *See* Reply 1–2.

Prelim. Resp. 22–23; *see also* Ex. 1032, 48 (IDS in '189 prosecution disclosing IPR petitions); Ex. 1032, 27, 38 (IDS in '189 prosecution disclosing Mueller PCT and Tacken, respectively). Patent Owner argues that the Examiner "expressly stated in many of his Office Actions that he considered each IDS submitted and, when making his rejections, noted that the references used were listed on an IDS," and evidence of such appears on the face of the child patents. *See* Prelim. Resp. 22 (citing Ex. 1002, 1036); Ex. 3002, code (56); Ex. 3003, code (56).

Like the claims at issue here, the claims of the child patents recite, in relevant part, a method of treating a patient suffering from PNH using an antibody that "comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." *See, e.g.*, Ex. 300xx, 39:15–24; Ex. 300xy, 39:14–20. Moreover, as with the present IPR, a major issue addressed by the Examiner in the child patents was whether the hybrid IgG4/IgG2 heavy chain described by SEQ ID NO: 2 was known or obvious over the prior art. *See*, *e.g.*, Ex. 2102, 14840–43 (Alexion's argument in the '019 prosecution that the prior art "repeatedly and consistently described 'eculizumab' as having an IgG4 heavy chain constant region" (capitalization normalized)), 14854–55 (similar), 14874 (Examiner's Reasons for Allowance for the '019 patent stating, e.g., that Evans, identified as the closest prior art, "does not teach an antibody that binds C5 which have a H and L chain with SEQ ID Nos: 2 and 4, respectively"). As such, and in light of the unique record before us, we agree with Patent Owner that all of the references relied on by Petitioner here "previously were presented to the

Office" as required by § 325(d) and *Advanced Bionics*. Accordingly, we proceed to part two of the analysis.

C. *Advanced Bionics* Part Two

In the second phase of our inquiry, we consider whether the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, 7–11. Petitioner raises at least four arguments for why the Examiner allegedly erred in the prosecution of '504 and child patents. *See* Pet. 70–78; Reply 3–6. For the purpose of our analysis, we find it sufficient to address only two of those arguments.

1. Tacken

Petitioner argues that the Examiner of the child patents overlooked or misapprehended the significance of Tacken's statement that eculizumab contains an IgG2/G4 constant region and, thus, did not appreciate the significance of the IgG2/G4 sequence disclosed in Mueller PCT. *See* Pet. 71–73; Reply 5–6; Ex. 1003 ¶¶ 178, 180–182. In this respect, Petitioner points to Alexion's Response to an Office Action in the prosecution of the '189 patent, which avers that

> the literature as of March 15, 2007 . . . consistently identified eculizumab as the antibody described in the "Thomas" publication . . . which has a naturally-occurring "IgG4" heavy chain constant region. Accordingly, a person of ordinary skill in the art as of March 15, 2007 would have had ***no doubt*** that "eculizumab" was Thomas's IgG4-isotpe humanized antibody, because the pertinent literature ***consistently and unambiguously*** said so[.]

Pet. 72 (citing Ex. 1036, 6). As noted by Petitioner, Alexion "the listed several references that purportedly referred to eculizumab as an IgG4

antibody," via citation to Thomas. *Id.* Ex. 1036, 6–8. Petitioner argues that Alexion's characterization of the art was incomplete and inaccurate for failing to account for Tacken. Pet. 73. For essentially the reasons discussed in Section II.K.1, above, we agree with Petitioner.

As such, we find it error for the Examiner to have not expressly considered Tacken in the context of the other references Alexion pointed to as allegedly demonstrating the "consistent teachings as of March 15, 2007 that 'eculizumab was the IgG4 antibody of Thomas." Ex. 2102, 14840–14843, 14854. But for this error, the Examiner would have better appreciated the disclosure of Mueller PCT. *See* Ex. 1003 ¶¶ 178, 180–182 (Dr. Ravetch's testimony that "most critically, Alexion failed to provide its own 2005 publication, the Tacken article, that teaches that "eculizumab" contains an IgG2/G4 constant domain").

2. Bowdish and Evans

Petitioner further argues that, during the examination of the child patents, the Examiner erred in evaluating Bowdish and Evans by relying on Alexion's comparison of Bowdish's *humanized* IgG2/G4 TPO-mimetic antibody (5G1.1+peptide antibody), with sequences of Evans's *mouse* 5G1.1 sequence, instead of using Evans's *humanized* 5G1.1 sequence as the comparator, which would have shown "no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert." Pet. 73–75; Reply 6; Ex, 1035, 6–7; Ex. 1036, 13–16. "This, unsurprisingly revealed a mismatch" in the sequences. Pet. 73; *see* Ex. 1036, 15 (showing alignment between Bowdish SEQ ID NO: 67 (Ex. 1004 ¶ 49) and the "heavy chain variable region of [mouse] antibody 5G1.1" (Evans Fig. 19 (Ex. 1005, 10:9–21, Fig. 19)). But,

according to Petitioner and its technical expert, Dr. Ravetch, one of ordinary skill in the art would have understood that the humanized nature of Bowdish's 5G1.1+peptide antibody, and that a comparison using Evans's humanized 5G1.1 sequence would have shown "no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert." Pet. 74; Ex. 1003 ¶¶ 83 (citing Ex. 1004 ¶ 192 as disclosing that Bowdish used "anti-human IgG" to detect 5G1.1), 85, 183– 184.

According to Petitioner, the comparison presented during prosecution was predicated on Alexion's representation to the examiner that Bowdish's "[c]onstruction of 5G1.1" would have directed a POSA only to Evans's mouse antibody in Examples 7–10. Pet. 74–76 (citing Ex. 1036, 13). Petitioner contends that Alexion's argument to the Examiner ignored the express description of other, more pertinent, examples in Evans. In particular,

> Evans'[s] Example 11 expressly teaches humanized 5G1.1 scFv **constructs** and is entitled "**Construction** and Expression of Recombinant mAbs." (EX1005, 42:56-45:33 (emphasis added).) Example 11 also states: "Recombinant DNA **constructions** encoding the recombinant mAbs comprising the 5G1.1 CDRs are prepared by conventional recombinant DNA methods[.]" (EX1005, 42:59-62 (emphasis added).) Evans also discloses "CDR sequences that are useful in the **construction** of the humanized antibodies of the invention[.]" (EX1005, 8:50-54 (emphasis added).)

Id. at 75. Instead, Petitioner argues, "Alexion focused the Examiner on [Evans's] Example 7, entitled "Preparation of anti-C5 Monoclonal Antibodies," which discloses preparing (not constructing) the parent 5G1.1

mouse antibody from prior art mouse hybridomas." *Id.* (citing Ex. 1005, 37:34–39:30).[26]

We agree with Petitioner that, the Examiner was persuaded by Alexion's comparison, as evidenced by the Reason for Allowance:

> Evan's [*sic*] scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for Bowdish's TPO mimetic compound would still have revealed a mismatch in amino acids beyond those that Bowdish identified as the TPO mimetic peptide insert.

Pet. 73 (citing Ex. 1035, 006–07; Ex. 1003 ¶ 183).

Patent Owner presents no specific rebuttal, instead merely asserting that Petitioner's "purported errors are the same flawed arguments Samsung asserts in its Petition, which are fully accounted for in Alexion's POPR." Reply 6. We address the teachings of Bowdish and Evans in Section II.K, above.

Considering the record before us, we agree with Petitioner that the Examiner erred in crediting Alexion's comparison between Bowdish's humanized IgG2/G4 TPO-mimetic antibody and Evans's mouse 5G1.1 sequence, without considering the more pertinent comparison between Bowdish's sequence and Evan's humanized 5G1.1 sequence.

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[26] Although not necessary to our finding of error sufficient to satisfy the second prong of *Advanced Bionics*, Petitioner plausibly argues that the Examiner was also misled by Alexion's incorrect characterization of Evans as disclosing "multiple options" for heavy chain CDR3—whereas, "all nine humanized scFv sequences of Evans have only one unique HCDR3 sequence (YFFGSSPNWYFDV), not 'multiple options.' (*See* EX1005, 42:56-45:33; *see also supra* VIII.C; EX1003, ¶186, Appendix A.)." Pet. 76.

3. Conclusion

Having considered the argument and evidence of record, and for the reasons above, we decline to exercise our discretion under section 325(d) to deny institution.

IV. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 314(a)

Patent Owner points to § 314(a)[27] as a basis for denying institution but provides no substantive argument or evidence on this point. *See* Prelim. Resp. 2 (citation), 4 (citation), 17 (section heading), 32 (citation in parenthetical). At best, Patent Owner asserts that if we find "that fewer than all five Grounds meet the standard for Section 325(d), institution of Samsung's petition should still be denied in full, because institution on all five Grounds 'would not be an efficient use of the Board's time and resources.'" Prelim. Resp. 32 (citing *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 41–43 (PTAB Jan. 24, 2019) (informative)). Because we decline to exercise our discretion with respect to any of the Grounds under § 325(d), the Board's *Deeper* decision is inapposite.

V. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of showing that claims 1–10 of the

[27] Under certain circumstances, the Board may apply its discretion under § 314(a) to deny institution in light of a parallel district court proceeding involving the same patent. *See*, *e.g.*, *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential). But as noted by Petitioner, the patent at issue here "has never been asserted in any litigation." Pet. 65.

'504 patent are unpatentable under at least one ground. Accordingly, we institute an *inter partes* review of the challenged claims of the '504 patent on all grounds alleged by Petitioner. This decision does not reflect a final determination on the patentability of the claim.

VI. ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claims 1–10 of the '504 patent, 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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