Trials@uspto.gov
571.272.7822

Paper 9
Entered: December 19, 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.

IPR2023-01070
Patent 10,703,809 B1

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

FLAX, *Administrative Patent Judge*.

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

I. INTRODUCTION

Alexion Pharmaceuticals, Inc. ("Patent Owner") is the owner of U.S. Patent 10,703,809 B1 ("the '809 patent"). Paper 3, 1. On June 16, 2023, Samsung Bioepis Co., Ltd. ("Petitioner") filed a Petition for *inter partes* review challenging the patentability of claims 1–29 (all claims) of the '809 patent. Paper 1, 1 ("Pet."). On October 13, 2023, Patent Owner filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). With our authorization (*see* Ex. 3001), Petitioner filed a Reply to the Preliminary Response (Paper 7, "Prelim. Reply"), and Patent Owner filed a respective Sur-Reply (Paper 8, "Prelim. Sur-Reply").

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute trial in an *inter partes* review. We may institute an *inter partes* review if the information presented in the petition filed under 35 U.S.C. § 311, and any preliminary response filed under § 313, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

After reviewing the parties' submissions in view of the preliminary record, we conclude Petitioner demonstrates a reasonable likelihood it would prevail in showing that at least one challenged claim of the '809 patent is unpatentable under the presented grounds. *See* Pet.; Prelim. Resp.; Prelim. Reply; Prelim. Sur-Reply. Therefore, we grant institution of *inter partes* review. 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 determine institution should be not be denied.

Our reasoning is discussed below.

A. REAL PARTIES-IN-INTEREST

Petitioner identifies itself, "Samsung Bioepis Co., Ltd.," as a real party-in-interest. Pet. 2. Patent Owner states, "Alexion Pharmaceuticals, Inc. is the owner of U.S. Patent No. 10,703,809 (the '809 patent") and the real-party-in-interest. Alexion Pharmaceuticals, Inc. is wholly owned by AstraZeneca PLC." Paper 3, 1.

B. RELATED MATTERS

Petitioner states,

> The '809 patent is not currently involved in any litigation or Patent Office proceedings; the '809 patent has not previously been challenged in any Patent Office proceeding. An *inter partes* review of related patent U.S. 9,725,504 filed by Amgen, Inc. was instituted as IPR2019-00739 ("Amgen IPR"). (EX1024.) No final written decision was issued because the Amgen IPR was terminated following settlement. (EX1026.) The '809 patent is related to U.S. Patent Nos. 9,732,149, 9,718,880, 9,725,504, and 10,590,189 which Petitioner recently challenged in petitions for *inter partes* review IPR2023-00933 ('149), IPR2023-00998 ('880), IPR2023-00999 ('504), and IPR2023-01069 ('189).

Pet. 2.

Patent Owner states,

> On June 16, 2023, Petitioner filed a Petition for *Inter Partes* Review of U.S. Patent No. 10,590,189 (IPR2023-01069), which is related to the '809 patent. This Petition is also related to:
>
> - *Amgen, Inc.* v. *Alexion Pharmaceuticals, Inc.*, IPR2019-00739 (U.S. Patent No. 9,725,504) ("the '504 patent")
> - *Amgen, Inc.* v. *Alexion Pharmaceuticals, Inc.*, IPR2019-00740 (U.S. Patent No. 9,718,880) ("the '880 patent")
> - *Amgen, Inc.* v. *Alexion Pharmaceuticals, Inc.*, IPR2019-00741 (U.S. Patent No. 9,732,149) ("the '149 patent")

- *Samsung Bioepis Co. Ltd.* v. *Alexion Pharmaceuticals, Inc.*, IPR2023-00933 (the '149 patent)
- *Samsung Bioepis Co. Ltd.* v. *Alexion Pharmaceuticals, Inc.*, IPR2023-00998 (the '880 patent)
- *Samsung Bioepis Co. Ltd.* v. *Alexion Pharmaceuticals, Inc.*, IPR2023-00999 (the '504 patent)

Each of the '504 patent, the '880 patent, and the '149 patent is also related to the '809 patent.

Paper 3, 1–2.

The '809 patent states that:

> This application is a continuation of U.S. patent application Ser. No. 16/750,978, filed Jan. 23, 2020, which is a continuation of U.S. Pat. No. 10,590,189, issued Mar. 17, 2020, which is a continuation of U.S. Pat. No. 9,732,149, issued Aug. 15, 2017, which is a continuation of U.S. Pat. No. 9,725,504, issued Aug. 8, 2017, which is a continuation of U.S. Pat. No. 9,718,880, issued Aug. 1, 2017, which is a continuation of U.S. patent application Ser. No. 13/426,973, filed Mar. 22, 2012, which is a continuation of U.S. patent application Ser. No. 12/225,040, filed on May 13, 2009, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/US2007/006606, filed Mar. 15, 2007. The contents of the aforementioned applications are hereby incorporated by reference in their entireties.

Ex. 1001, 1:9–22, code (63). The parties appear to agree that this first-listed March 15, 2007, filing date is the priority date of the '809 patent. Pet. 1; Prelim. Resp. 2.

C. THE '809 PATENT AND RELEVANT TECHNICAL BACKGROUND

The '809 patent issued on July, 7, 2020, from U.S. Application 16/804,567, which was filed on February 28, 2020. Ex. 1001, codes (10), (45), (21), (22). As noted above, the '809 patent indicates priority to an earlier application filed on March 15, 2007, and this priority date is not

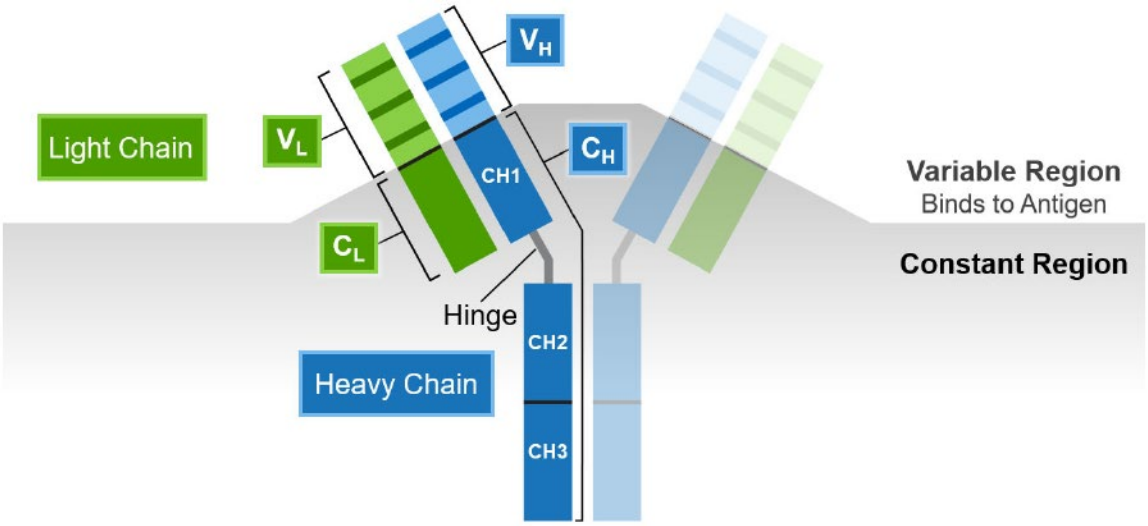
contested at this stage of the proceeding. The '809 patent identifies Leonard Bell, Russel P. Rother, and Mark J. Evans as inventors and "Alexion Pharmaceuticals, Inc." as the applicant and assignee.[1] *Id.* at codes (71), (72), (73). The invention of the '809 patent relates to the pharmaceutical antibody "eculizumab," which is a humanized anti-C5 antibody, and its use in treating patients with paroxysmal nocturnal hemoglobinuria (PNH). *See id.* at Abstract.

PNH is an acquired hemolytic disease resulting from loss of function in certain cytoprotective proteins. *Id.* at 1:35–63. 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 that 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." *Id.* As further explained by Petitioner's witness, Dr. Jeffrey V. Ravetch,[2] "[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] As discussed *infra*, these inventors are also named in several references asserted here as prior art, either as inventors or authors.

[2] Declaration of Jeffrey V. Ravetch, MD, PhD (Ex. 1003, "Ravetch Declaration").

For background, we reproduce a figure from the Ravetch Declaration, illustrating the basic structure of an antibody:



Basic domain structure of antibody

Id. ¶ 37; Pet. 5–6. The figure above shows a basic antibody structure having two hinged heavy chains (colored blue and labeled) and two accompanying light chains (colored green and labeled), each having constant regions (labeled C_H and C_L) and variable regions (labeled V_H and V_L), all arranged in a general "Y" shaped structure, as the variable regions and portions of the constant heavy chain regions are hinged away from one another. *See* Ex. 1003 ¶¶ 35–54. The constant regions do not bind antigens, but provide a structural framework for the antibody and coordinate the antibody's interactions with immune cells and effector molecules. *Id.* The variable regions of each chain also include three complementarity determining regions (CDR, shown as darker blue and darker green lines), which provide the antibody with antigen-binding specificity. *Id.* The constant heavy region includes sub-regions called CH1, CH2, and CH3 (the heavy chain

hinge is between CH1 and CH2), separated by framework regions. *Id.* Antibodies are composed, *inter alia*, of amino acids and can be described by their particular amino acid sequences. *Id.*

There are five classes of antibodies, with IgG being the most abundant class in humans and represented by the illustration above. *Id.* 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.*

The claims of the '809 patent are directed to using a C5 binding antibody having specific amino acid sequences at the heavy and light chains (SEQ ID NO: 2 and SEQ ID NO: 4, respectively), where C5 refers to the complement protein C5 convertase, to treat a patient having PNH. Ex. 1001, 39:13–40:57; *see also id.* at 4:60–67 (discussing SEQ ID NOS: 2 and 4), 19:60–28:42 (discussing the TRIUMPH trial treating patients with PNH), 30:38–54 ("Eculizumab Heavy chain SEQ ID NO: 2"), 30:61–31:5 ("Eculizumab Light chain SEQ ID NO: 4), 31–37 (claimed amino acid sequences).

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. *See generally id.* at 7:15–8:62. 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.* 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." *Id*. 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*. All pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase into C5a and C5b. *Id*.

Blocking the cleavage of C5 with specific antibodies, however, is known to prevent complement activation. *See, e.g.*, *id.* at 11:6–14 ("U.S. Pat. No. 6,353,245 [Evans[3]] 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."); 12:22–37 (describing "[c]ertain antibodies" known to be "specific to human complement are known (U.S. Pat. No. 6,353,245 [Evans])."). According to the '809 patent:

> [s]uitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Pat. No. 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Pat. No. 5,660,825), ***U.S. Pat. No. 6,353,245 [Evans] teaches an antibody which binds to C5*** and inhibits cleavage into C5a and C5b thereby decreasing the

[3] Mark J. Evans et al., US 6,355,245 B1, issued Mar. 12, 2002 (Ex. 1005, "Evans"). In addition to Mark J. Evans, this patent lists Russell P. Rother as an inventor, both of whom are listed on the '809 patent as inventors. Ex. 1005, code (75). Moreover, Evans, like the '809 patent, identifies "Alexion Pharmaceuticals, Inc." as the assignee. *Id.* at code (73).

> formation not only of C5a but also the downstream complement components.

Id. at 11:6–14 (emphasis added). The Specification further states,

> A preferred method of inhibiting complement activity is to ***use a monoclonal antibody which binds to complement C5 and inhibits cleavage***. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. ***Such antibodies which are specific to human complement are known (U.S. Pat. No. 6,355,245 [Evans]). These antibodies disclosed in U.S. Pat. No. 6,355,245 [Evans] include a preferred whole antibody (now named eculizumab)***.

Id. at 12:29–37 (emphasis added). The Specification also states, "[e]culizumab [is] a humanized monoclonal antibody against C5 that inhibits terminal complement activation" and "eculizumab treatment appears to be safe and effective therapy for PNH." *Id.* at Abstract, 1:66–2:1 (citing Thomas C. Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1010, "Thomas")[4]).

According to Patent Owner "[t]he challenged claims of the '809 patent generally cover methods of treating paroxysmal nocturnal hemoglobinuria ('PNH') patients comprising intravenously administering pharmaceutical compositions of a non-naturally occurring, uniquely-engineered humanized antibody developed by Alexion and marketed as SOLIRIS®." Prelim. Resp. 4, 9. It is undisputed in this proceeding that

[4] In addition to Thomas C. Thomas, the Thomas article lists as authors, *inter alia*, Russell P. Rother and Mark J. Evans, who are also listed as inventors on the '809 patent and of Evans. *Compare* Ex. 1001, code (72), *with* Ex. 1010, 1389, and Ex. 1005, code (75).

"eculizumab" is marketed by Patent Owner as Soliris, and refers to a specific antibody having the primary amino acid sequence of SEQ ID NO: 2 and SEQ ID NO:4. *See*, *e.g.*, Prelim. Resp. 1 ("claims covering the unique sequence of SOLIRIS® in . . . the '809 patent"); Pet. 13; Ex. 1001, 20:50–51 ("eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.)"); Ex. 2022 ¶¶ 98–103, 133.

The '809 patent identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab Heavy [C]hain" and "Eculizumab Light [C]hain," respectively. Ex. 1001, 30:37–54, 30:61–31:4. It is undisputed here 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. 9–11; Prelim. Resp. 4–5, 7, 9–10; Ex. 2100, 1258 (Figure 2).

The sole independent claim of the '809 patent reads as follows:

> 1. A method of treating a patient having paroxysmal nocturnal hemoglobinuria (PNH), wherein the method comprises intravenously administering to the patient 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, 39:15–20. We reproduce SEQ ID NO: 2 and SEQ ID NO: 4 from the '809 patent Specification below:

Eculizumab Heavy chain

SEQ ID NO: 2

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG

EILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR

YFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAAL

GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS

NFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFP

PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE

EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ

PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY

KTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS

LSLSLGK

Eculizumab Light chain

SEQ ID NO: 4

DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIY

GATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF

GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ

WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV

THQGLSSPVTKSFNRGEC

Id. at 30:37–54, 30:61–31:3, 31–33, 35–37. As these two reproduced sequences state, they represent the heavy and light chains of eculizumab, i.e., the antibody of the claimed therapy. *Id.*

Independent claim 1 is followed by claims 2–29, which depend directly or indirectly from claim 1. *Id.* at 39:21–40:57. These dependent claims further define the recited method by adding limitations regarding the dosage form used (e.g., single units or certain dosages), treatment regimen, characteristics of the treated patient (e.g., the patient is anemic), and results of treatment (e.g., the patient exhibits decreased lactate dehydrogenase levels). *Id.*

D. PETITIONER'S ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts twelve (12) grounds for unpatentability of the challenged claims, as follows:

Ground	Claims Challenged	35 U.S.C. §[5]	Reference(s)/Basis
1	1–3, 6–14, 17	103(a)	Bell,[6] Bowdish,[7] Evans, Tacken,[8] Mueller PCT[9]
2	15	103(a)	Bell, Bowdish, Evans, Hillmen,[10] Tacken, Mueller PCT
3	16	103(a)	Bell, Bowdish, Evans,

[5] The priority date of the '809 patent is March 15, 2007, which is before the relevant AIA revisions to the Patent Act took effect on March 16, 2013. 35 U.S.C. § 100 (note). Therefore, pre-AIA § 102 and § 103 apply.

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

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

[8] 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).

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

[10] Peter Hillmen, M.B., Ph.D., et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. ENGL. J. MED. 552–59 (2004) (Ex. 1011, "Hillmen").

Ground	Claims Challenged	35 U.S.C. §[5]	Reference(s)/Basis
			Hill,[11] Tacken Mueller PCT
4	4, 5, 18–26, 29	103(a)	Bell, Bowdish, Evans, Wang,[12] Tacken, Mueller PCT
5	27	103(a)	Bell, Bowdish, Evans, Wang, Hillmen, Tacken, Mueller PCT
6	28	103(a)	Bell, Bowdish, Evans, Wang, Brown,[13] Tacken, Mueller PCT
7	1–3, 6–14, 17	103(a)	Bell, Evans, Mueller PCT, Tacken
8	15	103(a)	Bell, Evans, Mueller PCT, Tacken
9	16	103(a)	Bell, Evans, Mueller PCT, Hill, Tacken
10	4, 5, 18–26, 29	103(a)	Bell, Evans, Mueller PCT, Wang, Tacken
11	27	103(a)	Bell, Evans, Mueller PCT, Wang, Hillmen, Tacken
12	28	103(a)	Bell, Evans, Mueller PCT, Wang, Brown, Tacken

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

[12] US 2005/0271660 A1, published Dec. 8, 2005 (Ex. 1044, "Wang").

[13] Duncan J.F. Brown, *The Correlation between Fatigue, Physical Function, the Systemic Inflammatory Response, and Psychological Distress in Patients with Advanced Lung Cancer*, 103(2) CANCER 377–82 (2005) (Ex. 1068, "Brown").

Id. In support of these grounds for unpatentability, Petitioner submits, *inter alia*, the Ravetch Declaration (Ex. 1003) and the Ippoliti Declaration (Ex. 1062). In support of its positions in the Preliminary Response, Patent Owner submits, *inter alia*, the Casadevall Declaration (Ex. 2022), the Trout Declaration (Ex. 2024), and the Nussenzweig Declaration (Ex. 2026). At this stage of the proceeding there is no dispute that each of these witnesses is competent to testify as to the subject matter of their respective declaration.

II. DISCUSSION

A. LEGAL STANDARDS

"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.[14] *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).

An *inter partes* review may be instituted if the information presented by a petitioner in the petition, in view of the patent owner's preliminary response and the preliminary record, shows that there is a reasonable

[14] At times we refer to certain of Patent Owner's arguments as not persuasive; however, we do not shift the ultimate burden from Petitioner. Such unpersuasiveness is in the context of the record and parties' arguments.

likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art;[15] and (4) considering objective evidence indicating obviousness or non-obviousness.[16] *KSR*, 550 U.S. at 406.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

B. ORDINARY LEVEL OF SKILL IN THE ART

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;

[15] *See infra* Section II.B.

[16] *See infra* Section II.E.

> EX1062, ¶¶14-18.) A POSA also would have knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same. (EX1003, ¶19; EX1062, ¶17.) 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. 17–18 (citing Ex. 1003 ¶¶ 16–20; Ex. 1062 ¶¶ 14–18).

Patent Owner responds,

> Alexion does not dispute Samsung's POSA definition (Petition at 17-18), 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. Under either description of a POSA, Samsung cannot prove unpatentability of the challenged claims of the '809 patent under any of its twelve fatally flawed Grounds.

Prelim. Resp. 49.

The two proposed definitions of the skilled artisan are very similar, except that Patent Owner's description more-specifically defines the field of experience of the skilled artisan.

At this stage in the proceedings, we accept and use Petitioner's proposed definition of the ordinarily skilled artisan, as being both generally unopposed by Patent Owner and inclusive of Patent Owner's supplemental definition. 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" includes Patent Owner's proposed level of experience. Pet. 17–18. We also take into account 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 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

Petitioner states, "Petitioner does not believe claim construction is necessary at this time." Pet. 19. Patent Owner does not mention claim construction at this stage of the proceeding. *See generally* Prelim. Resp.

For the purposes of this institution decision, we find it unnecessary to construe any claim language because it is readily understandable on its face and there is no dispute. *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))). As the case continues, we may determine that certain claim language should be interpreted.

D. PETITIONER'S ASSERTED PRIOR ART

1. Bell (Ex. 1007)

Bell is a U.S. Patent Application published on September 1, 2005. Ex. 1007, code (43). The first named inventor, Leonard Bell, as well as Russell P. Rother, appear to be inventors also listed on the '809 patent (and other asserted references). *Compare* Ex. 1001, code (72) *with* Ex. 1007, code (76). There is currently no dispute that Bell is prior art. *See generally* Prelim. Resp.

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." Ex. 1007 ¶ 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. *Id.* ¶ 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." *Id.* ¶¶ 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.

2. Bowdish (Ex. 1004)

Bowdish is a U.S. Patent Application published on December 18, 2003.[17] Ex. 1004, code (43). At this stage of the proceeding, there is no dispute that Bowdish constitutes prior art. *See generally* Prelim. Resp. Bowdish lists Alexion Pharmaceuticals, Inc. as the official correspondence address. Ex. 1004, code (76).

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 [thrombopoietin] peptide." *Id.* ¶ 17.

[17] According to Office records, Bowdish eventually issued as U.S. Patent 7,396,917 B2.

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 [Evans[18]], incorporated herein by reference. 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.

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.*

3. Evans (Ex. 1005)

Evans is a U.S. Patent, which issued on March 12, 2002, and indicates on its face having been assigned to Alexion Pharmaceuticals, Inc. Ex. 1005, codes (45), (73). First named inventor listed on the face of Evans, Mark J. Evans, and also named inventor Russell P. Rother, appear to be inventors also listed on the '809 patent (and other asserted references here). *Compare*

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

Ex. 1001, code (72), *with* Ex. 1005, code (75). At this stage of the proceeding, there is no dispute that Evans is prior art. *See generally* Prelim. Resp.

Evans is cited in the '809 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, 10:65–11:14, 12:29–37, 12:50–63; *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.

See id. at Fig. 19 (amino acids 85–113).

Evans describes making a series of different humanized 5G1.1 scFv[19] and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. *Id.* at 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 frame work sequence altered) scFv" which, according to Dr. Ravetch, "includes all six CDR sequences and variable regions of SEQ ID NOS: 2 and 4 of claim 1." Ex. 1003 ¶ 88 (citing Ex. 1005, Example 11 (No. 12)).

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.

4. Mueller PCT (Ex. 1009)

Mueller PCT is an international patent application published on April 3, 1997, listing Alexion Pharmaceuticals, Inc. as the applicant, and listing, *inter alia*, Mark J. Evans and Russell P. Rother as inventors (like the

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

'809 patent and other asserted references). Ex. 1009, codes (71), (72). At this stage of the proceeding, there is no dispute that Mueller PCT is prior art. *See generally* Prelim. Resp.

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." Ex. 1009, 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. 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 [t]hereinafter as 'HuG2/G4 mAb.'" *Id.* at 8:23–26.

Mueller PCT developed and tested "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, Figs. 11, 12, 15.

On pages 58–61 of Mueller PCT, the reference discloses the cDNA and amino acid sequence for the expression of "Human G2/G4."

5. Tacken (Ex. 1008)

Tacken is a journal article published in 2005. Ex. 1008, 1278. Tacken notes the reported 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), and is listed as an inventor on the '809 patent (Ex. 1001, code (72)) (and other references). There is currently no dispute that Tacken is prior art. *See generally* Prelim. Resp.

Tacken discloses "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, 1278 (Abstr.). In its section describing "Recombinant antibodies," Tacken discloses the DC-SIGN construct as comprising a humanized variable heavy chain region "genetically fused with a human hybrid IgG2/IgG4 constant domain." *Id.* at 1279 (citing Mueller 1997[20]). According to Tacken, "[a]n 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." *Id.* (citing Thomas (Ex. 1010)).

6. Hillmen (Ex. 1011)

Hillmen is a journal article published in 2004. Ex. 1011, 3.[21] In addition to Hillmen, the reference lists Russell P. Rother as an author, who is also an author of Thomas (Ex. 1010), and is listed as an inventor on the '809

[20] 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. 441–52 (1997) (Ex. 1006, "Mueller 1997").

[21] We cite Hillmen's added page numbering, as does Petitioner.

patent (Ex. 1001, code (72)). *Id.* At this stage of the proceeding, there is no dispute that Hillmen constitutes prior art. *See generally* Prelim. Resp.

Hillmen discloses a clinical trial for PNH treatment of transfusion-dependent patients with PNH by infusions of eculizumab at doses of 600 mg every week for 4 weeks, followed one week subsequent with an infusion of 900 mg, and then 900 mg every 2 weeks, for 12 weeks. Ex. 1011, 2. Hillmen states that "[c]linical and biochemical indicates of hemolysis were measured throughout the trial," which includes measuring lactate dehydrogenase levels, erythrocyte population, transfusion rates, episodes of hemoglobinuria, and quality of life. *Id.*

Hillmen concluded that "Eculizumab is safe and well tolerated in patients with PNH. This antibody against terminal complement protein CS reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion, with an associated improvement in the quality of life in patients with PNH." *Id.* According to Hillmen, the eculizumab treatments had the following results: "lactate dehydrogenase levels declined rapidly and remained reduced" (at levels slightly above normal), "significantly reduced transfusion requirements," and "a rapid improvement in the quality of life . . . as measured by the EORTC QLQ-C30." *Id.* at 9.

7. Hill (Ex. 1013)

Hill is a journal article published on June 28, 2005. Ex. 1013, 9.[22] In addition to Hill, the reference lists Russell P. Rother as an author, who is also an author of Thomas (Ex. 1010), and is listed as an inventor on the '809

[22] We cite to Hill's added page numbers, as does Petitioner.

patent (Ex. 1001, code (72)). *Id.* There is no present dispute that Hill constitutes prior art. *See generally* Prelim. Resp.

Hill reports on a clinical trial studying the long-term safety and efficacy of eculizumab in patients with PNH, where eculizumab was initially administered for 12 weeks (*see supra* summary of Hillmen) and then administered for 52 weeks at 900 mg every 12 to 14 days. Ex. 1013, 9–10, 15 (citing Hillmen). Hill states that, "[i]n no patients were antibodies against eculizumab detected." *Id.* at 13.

8. Wang (Ex. 1044)

Wang is a December 8, 2005, publication of U.S. Application 11/127,438, which was filed on May 11, 2005, and, on its face indicates it was assigned to Alexion Pharmaceuticals, Inc. Ex. 1044, codes (10), (43), (21), (22), (73). Presently, there is no dispute that Wang constitutes prior art. *See generally* Prelim. Resp.

Wang is directed to "an antibody that inhibits activation of the complement system." Ex 1044, Abstract. Wang discloses that its invention "include[s] anti-C5 antibody or antibodies that inhibit activation of the complement cascade, for example, the antibodies as described in U.S. Pat. No. 6,355,245 [Evans]." *Id.* ¶ 4; *see also id.* ¶¶ 42, 115, 174 (identifying that Wang's SEQ ID NO:2 is "described in [Evans]," which was incorporated by reference in its entirety).

Wang discloses formulations of eculizumab suitable for nebulization and pulmonary delivery. *See, e.g.*, *id.* ¶¶ 25, 60, 62, 67, 172. 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.

9. Brown (Ex. 1068)

Brown is an article published November 22, 2004, addressing the relationship between "the systemic inflammatory response and psychological distress [and] . . . fatigue." Ex. 1068, 1.[23] Presently, there is no dispute that Brown constitutes prior art. *See generally* Prelim. Resp.

Brown discloses "[t]he Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, . . . is a validated measure of fatigue," by which one may "assess quality of life in cancer patients suffering from fatigue and other anemia-related symptoms." Ex. 1068, 2. Brown further discloses that "[t]he 3-item Fatigue subscale of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30 (EORTC QLQ-C30) also was completed as a comparison measure" of quality of life. *Id.* Brown states that, "there were significant correlations between the FACIT-Fatigue and the EORTC QLQ-C30 Fatigue scales." *Id.* at 4.

E. OBJECTIVE EVIDENCE INDICATING NON-OBVIOUSNESS

Before moving on to Petitioner's grounds, which are based on obviousness, we address the parties' contentions concerning objective indicia of non-obviousness. Pet. 64–67; Prelim. Resp. 68–71.

"Objective indicia of nonobviousness can serve as an important check against hindsight bias and 'must always when present be considered.'"

[23] We cite to the added page numbering of Brown, as does Petitioner.

Merck & Cie v. Gnosis S.P.A., 808 F.3d 829, 837 (Fed. Cir. 2015). 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 objective indicia evidencing non-obviousness. *See Graham*, 383 U.S. at 17–18. Objective indicia, sometimes called secondary considerations, include, for example, commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406. Although evidence pertaining to objective indicia of non-obviousness 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 non-obviousness must have a nexus to the claimed invention. Pet. 64 (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, any long-felt and unrecognized need, or industry praise as objective evidence of non-obviousness, 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 64–66 (citing Ex. 1003 ¶¶ 189–192; Ex. 1062 ¶ 62; also discussing Ex. 1007 (Bell), Ex. 1011 (Hillmen), and Ex. 1013 (Hill)). 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 67 (citing 42 U.S.C. § 262(i)(2); Ex. 1003 ¶ 193).

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. 68–69 (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 69–70 (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 70. Patent Owner argues that, contrary to Petitioner's assertions, the claimed sequences were novel and nonobvious at the time of the invention. *Id.* at 70–71.

At this stage of the proceeding, we find Petitioner has shown sufficiently that Patent Owner's objective evidence of non-obviousness carries insufficient 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 a 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. Inc.*, 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. 68–71. At this stage of the proceeding, however, we are persuaded that Bell, Hillmen, and Hill each disclose that eculizumab was a useful treatment for PNH more than a year before the '809 patent was filed. *See* Pet. 6 (citing Ex. 1007; Ex. 1013; Ex. 1011); *see also infra* Sections II.D.1, II.D.6, II.D.7 and *supra* Section II.F. (discussing the disclosures of this, uncontested, prior art).

We also agree that the Federal Circuit's holding in *Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals USA, Inc.*, 25 F.4th 1354 (Fed. Cir. 2022), is instructive with respect to Patent Owner's evidence of copying. The Court noted that "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Id.* 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 non-obviousness 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, does not outweigh the strong evidence of obviousness. *See* Prelim. Resp. 70.

In light of the foregoing, we are not persuaded that Patent Owner's objective indicia evidence is sufficiently probative of non-obviousness 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*, 853 F.3d at 1331 (finding objective indicia evidence not probative of non-obviousness where prior art suggested the allegedly successful feature of the claimed invention).

We recognize, however, that consideration of objective indicia of non-obviousness 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, if necessary.

F. GROUNDS 1 THROUGH 6—OBVIOUSNESS OVER BELL, BOWDISH, EVANS, TACKEN, AND MULLER PCT, AND ALSO HILLMEN, HILL, WANG, AND BROWN

1. Parties' Positions

Under Ground 1, Petitioner challenges independent claim 1 and dependent claims 2, 3, 6–14, and 17 as obvious over Bell, Bowdish, Evans, Tacken, and Mueller PCT. Pet. 28–48 (citing, *inter alia*, Ex. 1003 ¶¶ 115–153; Ex. 1062 ¶¶ 25, 48, 50–51, 58–59). Regarding the obviousness of claim 15 (Ground 2), Petitioner adds the teachings of Hillmen to this prior art combination. *Id.* at 48–49 (citing, *inter alia*, Ex. 1003 ¶¶ 154–155). As for the obviousness of dependent claim 16 (Ground 3), Petitioner adds the teachings of Hill to the prior art combination. *Id.* at 50 (citing, *inter alia*, Ex. 1003 ¶ 156). Regarding the obviousness of limitations added by dependent claims 4, 5, 18–26, and 29 (Ground 4), Petitioner adds the teachings of Wang to the original combination. *Id.* at 50–55 (citing Ex. 1003 ¶¶ 142–153, 157–171; Ex. 1062 ¶¶ 53–57). For claim 27 (Ground

5), Petitioner adds both Hillmen and Wang. *Id.* at 55 (citing, *inter alia*, Ex. 1003 ¶¶ 154–155, 172). Finally, regarding the subject matter of claim 28 (Ground 6), Petitioner adds the teachings of Wang and Brown. *Id.* at 55–56 (citing, *inter alia*, Ex. 1003 ¶¶ 153, 173).

Patent Owner opposes. Prelim. Resp. 32–63 (citing, *inter alia*, Ex. 2022 ¶¶ 108–118, 123–124, 127–130, 203, 208, 210–234; Ex. 2024 ¶¶ 41, 43–56, 69–91; Ex. 2026).

Because each of Petitioner's Grounds 1–6 foundationally relies upon the same arguments and evidence and, generally, Patent Owner's arguments over these grounds are the same, we address them together.

To summarize, Petitioner asserts that the combined teachings of Bell, Bowdish, Evans, Tacken, and Mueller PCT render claim 1's method and administered antibody obvious because: (1) Bell teaches that the antibody, eculizumab, was used to treat PNH; (2) Bell points to and incorporates Evans for its teachings on eculizumab, which, paired with Bowdish, reveals the entire amino acid sequence of eculizumab, as claimed; (3) Tacken confirms that the eculizumab antibody disclosed by Bell and Evans, also known as 5G1.1 and h5G1.1, has an IgG2/IgG4 hybrid constant region; and (4) Mueller PCT also confirms that the h5G1.1 antibody has this IgG2/IgG4 constant region and also provides the sequence therefor. Pet. 28–29, 30–43. Concerning the specific limitations of dependent claims 2–29, Petitioner asserts, *inter alia*, that Bell, Wang, Hillmen, Hill, and Brown teach the specifics of the claimed dosage form, dosages, treatment regimen, patient characteristics, and therapeutic results. *Id.* at 43–56. Petitioner maps the elements/steps of independent claim 1 to the disclosures of the prior art combination, which it asserts is composed of analogous art and that there

would have been a reasonable expectation of success in its combination. *Id.* at 30–43.

Petitioner asserts that Bell (which incorporates Evans (Ex. 1005) and Thomas (Ex. 1010) by reference) discloses the eculizumab antibody by name and teaches its use as a treatment for PNH (in clinical trials, administered intravenously). Pet. 23–24, 30–31 (citing Ex. 1003 ¶¶ 115–117; Ex. 1004 ¶¶ 148–151; Ex. 1005, 18:29–43; Ex. 1007 ¶¶ 3, 12, 52, 60, 81–97; Figs. 1a, 1b, 3, 6a, 6b, 7–10; Ex. 1010; Ex. 1062 ¶¶ 39–40). Petitioner asserts that Bell's disclosure of successfully treating PNH with eculizumab was reason for the ordinarily skilled artisan to obtain the structure of the antibody and that, because Bell does not disclose it, but instead points to Evans as teaching it and how to produce it, one would look to Evans. *Id.* at 31 (citing Ex. 1003 ¶¶ 117–118, 136).

Petitioner asserts that Bowdish is also an "Alexion patent publication" that, like Bell, incorporates Evans (for its disclosure of an 5G1.1 antibody). *Id.* at 31. Petitioner asserts that the person of ordinary skill in the art looking to obtain the amino acid sequences of Bell's "h5G1.1 (eculizumab)" would also have known of Bowdish and its similar incorporation of Evans, and would have considered it analogous art as teaching the structure of the 5G1.1 (also called h5G1.1) antibody and as describing an Alexion antibody invention, like Evans and Bell. *Id.* at 36–37.

Petitioner asserts that Bowdish, which, like Bell, also incorporates Evans by reference, discloses the entirety of the claimed anti-C5 antibody, including both claimed 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. *Id.* at 31–38 (citing, *inter alia*, Ex. 1003 ¶¶ 121–130, App'x A; Ex. 1004,

page 1, Figs. 13A, 13B, ¶¶ 119–120, 191–192; Ex. 1005, page 1 (Title), Fig. 9, 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; Ex. 1022, 16:10–12; Ex. 1024, 45).

Petitioner asserts that Bowdish discloses all of claim 1's light chain sequence SEQ ID NO: 4 at its SEQ ID NO: 69, shown in Figure 13B, and all but 13 amino acids of claim 1's heavy chain sequence SEQ ID NO: 2 at its SEQ ID NO: 67, shown in Figure 13A. *Id.* at 31–32. Petitioner asserts that these missing 13 amino acids of claim 1 are due to Bowdish replacing the native CDR3 portion of Evans's antibody with a TPO mimetic peptide, but that Evans, incorporated into Bowdish by reference, discloses this native CDR3 and that this starter antibody is the claimed antibody. *Id.*

This argument is illustrated by the following figure from the Petition, incorporated from the Ravetch Declaration:

Id. at 34; *see also* Ex. 1003 ¶ 122. The figure above illustrates reverse engineering the Bowdish antibody based on its disclosure that Evans teaches 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's h5G1.1 scFv CO12,] with 5' ttg cca ATT GAA GGG CCG ACG CTG CGG CAA TGG CTG GCG CGC GCG cct gtt 3' (SEQ. ID. NO: 65)." Ex. 1004 ¶ 191; *see also* Ex. 1003 ¶ 122. Bowdish states that "[t]he 5G1+peptide was produced as a whole IgG

antibody (See **FIGS. 13A and 13B**)." Ex. 1004 ¶ 191. 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 full starting antibody having the amino acid sequence of Evans, which Petitioner asserts is eculizumab, i.e., the claimed antibody that binds C5, having SEQ ID NO: 2 and SEQ ID NO: 4.

Petitioner asserts that the ordinarily skilled artisan would have understood that Bowdish's 5G1.1 antibody framework referred to the same humanized monoclonal antibody elsewhere called h5G1.1, and that Bowdish's SEQ ID NOS: 67 and 69 "disclose the sequences of '5G1.1' antibody framework, into which only the HCDR3 was replaced for the TPO mimetic peptide graft." *See* Pet. 37–38 (citing Ex. 1003 ¶¶ 129–130; Ex. 1004, Figs. 13A, 13B, ¶ 192). Petitioner further contends that "[a] routine comparison of these sequences with Evans'[s] constructs in Example 11 would have quickly revealed that Evans'[s] SEQ ID NO:20 is identical to the variable regions in Bowdish's SEQ ID NO:69 and 67, except for the HCDR3 sequence," which could be readily replaced to generate the original eculizumab antibody. *See id*.

Petitioner also points to Tacken as analogous art because it is from the same field of study (humanized, anti-C5 antibodies, including eculizumab) as Bell and Bowdish (and the claims), represents more work of Alexion, and is pertinent to the issue of eculizumab's structure. *Id.* at 41 (citing Ex. 1008, 1278–79; Ex. 1003 ¶¶ 135–138). Petitioner asserts that Tacken further confirms that Bowdish discloses the hybrid IgG2/IgG4 heavy chain of eculizumab and as recited in challenged claim 1. *Id.* at 38–39 (citing, *inter*

alia, Ex. 1003 ¶¶ 118, 131, 135–136). Petitioner contends that (like Bell) Tacken equates the h5G1.1 antibody with eculizumab and, moreover, teaches that eculizumab contains "the same IgG2/IgG4 constant region" disclosed in Mueller 1997 (Tacken's reference 17, submitted here as Ex. 1006), which Petitioner indicates has a "companion patent application" in Mueller PCT. *Id.* at 39 (citing Ex. 1008, 1279; Ex. 1003 ¶¶ 131–132).

Petitioner asserts that Mueller PCT is analogous art because, like Bell, Bowdish, Evans, and Tacken, it relates to the same field as the challenged patent and is concerned with recombinant antibodies, especially 5G1.1, and is also associated with Alexion and the common inventors among the asserted prior art. *Id.* at 42 (citing Ex. 1009, cover, 12:19–27; Ex. 1005, cover; Ex. 1003 ¶ 137). Petitioner asserts further that "Mueller PCT . . . expressly discloses the full amino acid sequence for the IgG2/IgG4 constant domain heavy chain used in the 'h5G1.1 HuG2/G4' antibody," and 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 1. *Id.* at 39–40 (citing Ex. 1009, 14, 58–59, 97; Ex. 1003 ¶¶ 132–134 (showing comparison of heavy chain constant regions)). Petitioner asserts that with this information, the ordinarily skilled artisan would have understood the Bowdish-Evans relationship regarding the 13 amino acids replaced with the TPO mimetic. *Id.* at 40–41 (citing Ex. 1003 ¶ 134).

Regarding the dependent claims, Petitioner asserts that Bell renders obvious: the single unit dosage form of claim 2; the 300 mg dosage of claim 3; that treated patients with PNH are anemic as in claims 6 and 19; the

treatment dosage of 5–50 mg/kg per patient of claim 7; the dose and treatment regimen of claims 8 and 21; the treated patient exhibiting decreased LDH levels of claims 9–11 and 22–24 (as verified by, *inter alia*, Hillmen); the dosing regimen of claims 12 and 25; that the treated patient has a 100,000 per microliter platelet count before treatment as in claims 13, 14, and 26; that the treated patient exhibits improved quality of life as measured by EORTC or FACIT, as in claims 17 and 29; and the treatment duration of claim 18. *Id.* at 43–48, 54–55 (citing, *inter alia*, Ex. 1003 ¶¶ 141–153, 164–171).

Regarding dependent claim 15, Petitioner asserts that Hillmen, combined with the other references, teaches that the patient has about a 51% likelihood of transfusion avoidance after treatment, as claimed. *Id.* at 48–49 (citing, *inter alia*, Ex. 1003 ¶ 154). As for dependent claim 16, Petitioner asserts Hill teaches the less than 3% likelihood of a treated patient developing eculizumab antibodies, as claimed. *Id*. at 50 (citing, *inter alia*, Ex. 1003 ¶ 156).

Claim 4 requires a 300 mg dose in 30 mL at 10 mg/ml of a sterile, preservative-free solution, which Petitioner asserts is obvious in view of the teachings of Wang, Bell, Bowdish, and Evans. *Id.* at 50–52 (citing, *inter alia*, Ex. 1003 ¶¶ 142, 157–161; Ex. 1062 ¶¶ 51–56). Petitioner asserts that a person of ordinary skill in the art would know that eculizumab could be formulated at 10 mg/ml based on the teachings of Wang and that each of Bell, Bowdish, and Evans teaches that eculizumab formulations "must be sterile" and may be preservative free. *Id.* at 50–51 (citing, *inter alia*, Ex. 1044 ¶¶ 170–173; Ex. 1007 ¶ 62; Ex. 1004 ¶ 150; Ex. 1005, 18:29–43).

Petitioner asserts that claim 5 recites that "the antibody is diluted to a concentration of 5 mg/mL prior to administration," which Petitioner asserts is entitled to no patentable weight because it was commonplace to so-dilute IV drugs. *Id.* at 53 (citing, *inter alia*, Ex. 1003 ¶¶ 162, 163; Ex. 1062 ¶ 57).

Regarding claim 27, Petitioner asserts that Hillmen discloses the likelihood of transfusion avoidance for treated patients, as claimed. *Id.* at 55 (citing, *inter alia*, Ex. 1003 ¶¶ 154–155, 172).

Regarding claim 28, Petitioner asserts that the required quality of life improvement under the FACIT-Fatigue scale would have been obvious because Brown reports a close correlation between this scoring method and the EORTC scoring method of Bell. *Id.* at 55–56 (citing, *inter alia*, Ex. 1003 ¶¶ 153, 173).

Turning to Patent Owner's positions, Patent Owner states that, "[t]he challenged claims of the '809 patent generally cover methods of treating paroxysmal nocturnal hemoglobinuria ('PNH') patients comprising intravenously administering pharmaceutical compositions of a non-naturally occurring, uniquely-engineered humanized antibody developed by Alexion and marketed as SOLIRIS®." Prelim. Resp. 4. Patent Owner further states that "[a] [person of ordinary skill in the art] as of March 15, 2007 would have understood that Alexion had developed a humanized antibody named 'eculizumab,' which bound to human C5 and blocked its cleavage," and that "[t]oday, but ***not*** before the March 15, 2007 priority date for the '809 patent, it is known that SOLIRIS® has the amino acid sequence recited in the '809 patent's claims, namely, 'a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4,'" i.e., eculizumab. *Id.* at 7, 9.

These statements provide context for the following arguments of Patent Owner as well as Petitioner's asserted evidence.

Patent Owner's over-arching argument is that, as of the '809 patent's priority date, the ordinarily skilled artisan would mistakenly believe that the claimed eculizumab antibody used to treat PNH had an IgG4 constant region as taught by Thomas, rather than an IgG2/IgG4 constant region, as is known today. *See id.* at 9–14, 33–39. Patent Owner argues that those of ordinary skill in the art as of March 15, 2007, would have relied on Thomas's humanized IgG4 antibody for eculizumab's structure (which is not the amino acid sequences recited by claim 1) because Bell, Hillmen, Hill, and Tacken cite Thomas. *Id.* at 33–39. Patent Owner argues that Petitioner's assertions rely on impermissible hindsight and are "unduly selective." *Id.* at 32. Patent Owner argues the asserted prior art "hav[e] nothing to do with the design of antibodies for blocking C5 cleavage of treating PNH." *Id.*

Patent Owner argues that "Evans neither used the term 'eculizumab,' nor disclosed the heavy chain or full sequence of the claimed antibody of the '809 patent," only describes the antibody constant regions generically, and does not suggest the eculizumab SEQ ID NO: 2 heavy chain, so an ordinarily skilled artisan would have looked to Thomas's IgG4 isotype antibody. *Id.* at 39–40. Patent Owner argues that Evans, rather, was directed to mouse antibodies with humanized fragments. *Id.* at 40–41 (citing Ex. 2022 ¶¶ 127–130).

Patent Owner argues that neither Bowdish nor Mueller PCT disclosed the eculizumab amino acid sequence, or that such was not what Thomas taught, i.e., an IgG4 heavy chain. *Id.* at 41–45. Patent Owner argues that Bowdish had nothing to do with C5 binding or blocking complement-

mediated lysis. *Id.* at 42. Further, Patent Owner argues that Mueller PCT (and the associated Mueller 1997) concerns issues unrelated to the '809 patent, that is, developing antibodies to VCAM molecules, which were IgG2/IgG4 antibodies. *Id.* at 42–43. Patent Owner argues the neither reference uses the term "eculizumab," which is a reason no person of ordinary skill in the art would have looked to these references to produce eculizumab. *Id.* at 43.

Patent Owner also argues that the art was too unpredictable for the ordinarily skilled artisan to have been motivated to "alter" the structure of eculizumab from Thomas's IgG4 antibody. *Id.* at 45–48 (citing, *inter alia*, Ex. 2022 ¶¶ 108–118). Patent Owner argues that such deviation from Thomas's antibody would have foreclosed a reasonable expectation of success. *Id.* at 48.

Next, Patent Owner argues that Bell, although discussing "eculizumab," fails to expressly or inherently disclose the claim elements because it omits "the exact amino [acid] sequence of eculizumab." *Id.* at 49 (alteration in original). Patent Owner argues that Bell references Thomas's IgG4 antibody as eculizumab, but Thomas's antibody does not have the amino sequence of (claimed) SEQ ID NO: 2. *Id.* at 50.

Patent Owner argues that Bowdish does not disclose the claimed amino acid sequence and that Bowdish's incorporation by reference of Evans's 5G1.1 antibody would have been limited to only a murine (in this case, mouse) monoclonal antibody, which, following the reverse-engineering of Petitioner's ground, results in a different sequence than claimed. *Id.* at 50–53. Patent Owner argues that Bowdish makes no reference to "eculizumab" or any other C5-binding antibody, and does not

identify the "native CDR3" of Evans's antibody that was replaced by the TPO mimetic graft. *Id.* at 54. Patent Owner also argues that Petitioner's ground relies on improper hindsight. *Id.*

Patent Owner argues that Bowdish is not analogous art to the '809 patent because Bowdish "has nothing to do with blocking C5 cleavage or treating PNH. *Id.* at 55.

Patent Owner further argues that one of ordinary skill in the art would not have been motivated to combine Bowdish and Evans because Bowdish's citing to a 5G1.1 antibody is too broad and Evans discloses only fragments of anti-C5 antibodies and never uses the word "eculizumab." *Id.* at 55–56. Patent Owner also argues that, even were Bowdish and Evans combined per Petitioner's theory, the ordinarily skilled artisan would not have expected a resulting antibody to prevent C5 cleavage to effectively treat PNH. *Id.* at 57.

Patent Owner argues that Tacken and Bell taught eculizumab by referencing Thomas, which disclosed an IgG4 isotype antibody." *Id.* at 58. Then, addressing Mueller PCT, Patent Owner argues that it identifies only an IgG4 isotype antibody, i.e., Thomas's isotype, as an anti-C5 antibody, but "taught nothing about the C5 binding or clinical properties of 'h5G1.1 CO12 HuG2/G4 mAb.'" *Id.*

Patent Owner also mentions the dosage form limitation of claim 3 as not taught by Bell, and the dosage form or formulation limitations of other dependent claims as not taught by Wang. *Id.* at 59–63.

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood of showing at trial that the claims of the '809 patent would have been obvious

under Grounds 1–6. We find the parties' positions and arguments, the claim language challenged, and the prior art asserted here to be substantially the same as was addressed in the related *inter partes* review proceedings noted in Section I.B above and, therefore, warrant a similar result.

We first address Patent Owner's argument as to whether Bowdish is analogous art, as Bowdish is the only reference immediately challenged as not analogous art. Regarding this issue,

> 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). Petitioner, supported by the testimony of Dr. Ravetch, contends that Bowdish is analogous art. Pet. 36–37 (citing Ex. 1003 ¶ 128). 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 ¶ 128. On the present record before us, it appears that Bowdish is both reasonably pertinent and within the same field of endeavor as the '809 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, 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. Moreover, it is reasonable that an ordinarily skilled artisan seeking to understand the Alexion anti-C5 antibody disclosed in, for example, Bell or Hillmen or Hill as a treatment for PNH, would look to other Alexion prior art for guidance.

On this record, we are also unpersuaded by Patent Owner's overarching argument that Petitioner's positions are fatally flawed by hindsight or that "[a] POSA as of March 15, 2007[,] would have understood that Alexion had developed a humanized antibody named 'eculizumab,' . . . [b]ut a POSA at that time would ***not*** have known that "eculizumab" had the sequence claimed in the '809 patent." *See* Prelim. Resp. 4, 7, 9. It appears that Petitioner's positions here consider only the disclosures of the prior art and how the person of ordinary skill in the art would have read prior art references in view of one another.

Regarding Patent Owner's foundational preliminary argument that all prior art pointed exclusively to Thomas for the structure of eculizumab, rather than to Evans or Tacken or Mueller PCT, for example, we are unconvinced.

We find Patent Owner's position mischaracterizes Bell's incorporation of Thomas by wholly ignoring that, in the very same sentence, and preceding the cite to Thomas, Bell also incorporates Evans by reference. Ex. 1007 ¶ 52. Bell incorporates Evans as disclosing "[p]articularly useful anti-C5 antibodies . . . h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1," and "[m]ethods for the preparation" of these. *Id.* It appears that the ordinarily skilled artisan, like Bell's inventors, would not

have looked solely to Thomas for eculizumab's structure. Moreover, the '809 patent itself states that Evans, which is a part of Bell, discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001 12:34–37. Thus, even the '809 patent, like Bell, acknowledges that Evans is an important reference regarding eculizumab, its structure, and how to make it.

Concerning Tacken, Dr. Ravetch testifies that,

> Tacken equates h5G1.1 with eculizumab, and calls it Alexion's "potential product." (EX1008, 010.) Tacken further teaches that eculizumab contains an IgG2/G4 constant domain that is the "same" as the human hybrid IgG2/G4 constant domain disclosed in its cited reference 17, which is the Mueller 1997 article. (*Id.*, 011 (citing EX1006).)

Ex. 1003 ¶ 131. As noted in Section II.D.5, 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]." Ex. 1008, 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.*

We find it plausible that Tacken's, i.e., Alexion's researchers', description of Alexion's own product 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 ¶¶ 62, 68–70 (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")).

On the present record, we do not favor Patent Owner's interpretation of Tacken, particularly in view of what appears to be the close association between Alexion and the authors of Tacken. *See* Ex. 1008, 1278 (footnote). Specifically, Tacken discloses that the reported lectin-specific antibody research was supported by "funding from Alexion Pharmaceuticals" to the lead author, and that three of the other authors were "employed by Alexion Pharmaceuticals, whose potential product was studied in the present work." *Id.* Notably, one of the Tacken authors, Russell P. Rother, is also an author of Thomas, published some nine years earlier. *See* Ex. 1010, 1389. If it would have been reasonable for anyone to have known that eculizumab had a human hybrid IgG2/IgG4 constant domain and was an h5G1.1-mAb, specific for the human terminal complement protein C5, as reported in Tacken, the Tacken authors would have been such people.

Further, we find it unlikely that Mr. Rother and the other Tacken authors mistakenly referred to eculizumab as having an IgG2/IgG4 constant region. We find it more plausible that Tacken cites to Thomas as describing eculizumab's C5-specific CDRs, and refers to Mueller 1997 (Ex. 1006) 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. 12–13, 55.

We invite the parties to further address this issue at trial.

Our review of the asserted prior art also reveals that Bell uses the word "eculizumab" at least 25 times throughout its disclosure, without ever expressly explaining more than that it is an anti-C5, h5G1.1-mAb therapeutic antibody. *See generally* Ex. 1007. The record suggests "eculizumab" meant something to the person of ordinary skill in the art. *See, e.g.*, Ex. 1008, 1279 ("An isotype control 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).

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. Thus, it appears on the present record that Bell identifies a useful antibody for treating PNH as eculizumab and points to Evans for its specific identity and how to produce it.

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 that, 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 '809 patent, itself, states that

Evans, which is a part of Bell, discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001, 12:34–37.

On the present record we also disagree with Patent Owner's contention that Bowdish's incorporation of Evans's disclosure would have been limited to a murine antibody or framework. Similarly, we are not persuaded on this preliminary record that the ordinarily skilled artisan seeking to identify the structure of eculizumab in the prior art would not look to Evans and Bowdish, each of which would have been known to such an artisan, as would their relationship to one another.

Bowdish states: "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." Ex. 1004 ¶ 191 (emphasis added). It is not disputed here that U.S. Application 08/487,283 issued as Evans.[24] *See* Ex. 1005, code (21); *see generally* Prelim. Resp. The portion of Evans relating to "***Construction*** of 5G1.1" (*see* Ex. 1004 ¶ 191) appears to be (or at least includes) Example 11, which is titled "***Construction*** and Expression of Recombinant mAbs." 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 ¶ 204. None of the other Evans Examples addressing an anti-C5 antibody or a 5G1.1 antibody designate their

[24] Any argument that citation to the Evans application is substantively different than citation to the Evans patent appears to be a distinction without a difference. If there is a material difference in such disclosures, we invite the parties to address the matter at trial.

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. 1004 ¶ 191.

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 (and Bell's) invention to be more reasonable than Patent Owner's arguments that antibodies would have been selected from some other examples.

Furthermore, Patent Owner does not dispute that, if Bowdish and Evans are read as asserted by Petitioner and its witness, Dr. Ravetch, the antibody sequences of claim 1, i.e., SEQ ID NO: 2 and SEQ ID NO: 4, are disclosed. Petitioner's reading is also consistent with the '809 patent, which states that Evans "teaches an antibody which binds to C5" and is a "[s]uitable anti-C5 antibod[y]" with respect to its invention and was "known to those of skill in the art," and, in fact, that Evans teaches the "antibod[y] . . . specific to human complement[,] . . . whole antibody (now named eculizumab)," as well as "methods of engineering such antibodies." Ex. 1001, 10:66–11:14, 12:29–37, 12:50–63. Therefore, we do not find any error in Petitioner's assertion that Bowdish/Evans discloses the antibody of claim 1.

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*"). We recognize that these cases address anticipation, which has different legal requirements than

obviousness; however, we find them highly relevant as to the issue of whether the prior art disclosed the claimed antibody.

In *Crish*, the claimed invention 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." *Id.* Each is a sequence of biological building blocks with a function.

Further, the issue in *Crish* was whether a publication by inventor Crish that disclosed the complete structure of hINV as a plasmid, but not the 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 published plasmid and sequenced it to obtain a different promoter sequence from the claimed sequence. *Id.* at 1255. Crish argued, 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 the claimed composition, eculizumab, but possibly not its specific sequence. 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 '809

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. Ex. 1001, 12:34–37. And, here it is undisputed that the actual eculizumab antibody has the claimed sequences.

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." *Crish*, 393 F.3d at 1258 (emphasis added). The Court further recognized that "one cannot establish novelty by claiming a known material," in *Crish* a gene/promoter, "by its properties," i.e., its sequence of nucleotides (which the Federal Circuit identified is the gene's identity, akin to all its properties) and related promoter activity. *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 1258–59.

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., Bowdish/Evans, as well as each of Bell, Tacken, Mueller PCT, Hillmen, Hill, and Wang, is Alexion's and, at least to a degree, the '809 patent's inventors' own work.[25] Further, here, like *Crish*, the prior art discloses the claimed antibody, eculizumab, and how to construct it, even if there may have arguably been some confusion by those in the field over precisely the structure of the antibody (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

[25] Both Bowdish and Evans are associated with Alexion Pharmaceuticals, Inc., and two of the named inventors of the '809 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). Bell, Tacken, Mueller PCT, Hillmen, Hill, and Wang, similarly, each name inventors or authors that overlap the '809 patent's inventors, or are associated with Alexion Pharmaceuticals, Inc. Exs. 1007–1009; Ex. 1011; Ex. 1013; Ex. 1044.

dispute that the Bowdish/Evans antibody according to Petitioner's reading (and seemingly undisputed here) is eculizumab, which has the claimed amino acid sequences. As noted above, the '809 patent itself indicates that Evans discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001, 12:34–37. 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 published 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.* Here, Patent Owner's argument is that skilled artisans would have not known eculizumab's amino acid sequence and, in fact, would have been led toward the wrong antibody (by Thomas).

The Federal Circuit held in *Nichols* 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.* Here, the prior art discloses eculizumab, including the amino acid sequences therefor. Thus, it would appear that, here, the same conclusion as in *Nichols* would be appropriate.

Also, as discussed above, each of Bell (Ex. 1007, *inter alia*, ¶ 12), Tacken (Ex. 1008, 1279), Hillmen (Ex. 1011, *inter alia*, 3), Hill (Ex. 1013, *inter alia*, 9), and Wang (Ex. 1044, *inter alia*, ¶ 67) discloses the eculizumab antibody, which is the undisputed antibody of claim 1, and Bell, Hillmen and Hill disclose its use in PNH treatment. According to *Crish*, this disclosure

of eculizumab is the disclosure of the identity of the antibody of claim 1. According to *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 unappreciated at the time.

We note Patent Owner's argument that Petitioner ignores "the complexity and unpredictability of designing [or altering] 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. 45–48 (capitalization normalized). Although 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 of eculizumab, an *existing* antibody, which, as evidenced by Bell, Hillmen, and Hill (*see supra* Sections II.D.1, II.D.6, and II.D.7), was already shown to be safe and effective in clinical trials. 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. Additionally, as discussed above, we are not convinced by Patent Owner's arguments that deviation from Thomas's antibody was required or would have been contemplated by the ordinarily skilled artisan.

As to the claim element of treating a PNH patient with eculizumab, this does not appear to be in dispute. Moreover, it appears to be disclosed by Bell, Hillmen, and Hill. *See* Ex. 1007; Ex. 1011; Ex. 1013.

Recognizing that the dependent claims are also at issue and require certain dosage forms, dosages, dosing regimens, patient characteristics, and treatment results, we decline to fully address the merits of Petitioner's challenges or Patent Owner's limited arguments over these claims here because we have found, on the present record, sufficient evidence to proceed to trial based on the challenge to claim 1. We do note, however, that it appears that Petitioner has accounted for each additional limitation of these dependent claims as taught in the prior art combinations discussed above.

3. Summary

Based on the evidence presented at this stage in the proceedings, it has been shown under Grounds 1–6 that there is reasonable likelihood that at least one of the '809 patent's claims would have been obvious over Bell, Bowdish, Evans, Tacken, Muller PCT, Hillmen, Hill, Wang, and Brown.

G. GROUNDS 7 THROUGH 12—OBVIOUSNESS OVER BELL, EVANS, MUELLER PCT, AND TACKEN, AND ALSO WANG, HILLMEN, HILL, AND BROWN

1. Parties' Positions

Grounds 7–12 are very similar to Grounds 1–6, discussed above. In Ground 7, Petitioner challenges independent claim 1 and dependent claims 2, 3, 6–14, and 17 as obvious over Bell, Evans, Tacken, and Mueller PCT, notably, omitting Bowdish. Pet. 29–30, 56–62 (citing, *inter alia*, Ex. 1003 ¶¶ 115–153; Ex. 1062 ¶¶ 25, 48, 50–51, 58–59). Regarding the obviousness of claim 15 (Ground 8), Petitioner adds the teachings of Hillmen to this prior art combination. *Id.* at 62 (citing the earlier rationale under Ground 2; also citing Ex. 1003 ¶ 184). As for the obviousness of dependent claim 16 (Ground 9), Petitioner adds the teachings of Hill to the prior art combination. *Id.* (citing the earlier rationale under Ground 2; also citing Ex. 1003 ¶ 185).

Regarding the obviousness of limitations added by dependent claims 4, 5, 18–26, and 29 (Ground 10), Petitioner adds the teachings of Wang to the original combination. *Id.* at 63 (citing the earlier rationale under Ground 3; also citing Ex. 1003 ¶¶ 157–171, 186). For claim 27 (Ground 11), Petitioner adds both Hillmen and Wang. *Id.* at 63 (citing the earlier rationale under Ground 5; also citing Ex. 1003 ¶ 187). Finally, regarding the subject matter of claim 28 (Ground 12), Petitioner adds the teachings of Wang and Brown. *Id.* at 63 (citing the earlier rationale under Ground 6; also citing Ex. 1003 ¶ 188).

Patent Owner again opposes. Prelim. Resp. 32–48, 63–68 (citing, *inter alia*, Ex. 2022 ¶¶ 108–118, 123–124, 127–130, 203, 208, 238–262; Ex. 2024 ¶¶ 69–91).

Because each of Petitioner's Grounds 7–12 foundationally relies upon the same arguments and evidence and, generally, Patent Owner's arguments over these grounds are the same, we address them together, as we did Grounds 1–6, above. We will not restate our above analysis that overlaps with that of these prior grounds.

To summarize, Petitioner asserts that the combined teachings of Bell, Evans, Tacken, and Mueller PCT render claim 1's method and administered antibody obvious because: (1) Bell teaches that the antibody, eculizumab (also known as h5G1.1), was used to treat PNH; (2) Bell points to and incorporates for its teachings on eculizumab Evans, which reveals the entire amino acid sequence of eculizumab's (humanized 5G1.1) variable region, as claimed; (3) Mueller PCT teaches an h5G1.1 CO12 HuG2/G4 antibody, which points to Evans's CO12 exemplary antibody (Example 11, No. 12), and paired with Evans teaches the antibody has a IgG2/IgG4 constant region

and provides the entire sequence for the antibody; and (4) Tacken supports combining Evans and Mueller PCT and confirms that the eculizumab antibody has an IgG2/IgG4 hybrid constant region. Pet. 29–30, 56–63. Concerning the specific limitations of the dependent claims, Petitioner again asserts, *inter alia*, that Bell, Wang, Hillmen, Hill, and Brown teach the specifics of the claimed dosage form, dosages, dosing regimens, patient characteristics, and therapeutic results. *Id.*

As was the case under Grounds 1–6, Petitioner points to Bell as both disclosure of the use of eculizumab to treat PNH and as motivation for the ordinarily skilled artisan to turn to Evans's Example 11 as teaching the structure of 5G1.1 antibodies, eculizumab's variable domains, specifically. *Id.* at 56–57 (citing, *inter alia*, Ex. 1003 ¶¶ 174–176). 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.* at 57–58 (citing, *inter alia*, *KSR*, 550 U.S. at 421; Ex. 1003 ¶¶ 176–177).

Petitioner points to Mueller PCT as focusing such an ordinarily skilled artisan upon an antibody construct identified in Evans as CO12, because Mueller PCT discusses an h5G1.1 *CO12* HuG2/G4 antibody, which would point such an artisan to Evans's CO12 Example, which, united with Mueller PCT's disclosed G2/G4 constant regions, would result in "a perfect match to SEQ ID NOS:2 and 4 recited in challenged claim 1." *Id.* at 58–60 (citing Ex. 1009, 14; Ex. 1003 ¶¶ 178–179). In this way, Petitioner omits any discussion of or reliance on Bowdish, which was a part of Grounds 1–6.

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 Mueller 1997 and Mueller PCT). *Id.* at 60 (citing Ex. 1003 ¶ 180).

Petitioner also addresses dependent claims 2–29 as obvious when the teachings of Hillmen, Hill, Wang, and Brown are added to the above prior art combination. *Id.* at 62–63 (citing, *inter alia*, Ex. 1003 ¶¶ 184–188).

Patent Owner's arguments over Grounds 7–12 are substantially the same as those addressed above, for example, improper hindsight, reliance on Thomas was expected, only Evans's murine antibodies would have been considered, and Mueller PCT's anti-VCAM antibody is not relevant to eculizumab. *See* Prelim. Resp. 63–65 (citing, *inter alia*, Ex. 2022 ¶¶ 238–262).

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 1–6.

We find compelling Petitioner's assertion that Bell and Tacken would have provided 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. Ex. 1007 ¶¶ 12, 52; Ex. 1008, 1279. We also 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 claimed. Mueller PCT discloses the amino acid sequence of such a human G2/G4 constant region; thus, a skilled artisan would have also found it useful in such an endeavor. Bell, and other references, teach using eculizumab to treat PNH. Ex. 1007. Thus, at this stage of the proceeding, we find no fatal flaw to Petitioner's case under Grounds 7–12.

3. Summary

Based on the evidence presented at this stage in the proceedings, it has been shown under Grounds 7–12 that there is reasonable likelihood that at least one of the '809 patent's claims would have been obviousness over Bell, Evans, Mueller PCT, Tacken, Wang, Hillmen, Hill, and Brown.

III. DISCRETIONARY DENIAL

Patent Owner presents arguments that we should exercise our discretion to deny institution in this proceeding. Prelim. Resp. 15–31. As explained below, we are not persuaded by any of these arguments and will not deny institution.

A. 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, 15–31; Prelim. 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. 15–24. Patent Owner also argues that Petitioner has not shown the Office erred in a manner material to patentability of challenged claims. *Id.* at 25–31. Petitioner

disagrees as to both points. Pet. 67–79; Prelim. Reply 1–6; Ex. 1003 ¶¶ 191, 193, 195–208.

In determining whether to deny institution under § 325(d), we use the following two-part framework:

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). The *Becton, Dickinson* factors provide useful insight into how to apply the framework under 35 U.S.C. § 325(d). *Id.* at 9 (referencing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph)).

Under § 325(d), the art and arguments must have been previously presented to the Office during proceedings, such as examination of the underlying patent application, pertaining to the challenged patent. *Id.* at 7. Previously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement ("IDS"), in the prosecution history of the challenged patent. *Id.* at 7–8.

1. Whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office

Under the first part of the *Advanced Bionics* framework, we consider "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.* at 8. We evaluate *Becton, Dickinson* factors (a), (b), and (d) to determine whether Petitioner has demonstrated material error. *Id.* at 10. Those factors are:

> (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; and
>
> (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.

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

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)").[26] Patent Owner contends that

[26] 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*.

Evans and Mueller 1997 (asserted to be cumulative to Mueller PCT), as well as counterpart references for Bowdish ("U.S. Patent No. 7,482,435—also published as U.S. Pub. No. 2003/0049683—is the parent patent to Bowdish") and Bell ("published six different times as U.S. 2005/169921; U.S. 2010/068202; U.S. 2011/086040; U.S. 2012/308559; WO 2005/074607; and EP1720571"), were disclosed in the prosecution leading to the issuance of the '809 patent. Prelim. Resp. 17–24.

In response, Petitioner notes, *inter alia*, that Brown is a new reference and, "although Bell, Bowdish, Tacken, Mueller PCT and Hill were cited in Information Disclosure Statements during prosecution, there is no evidence that these references were considered by the Examiner." Pet. 68–69; Prelim. Reply 2.

In view of the unique record before us, we agree with Patent Owner that all of the references relied on by Petitioner here, "were previously presented to the Office" as required by § 325(d) and *Advanced Bionics*. Accordingly, we proceed to part two of the analysis.

2. Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims

Under the second part of the *Advanced Bionics* framework, we consider "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics* at 8. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Id.* at 8 n.9. We

evaluate *Becton, Dickinson* factors (c), (e), and (f) to determine whether Petitioner has demonstrated material error. *Id.* at 10. Those factors are:

> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; . . .
>
> (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, Paper 8 at 17–18.

Petitioner raises at least four non-trivial arguments for why the Examiner allegedly erred in the prosecution of '809 patent and the identified child patents. *See* Pet. 70–79; Prelim. Reply 2–6. For the purpose of our analysis, we find it sufficient to address only two of those arguments.

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; Prelim. Reply 5–6; Ex. 1003 ¶¶ 199–201. In this respect, Petitioner points to Alexion's Response to an Office Action in the prosecution of the '189 patent, which avers that

> [T]he 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) (alterations in original). As noted by Petitioner, Alexion "went on to list several references that purportedly referred to eculizumab as an IgG4 antibody," via citation to Thomas. *Id.* at 72–73; 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. We agree with Petitioner.

As noted in Sections II.D.5 and II.F, 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]." Ex. 1008, 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.

On its face, we find it plausible that Tacken's authors understood and reported 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 ¶¶ 62, 68–70 (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 the above passage from Tacken merely "point[s] to Thomas's IgG4 antibody," in the same manner as the prior art it raised with the Examiner. Prelim. Sur-Reply 2–3.

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 expert downplays the passage 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." Ex. 2022 ¶¶ 142, 143; Ex. 1008, 1279.

On the present record, we do not favor this interpretation, particularly in view of what appears to be the close association between Alexion and the authors of Tacken. In this respect, 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." Ex. 1008, 1278. Notably, one of these authors, Russell P. Rother, is also an author of Thomas, published some nine years earlier.

On the present record, we find it unlikely that Mr. Rother and the other Tacken authors mistakenly referred 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.

As such, we find it error for the Examiner of the relevant applications 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. 1002, 14840–14843, 14854. But for this error, the Examiner would have better appreciated the disclosure of Mueller PCT. *See* Ex. 1003 ¶¶ 131–133.

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 between 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 Evan'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. 73–77; Prelim. Reply 6; Ex. 1036, 13–16. "This, unsurprisingly revealed a mismatch in the sequences." Pet. 73–74; *see* Ex. 1036, 14 (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' humanized 5G1.1 sequence would have shown "no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert." Pet. 73–75; Ex. 1003 ¶ 81 (citing Ex. 1004 ¶ 192 as disclosing that Bowdish used "anti-human IgG" to detect 5G1.1).

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. 75 (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' 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 75–76 (alterations in original). Instead, Petitioner argues, "Alexion focused the Examiner on [Evans'] Example 7, entitled 'Preparation of anti-C5 Monoclonal Antibodies,' which discloses preparing (not constructing) the parent 5G1.1 mouse antibody from the mouse hybridomas of the prior art." *Id.* at 76 (citing Ex. 1005, 37:34–39:30).[27]

We agree with Petitioner that the Examiner was misled by Alexion and misapprehended Evans as evidenced by the Reason for Allowance:

---

[27] 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, ¶178, Appendix A.)." Pet. 60.

"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." *Id.* at 74–77 (citing Ex. 1035, 006–07; Ex. 1003 ¶ 202).

Patent Owner presents no specific rebuttal, 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." Prelim. Sur-Reply 5–6. We address the teachings of Bowdish and Evans in Section II.D, 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 Evans's humanized 5G1.1 sequence.

3. Summary

For the reasons discussed above, we decline to exercise our discretion under 35 U.S.C. § 325(d) to deny the Petition.

B. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 314(a) AND *FINTIV*

Patent Owner points to § 314(a)[28] as a basis for denying institution, but provides no substantive argument or evidence on this point. *See* Prelim.

[28] 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. 67.

Resp. 15, 31; *see generally* Prelim. Sur-Reply 6. At best, Patent Owner asserts that if we find "that fewer than all twelve Grounds meet the standard for Section 325(d), institution of Samsung's petition should still be denied in full, because institution on all twelve Grounds 'would not be an efficient use of the Board's time and resources.'" Prelim. Resp. 31 (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 to deny institution with respect to any of the Grounds under § 325(d), the Board's *Deeper* decision is inapposite.

IV. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of showing at trial that at least one claim of the '809 patent is unpatentable under at least one ground. Accordingly, we institute an *inter partes* review of the challenged claims of the '809 patent on all grounds alleged by Petitioner. This decision does not reflect a final determination on the patentability of the claims.

ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claims 1–29 of the '809 patent, in accordance with each ground of challenge 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 '809 patent will commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

For PETITIONER:

Michelle Rhyu
Daniel Knauss
COOLEY LLP
rhyums@cooley.com
dknauss@cooley.com

For PATENT OWNER:

Gerald Flattmann
Andrew Cochran
CAHILL GORDON & REINDEL LLP
gflattmann@cahill.com
acochran@cahill.com