UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2023-01070
U.S. Patent No. 10,703,809 B1
Issue Date: July 7, 2020

Title: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,703,809 B1

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1001	U.S. Patent No. 10,703,809 B1 issued to Leonard Bell et al. (filed Feb. 28, 2020, issued July 17, 2020) ("'809 patent")
1002	Prosecution History for U.S. Patent No. 10,703,809 B1
1003	Declaration of Jeffrey V. Ravetch, M.D., Ph.D.
1004	U.S. Patent Application Publication No. 2003/0232972 A1 issued to Katherine S. Bowdish et al. (filed Dec. 2, 2002, published Dec. 18, 2003) ("Bowdish")
1005	U.S. Patent No. 6,355,245 B1 issued to Mark J. Evans et al. (filed June 7, 1995, issued Mar. 12, 2002) ("Evans")
1006	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 Molecular Immunology 441 (1997) ("Mueller 1997")
1007	U.S. Patent Application Publication No. 2005/0191298 A1 issued to Leonard Bell et al. (filed Feb. 3, 2005, published Sept. 1, 2005) ("Bell")
1008	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 (2005) ("Tacken")
1009	World Intellectual Property Organization International Publication No. WO 97/11971 issued to John P. Mueller et al. (filed Sept. 27, 1996, published Apr. 3, 1997) ("Mueller PCT")
1010	Thomas C. Thomas et al., *Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv*, 33 Molecular Immunology 1389 (1996) ("Thomas")

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1011	Peter Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. Engl. J. Med. 552 (2004) ("Hillmen")
1012	Anita Hill et al., *Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy*, 104 Blood 772a (2004) ("Hill 2004")
1013	Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 Blood 2559 (2005) ("Hill")
1014	Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006")
1015	Neal S. Young et al., *Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study*, 108 Blood 290a (2006) ("Young")
1016	Peter Hillmen et al., *Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent*, 100 Blood 44a (2002) ("Hillmen 2002")
1017	Peter Hillmen et al., *Abstract# 1858: Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy*, 102 Blood 509a (2003) ("Hillmen 2003")
1018	Excerpts from *Recommended INN List 49, International Nonproprietary Names for Pharmaceutical Substances*, 17 WHO Drug Information 115, World Health Organization (2003)

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1019	*Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, Programme on International Nonproprietary Names (INN), Division of Drug Management & Policies, World Health Organization, Geneva (1997)
1020	Alexion Press Release, *Alexion Issued Key C5 Complement Inhibitor Patent for Inflammatory Diseases* (Mar. 15, 2002), https://web.archive.org/web/20030621141230/http://www.alxn.com/products/index.cfm
1021	World Intellectual Property Organization International Patent Publication No. WO 2005/007809 A2 issued to Russell P. Rother et al. (filed May 28, 2004, published Jan. 27, 2005)
1022	World Intellectual Property Organization International Patent Publication No. WO 2005/110481 A2 issued to Russell P. Rother et al. (filed May 16, 2005, published Nov. 24, 2005)
1023	Mariana Kaplan, *Eculizumab Alexion*, 3 Curr. Opin. Investig. Drugs 1017 (2002)
1024	*Amgen Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, Paper 15, Decision – Institution of *Inter Partes* Review (PTAB Aug. 30, 2019)
1025	*Reserved*
1026	IPR2019-00741, "Termination – Due to Settlement After Institution of Trial," (Paper 48)
1027	Opposition File History for European Patent No. 1 720 571 B1
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1029	Excerpt from the File History for U.S. Patent Application No. 11/127,438, Amendment in Response to Non-Final Office Action (Aug. 2, 2011)

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1030	Application for Extension of Patent Term under 35 U.S.C. § 156 and 37 CFR § 1.740, U.S. Patent No. 6,355,245, Alexion Pharmaceuticals (May 11, 2007)
1031	Certificate Extending Patent Term, U.S. Patent No. 6,355,245 (June 11, 2010)
1032	Excerpt from the File History of U.S. Patent No. 10,590,809, Information Disclosure Statement by Applicant, considered by Examiner James L Rogers, May 31, 2019
1033	Esther M. Yoo et al., *Human IgG2 Can Form Covalent Dimers*, 170 J. Immunol. 3134 (2003) ("Yoo 2003")
1034	Excerpt from the File History of U.S. Patent No. 10,590,809, Non-Final Rejection, mailed June 11, 2019
1035	Excerpt from the File History of U.S. Patent No. 10,590,809, Notice of Allowance, mailed Jan. 22, 2020
1036	Excerpt from the File History of U.S. Patent No. 10,590,809, Amendment in Response to Non-Final Office Action Under 37 C.F.R. § 1.111, mailed Dec. 11, 2019
1037	Jette Wypych et al., *Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms*, 283 J. Biol. Chem. 16194 (2008) ("Wypych")
1038	Stylianos Bournazos et al., *Fc-optimized* antibodies *elicit CD8 immunity to viral respiratory infection*, 588 Nature 485 (2020) ("Bournazos 2020")
1039	Stylianos Bournazos et al., *Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity*, 124 J. Clinical Investigation 725 (2014) ("Bournazos 2014")

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1040	Lucie Baudino et al., *Impact of a Three Amino Acid Deletion in the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions*, 181 J. Immunology 4107 (2008)
1041	Toshiyuki Takai et al., *FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects*, 76 Cell 519 (1994)
1042	Falk Nimmerjahn & Jeffrey V. Ravetch, *Fcγ receptors as regulators of immune responses*, 8 Nat. Rev. Immunol. 34 (2008)
1043	Jeffrey V. Ravetch & Jean-Pierre Kinet, *Fc Receptors*, 9 Annu. Rev. Immunol. 457 (1991)
1044	U.S. Patent Application Publication No. 2005/0271660 A1 issued to Yi Wang (filed May 11, 2005, published Dec. 8, 2005) ("Wang")
1045	Charles A. Janeway, Jr. et al., *Chapter 1: Basis Concepts in Immunology*, and *Chapter 3: Antigen Recognition by B-cell and T-cell Receptors*, Immunobiology: the immune system in health and disease, pp. 1-34, 93-122 (5th ed. 2001)
1046	Excerpts from Pei-Show Juo, Ph.D., Concise Dictionary of Biomedicine and Molecular Biology (2nd ed. 2001)
1047	Tina Völkel et al., *Optimized linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies*, 14 Protein Engineering 815 (2001) ("Völkel")
1048	Evelyn D. Lobo et al., *Antibody Pharmacokinetics and Pharmacodynamics*, 93 Journal of Pharmaceutical Sciences 2645 (2004) ("Lobo 2004")
1049	Neil S. Lipman et al., *Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources*, 46 ILAR Journal 258 (2005) ("Lipman 2005")

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1050	Benny K.C. Lo, *Chapter 7: Antibody Humanization by CDR Grafting*, Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols, pp. 135-159 (2004) ("Lo 2004")
1051	Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 Nature 323 (1988) ("Riechmann")
1052	Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012) ("Reichert")
1053	Bruce Alberts et al., *Chapter 12: Intracellular Compartments and Protein Sorting*, Molecular Biology of the Cell, pp. 551-98 (1994)
1054	Elisabeth E. Adderson et al*., Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenzae Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations*, 89 J Clin. Invest. 729 (1992)
1055	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
1056	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm
1057	ImClone Systems, Inc., Erbitux 2004 Package Insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125084lbl.pdf
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1059	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
1060	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
1061	Ann L. Daugherty & Randall J. Mrsny, *Formulation and delivery issues for monoclonal antibody therapeutics*, 58 Advanced Drug Delivery Reviews 686 (2006)
1062	Declaration of Cindy Ippoliti, Pharm.D.
1063	Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product, European Agency for the Evaluation of Medicinal Products (2003)
1064	Excerpt from The Merck Manual (17th ed. 1999)
1065	Health, United States, 2005 with Chartbook and Trends in the Health of Americans, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2005)
1066	Excerpt from the File History of U.S. Patent No. 9,718,880, Response to Non-Final Office Action Under 37 C.F.R. § 1.111, dated May 12, 2017
1067	Excerpt from the File History of U.S. Patent No. 9,718,880, Declaration Pursuant to 37 C.F.R. § 1.132 By Dr. Laural Boone, signed May 11, 2017
1068	Duncan J. F. Brown et al., *The Correlation between Fatigue, Physical Function, the Systemic Inflammatory Response, and Psychological*

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Exhibit No.	Description of Document
	Distress in Patients with Advanced Lung Cancer, 103 Cancer 377 (2004) ("Brown")

Petitioner respectfully requests institution of *inter partes* review (IPR) of United States Patent No. 10,703,809 B1 ("'809 patent" or "EX1001") claims 1-29, as shown below.

I. INTRODUCTION

The '809 patent never should have issued. Its sole independent claim covers a method of treating the debilitating condition called paroxysmal nocturnal hemoglobinuria ("PNH") using the heavy and light chains of the antibody known as eculizumab as a pharmaceutical composition. But years before 2007, eculizumab was known as an anti-C5 antibody that was an effective treatment for PNH. And despite Alexion's recent efforts to argue that the scientific community did not know the amino acid sequence of eculizumab before the March 15, 2007 priority date, the sequence was in fact available to researchers long before that date. Several prior art publications disclose outright the exact sequence of eculizumab by providing a simple roadmap for its assembly, rendering the claimed sequence anticipated and obvious. Various trivial limitations presented in the dependent claims add nothing of patentable significance to the basic method claim.

Arguments similar (but not identical) to those presented here were the basis of a previously-instituted IPR pursued by Amgen, Inc., against Alexion's U.S. Patent No. 9,725,504, with claims that are extremely similar to the '809 claims challenged here. That IPR never reached a final written decision because the parties settled and

the IPR was terminated. As explained below, IPR should be instituted against the '809 patent to prevent Alexion from asserting a patent to an antibody sequence that was firmly in the public domain long before Alexion filed its patent application.

II. MANDATORY NOTICES UNDER §42.8(A)(1)

A. Real Party-In-Interest under §42.8.(b)(1)

Samsung Bioepis Co., Ltd. is the real party-in-interest to this IPR petition.

B. Related Matters under §42.8(b)(2)

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).

C. Lead and Back-Up Counsel under §42.8(b)(3)

Petitioner provides the following designation of counsel.

LEAD COUNSEL	BACK-UP COUNSEL
Michelle S. Rhyu (Reg. No. 41,268) rhyums@cooley.com	Daniel J. Knauss (Reg. No. 56,393) dknauss@cooley.com

LEAD COUNSEL	BACK-UP COUNSEL
COOLEY LLP ATTN: Patent Group 1299 Pennsylvania Ave. NW, Suite 700 Washington, DC 20004 Tel: (650) 843-5505 Fax: (650) 849-7400	COOLEY LLP ATTN: Patent Group 1299 Pennsylvania Ave. NW, Suite 700 Washington D.C. 20004 Tel: (650) 843-5287 Fax: (650) 849-7400

D. Service Information

This Petition is being served by Federal Express to the attorney of record for the '809 patent, NELSON MULLINS RILEY & SCARBOROUGH LLP, One Financial Center, Ste. 3500, Boston, MA 02111. Petitioner consents to electronic service at the addresses provided above for counsel.

III. FEE PAYMENT

Petitioner requests review of 29 claims, with a $51,625 payment.

IV. REQUIREMENTS UNDER §§ 42.104 AND 42.108

A. Standing

Petitioner certifies that the '809 patent is available for IPR and that Petitioner is not barred or otherwise estopped.

B. Identification of Challenge

Petitioner requests institution of IPR of claims 1-29 based on the following grounds:

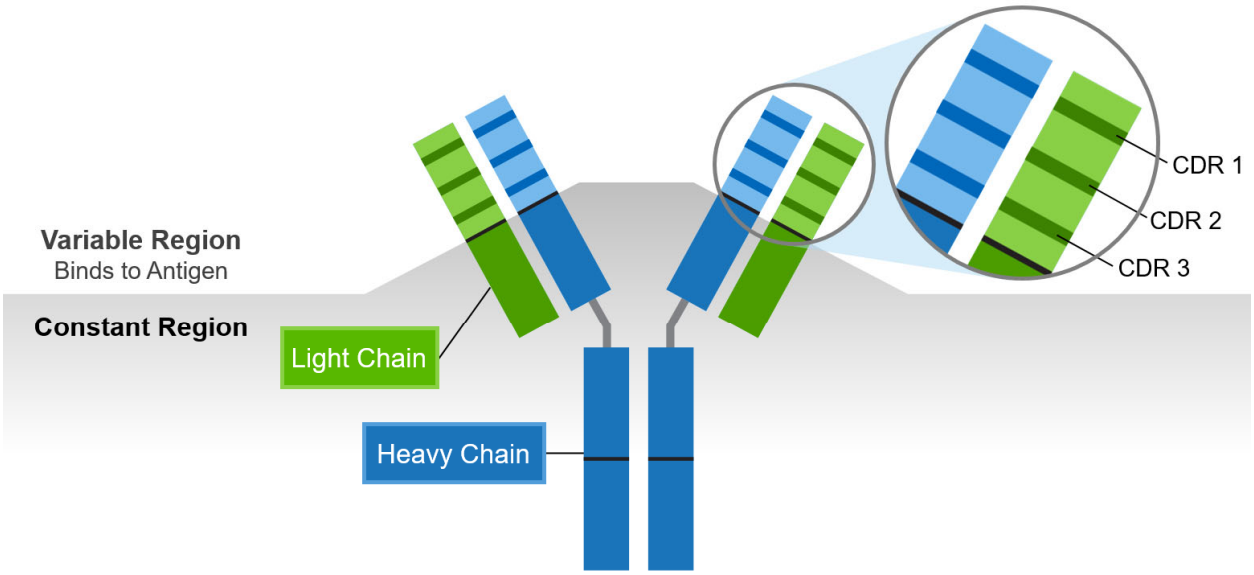
Ground	Claim(s)	Basis for Challenge
1	1-3, 6-14, 17	Obvious over Bell (EX1007), Bowdish (EX1004), and Evans (EX1005) in view of Tacken (EX1008) and Mueller PCT (EX1009)
2	15	Obvious over Bell, Bowdish, Evans, and Hillmen (EX1011) in view of Tacken and Mueller PCT
3	16	Obvious over Bell, Bowdish, Evans, and Hill (EX1013) in view of Tacken and Mueller PCT
4	4-5, 18-26, 29	Obvious over Bell, Bowdish, Evans, and Wang (EX1044) in view of Tacken and Mueller PCT
5	27	Obvious over Bell, Bowdish, Evans, Wang, and Hillmen in view of Tacken and Mueller PCT
6	28	Obvious over Bell, Bowdish, Evans, Wang, and Brown (EX1068) in view of Tacken and Mueller PCT
7	1-3, 6-14, 17	Obvious over Bell, Evans, and Mueller PCT in view of Tacken
8	15	Obvious over Bell, Evans, Mueller PCT, and Hillmen in view of Tacken
9	16	Obvious over Bell, Evans, Mueller PCT, and Hill in view of Tacken
10	4-5, 18-26, 29	Obvious over Bell, Evans, Mueller PCT, and Wang in view of Tacken
11	27	Obvious over Bell, Evans, Mueller PCT, Wang, and Hillmen in view of Tacken
12	28	Obvious over Bell, Evans, Mueller PCT, Wang, and Brown in view of Tacken

Submitted with this petition are the declarations of qualified experts Jeffrey V. Ravetch, M.D., Ph.D. and Cindy Ippoliti, Pharm.D. (EX1003, ¶¶1-14, Ex. A; EX1062, ¶¶1-10, Ex. A.)

V. FACTUAL BACKGROUND

A. Antibody Structure and Humanization of Antibodies

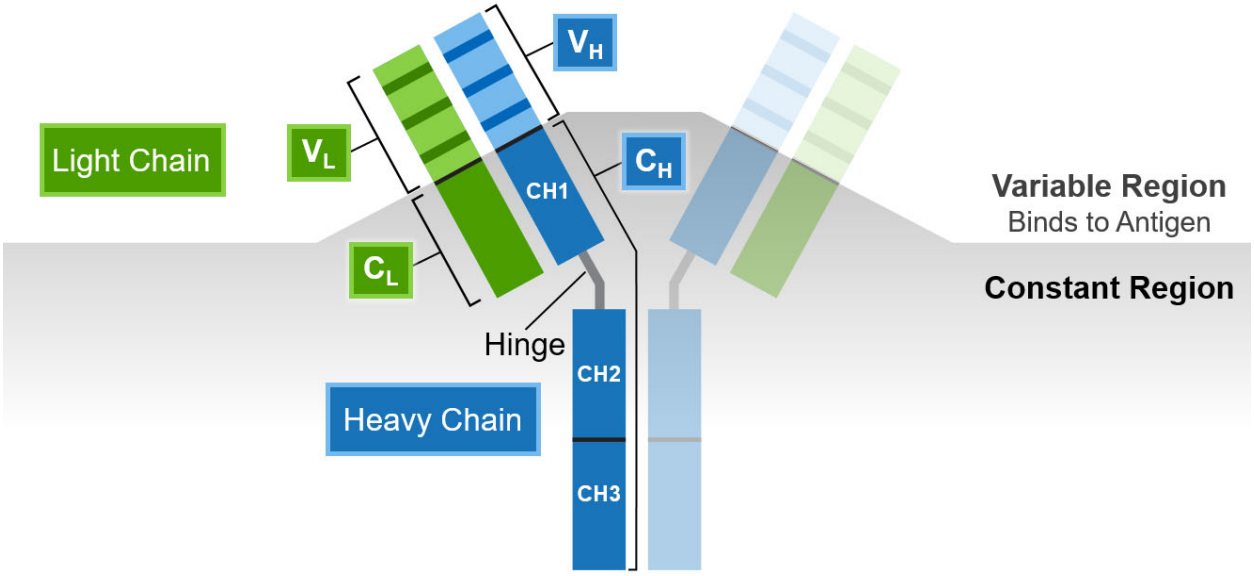
As relevant here, an antibody consists of two pairs of amino acid chains referred to as heavy and light chains. (EX1003, ¶¶35-36.) Each of these chains has a constant and a variable domain. (*Id.*, ¶37; EX1046, 004-06.) The variable domains contain subportions responsible for antigen recognition called Complementarity-Determining Regions ("CDRs"); there are three CDRs each in the variable domains of each heavy and light chain, as shown below:



Basic domain structure of antibody

(EX1003, ¶38; EX1045, 055-57.)

The variable regions of the heavy and light chains are abbreviated as "V_H" and "V_L." The constant region of the heavy chain is broken up into subregions called CH1, CH2, and CH3. CH1 is separated from CH2 and CH3 by a hinge region, as shown below.



Basic domain structure of antibody

(EX1003, ¶¶40-44.) Well before 2007, the process of "humanization" of antibodies – in which mouse antibodies to human targets were converted into mostly human sequences while retaining target-binding function – was well known and routinely practiced by artisans developing antibodies for use as therapies in humans. (*Id.*, ¶¶49-54.)

B. Therapeutic Antibodies Were Routinely Used as Pharmaceutical Compositions by 2007

Before 2007, more than a dozen antibodies had been approved by the FDA

for therapeutic use in humans, including several humanized antibodies. (EX1052; EX1003, ¶55; EX1062, ¶24.) Such antibodies were the basis of pharmaceutical compositions that were most commonly formulated in sterile, preservative-free single use dosage forms and administered by intravenous ("IV") infusion. (EX1003, ¶55; EX1062, ¶25; *see also e.g.*, EX1055, 002.)

C. By 2007, the C5-Binding Antibody Called Eculizumab Was Known as a Treatment for PNH

PNH is a disease of blood cells caused by a genetic mutation that renders the cells more susceptible to destruction by the complement system. (EX1007, [0005]; EX1013, 009.) It is characterized by paroxysmal nocturnal (sudden attacks in the night) hemoglobinuria (hemoglobin in the urine, causing dark coloring). (EX1007, [0007]; EX1013, 009.) Other known clinical symptoms include anemia, fatigue, thrombosis, and pain. (EX1007, [0007]; EX1013, 009; EX1011, 004.) Inhibition of the complement cascade at the step in which C5 is converted to C5a and C5b was recognized as useful for inhibiting PNH symptoms, while retaining upstream complement system activity necessary for immune system function and clearance of microorganisms. (EX1013, 009; EX1011, 004; EX1003, ¶¶56-57; EX1062, ¶26-27.) Each of the Bell, Hill, and Hillmen references disclose the use of pharmaceutical compositions, namely antibody formulations delivered intravenously to PNH patients. (EX1007, [0062], [0082]; EX1013, 010; EX1011, 005.)

By March 15, 2007, one known inhibitor of C5 conversion was the anti-C5 antibody eculizumab. Indeed, more than a year before the '809 patent was filed, several clinical publications disclosed that eculizumab was a useful treatment for PNH. (EX1007, [0052]; EX1013, 009; EX1011, 003; EX1003, ¶58; EX1062, ¶28; *see also* EX1016; EX1017.) As shown in the table below, the prior art contained many express disclosures regarding the successful use of eculizumab as a treatment for PNH; several of these relate to the same eleven patient trial and various extensions of that trial. (*See* EX1007; EX1011; EX1012; and EX1013.)

Reference	Study Identifier	Description
EX1011	C02-001: Phase 2 Pilot	11 PNH patients
EX1013	E02-001: Phase 2, 1st Extension	11 PNH patients, 64 weeks
EX1012	X03-001: Phase 2, 2nd Extension	10 of 11 PNH patients, two years
EX1007	Phase 2, Second Extension	10 of 11 PNH patients, two years
EX1014	Phase 3 "TRIUMPH"	87 PNH patients
EX1015	Phase 3 "SHEPHERD	97 PNH patients

(*See* EX1003, ¶58; EX1067, 003-04.)

D. As of the 2007 Priority Date, Alexion Believed the Sequence of Eculizumab Had Been Publicly Disclosed

By seeking a patent on the amino acid sequence of eculizumab, Alexion represented to the Patent Office that the sequence was novel and nonobvious, but this was not so. On the contrary, Alexion presumably intended to disclose the full amino acid sequence of eculizumab in 1999 and made a submission to Chemical

Abstracts Services ("CAS") for that purpose. In Alexion's words to the European Patent Office, "the sequence for eculizumab was publicly available [before Feb. 3, 2004]," and the "sequence for eculizumab was submitted to [CAS] and entered into their STN database on 14 February 1999[.]" (EX1027, 277, 291 (5.1.2.); EX1003, ¶59.) Alexion later claimed in the European counterpart patent application to the '809 patent that it was not until ten years later, in 2009, that Alexion "learned" that the sequence for eculizumab had "inadvertently" been submitted with errors in the sequences. (EX1028, 235-42, 280-81, 412-13, 522-23.)[1]

Even setting aside the implausibility of Alexion's ten-year delay in discovering that it had submitted erroneous sequence information to CAS, as discussed in Part VIII below, the prior art still anticipated and rendered these sequences obvious.

E. Eculizumab Development and Naming History

When first identified as a mouse antibody that specifically binds C5, Alexion scientists gave it the name "5G1.1." (EX1010, 006-07.) This mouse antibody was then "humanized," meaning that the CDR domains responsible for C5 binding were

[1] The EPO refused to grant the application, in part based on its conclusion that "[e]culizumab is considered to have been available to the public before the filing date of the present application." (EX1028, 1444.)

grafted into a human "framework" variable region, using techniques that were well-developed by the mid-1990s. (*Id.*, 007-08; EX1003, ¶¶54, 61; EX1050, 010-12; EX1051; EX1052.) The resulting humanized antibody maintains fully mouse sequences in each of its six CDR domains, but otherwise uses human sequences for the variable region to varying degrees; this antibody was given the name "h5G1.1" by Alexion. (EX1010, 010-12; *see also* EX1005, 43:6-14, 43:62-45:4.) After confirming that the humanized antibody variable domain retained its C5-binding function, Alexion scientists assembled it into a full-length antibody of the human IgG4 isotype, which they named "h5G1.1 HuG4." (EX1010, 013; EX1003, ¶61.)

Soon after creating this antibody, Alexion set about improving it by modifying the constant region to give it a hybrid IgG2/IgG4 backbone. (EX1006, 013-14; *see also* EX1009, 014, 097 (referencing "h5G1.1 G2/G4").) Alexion sought to reduce or eliminate binding by the constant region of the IgG4 isotype to other proteins such as FcR and C1q that are involved in human immune responses and the complement system, by replacing it with comparable IgG2 sequences. (EX1006, 015-16; EX1003, ¶¶45-48, 62; *see also* EX1048, 013-14.) Specifically, the improved antibody contained the CH1 and hinge region from IgG2 and the CH2 and CH3 regions from IgG4; Alexion confirmed that this modification did not impact binding to C5. (EX1006, 015-16.) Alexion called this antibody "h5G1.1 HuG2/G4." (*Id.*; EX1003, ¶62.) In a companion patent application describing the same work,

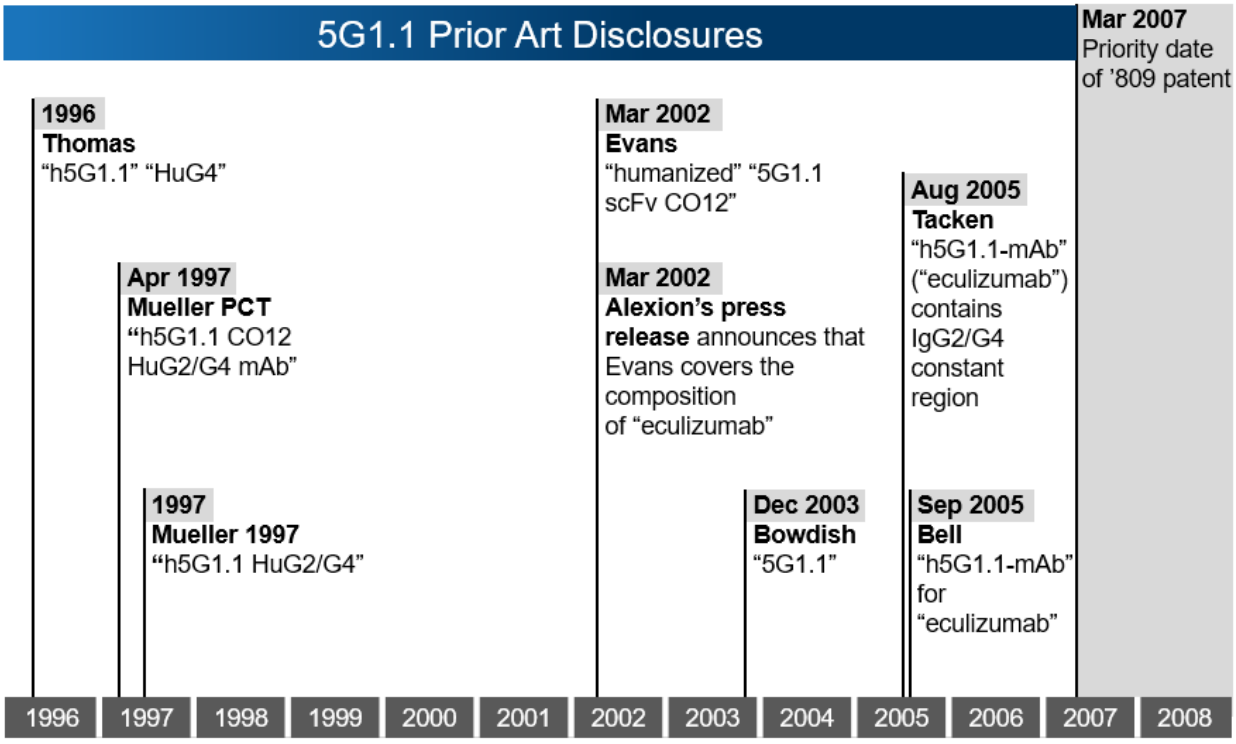
Alexion referred to this antibody interchangeably as "h5G1.1 G2/G4" and "h5G1.1 CO12 HuG2/G4." (EX1009, 014, 097; EX1003, ¶62.)

By 2002, Alexion had obtained a unique name for this antibody pursuant to the World Health Organization's guidelines for international nonproprietary names ("INNs"). Under INN rules in place since the 1990s, antibodies are named as follows: A random prefix of a few letters chosen by the product sponsor for uniqueness (in this case "ecu-") is followed by a "sub-stem" indicating its function (immunomodulators use "-li-"), followed by another sub-stem indicating humanization ("-zu-"), finally followed by the stem "-mab" applied to all monoclonal antibodies. (EX1019, 031-32.) Thus, Alexion's antibody received the nonproprietary name ecu-li-zu-mab. (EX1003, ¶63.)

Publications and statements by Alexion and others before 2007 clearly disclosed that the humanized 5G1.1 antibody *with* a hybrid G2/G4 constant domain <u>*was*</u> eculizumab. The Tacken reference referring to eculizumab as Alexion's "potential product" specifically identified eculizumab as the h5G1.1 antibody with an "IgG2/IgG4 constant region." (EX1008, 010-11.) Tacken further cited to the Mueller 1997 article discussed above, which discloses the conversion of h5G1.1 to

the HuG2/G4 form. (*Id.*, 011, 017 (ref. 17); EX1003, ¶64.)[2] Similarly, in a 2002 press release, Alexion announced the issuance of the Evans patent, which Alexion said "cover[s] the composition and use of Alexion's lead drug candidate[] eculizumab (formerly known as 5G1.1)." (EX1003, ¶65; *see also* EX1022, 18:7-13.) Alexion also disclosed in Bowdish that it used the 5G1.1 antibody as a framework to create antibodies for other targets. (EX1004, [0191].) Bell uses parentheses to equate the two terms: "h5G1.1-mAb (eculizumab)." (EX1007, 13; EX1003, ¶68.) Likewise, a 2002 review of eculizumab identified its "synonyms" as 5G1.1 and h5G1.1. (EX1023, 001; EX1003, ¶66; *see also* EX1018, 011.) *No* reference states that eculizumab has exclusively IgG4 constant domain. (EX1003, ¶¶66-69.) A figure of the publications that discussed development of the 5G1.1 antibody before 2007 is shown below:

[2] Although Tacken includes an obvious typo in its spelling of eculizumab ("eculizamab"), under the INN guidelines discussed above there are no allowed names for antibodies with the stem "-zamab," and a POSA would know that a humanized antibody such as eculizumab would have the stem "-zumab." (EX1003, ¶64.)



Alexion admitted in other patent office proceedings that "it was well-known to one of ordinary skill in the art [as of 2002] that eculizumab has a G2/G4 Fc portion, *i.e.*, a mutated Fc portion" and that "h5G1.1 … [was] well-known to one of ordinary skill in the art as eculizumab[.]" (EX1029, 010-11; *see also* EX1003, ¶70.) Alexion based these statements on the disclosures of the same Evans and Mueller 1997 references used by Petitioner in the Grounds below. (*Id.*)

Alexion also stated publicly that its eculizumab/Soliris product corresponds to the sequences disclosed in the Evans patent. For example, Alexion announced in a 2002 press release that the Evans patent "cover[s] the composition and use of … eculizumab (formerly known as 5G1.1)." (*See* EX1020, 001; EX1003, ¶65.) Having to choose one patent for patent term extension for the eculizumab product

(*see* 35 U.S.C. § 156(c)(4)), Alexion chose Evans, not the '809 patent at issue here. In its application for PTE, Alexion represented that "U.S. Patent 6,355,245 [Evans] claims the Approved Product [eculizumab]" and provided a claim chart comparing the Evans patent claims to eculizumab. (*See* EX1030, 004-07; EX1031.)

VI. OVERVIEW OF THE '809 PATENT

The '809 patent has 29 issued claims; claim 1 is independent:

> 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.
>
> 2. The method of claim 1, wherein the antibody is formulated in a pharmaceutical composition comprising a single unit dosage form.
>
> 3. The method of claim 2, wherein the single unit dosage form is a 300 mg single unit dosage form.
>
> 4. The method of claim 3, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.
>
> 5. The method of claim 4, wherein the antibody is diluted to a concentration of 5 mg/mL prior to administration.
>
> 6. The method of claim 1, wherein the patient is anemic.
>
> 7. The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.
>
> 8. The method of claim 1, wherein the patient is dosed as follows: 600

mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. The method of claim 1, wherein the patient exhibits decreased lactate dehydrogenase levels after treatment with the antibody.

10. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

11. The method of claim 10, wherein the immediate decrease occurs within one week of administration of the antibody.

12. The method of claim 1, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

13. The method of claim 1, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

14. The method of claim 12, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

15. The method of claim 1, wherein the patient has about a 51% likelihood of transfusion avoidance after administration of the antibody.

16. The method of claim 1, wherein the patient has less than a 3% likelihood of developing antibodies to the antibody that binds C5 after 26 weeks of treatment.

17. The method of claim 1, wherein the patient exhibits improved quality of life as measured by a FACIT-Fatigue score or an EORTC QLQ-C30 score.

18. The method of claim 5, wherein the patient is treated with the antibody for at least 26 weeks.

19. The method of claim 5, wherein the patient is anemic.

20. The method of claim 5, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

21. The method of claim 5, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

22. The method of claim 5, wherein the patient exhibits decreased lactate dehydrogenase levels after treatment with the antibody.

23. The method of claim 5, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

24. The method of claim 23, wherein the immediate decrease occurs within one week of administration of the antibody.

25. The method of claim 5, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

26. The method of claim 5, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration

of the antibody.

27. The method of claim 5, wherein the patient has about a 51% likelihood of transfusion avoidance after administration of the antibody.

28. The method of claim 5, wherein the patient exhibits improved quality of life as measured by a FACIT-Fatigue score.

29. The method of claim 5, wherein the patient exhibits improved quality of life as measured by an EORTC QLQ-C30 score.

(EX1001, 39:14-40:57; EX1003, ¶71; EX1062, ¶29.)

A. Person of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") would have knowledge of the scientific literature and have skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007. (EX1003, ¶¶16-20; EX1062, ¶¶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*.)

B. Overview of the Specification

The '809 patent describes the use of antibodies binding to the complement cascade protein C5 as a treatment for PNH. In particular, the '809 teaches that such antibodies "are known," and that a preferred antibody is disclosed in the Evans reference and "now named eculizumab." (EX1001, 12:34-37.) The patent describes details of the Phase 3 "TRIUMPH" clinical trial in which one such antibody, eculizumab, was evaluated in PNH patients. (*Id*., 19:63-28:42.) The patent also provides amino acid sequences for eculizumab's heavy and light chains as SEQ ID NOS:2 and 4, respectively. (*Id.*, Cols. 30-37; EX1003, ¶¶72-73.) The patent also provides details relating to the route of administration of eculizumab (IV infusion), the dose format (single use, sterile, preservative-free), the dose unit (300 mg), the formulation volume size and concentration (30 mL of a 10 mg/ml solution), and final dilution (5 mg/ml), although it makes no claims of novelty as to any of these conventional features. (EX1062, ¶¶31-32.)

C. '809 Prosecution History

Alexion's original claims were rejected for nonstatutory obviousness-type double patenting over claims of other Alexion patents in view of Hillmen, Evans and Wang. (EX1002, 634-67.) The Examiner also noted: "Evans teaches the antibody

5G1.1. However, Evans does not teach an antibody that binds C5 having SEQ ID NO: 2 for the H chain and SEQ ID NO: 4 for the L chain." (*Id*., 667.)

Alexion responded by filing terminal disclaimers, and further argued that "Evans does not disclose or even mention 'eculizumab.'" (*Id.*, 776-77 (emphasis omitted).) The Examiner then allowed the claims, "confirm[ing] … Evans does not disclose or mention 'eculizumab." (*Id*., 1877.) The Examiner also noted that "Evans does teach scFVs which comprise the CDRs of 5G1.1 (example 11) but these lack at least the constant region of the antibodies in the claimed methods." (*Id.*, 1878.) As explained in this Petition and further in Part X.B, the Examiner erred in allowing the claims by overlooking disclosures of several other prior art references that, in combination, disclose the complete antibody sequence. (*See infra* X.B; EX1003, ¶¶74-76.)

VII. CLAIM CONSTRUCTION

Petitioner does not believe claim construction is necessary at this time.

VIII. THE CHALLENGED CLAIMS ARE UNPATENTABLE

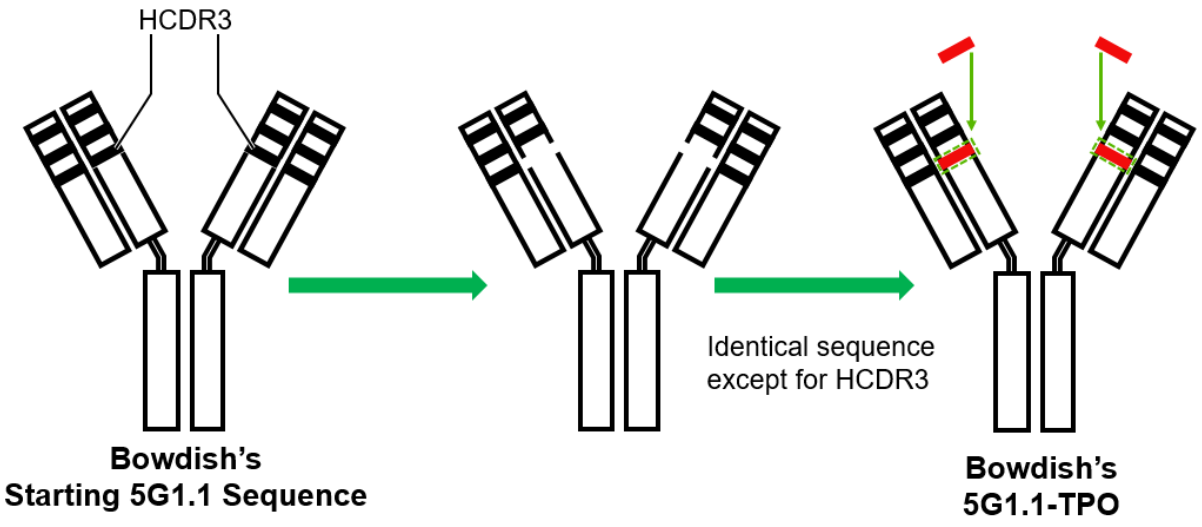
A. Prior Art References Cited in Proposed Grounds

The priority date of the '809 patent is March 15, 2007.[3] Each reference in Grounds 1-12 (*see supra* IV.B) qualifies as prior art under 35 U.S.C. § 102(b).

1. Bowdish [EX1004]

Bowdish is a U.S. patent application, published on December 18, 2003, and is thus prior art under 35 U.S.C. §102(b). Bowdish's 5G1.1 antibody discloses outright the light chain sequence (SEQ ID NO:4) in claim 1 of the '809 patent in Figure 13B. (EX1004, Fig. 13B; EX1003, ¶¶80-83.) Bowdish's 5G1.1 was also a starting point for making a new heavy chain that includes a "TPO mimetic peptide," as illustrated below. (EX1004, Fig. 13A & [0191]; EX1003, ¶84.)

[3] Petitioner assumes this date for this Petition without waiving its right to challenge this priority date.



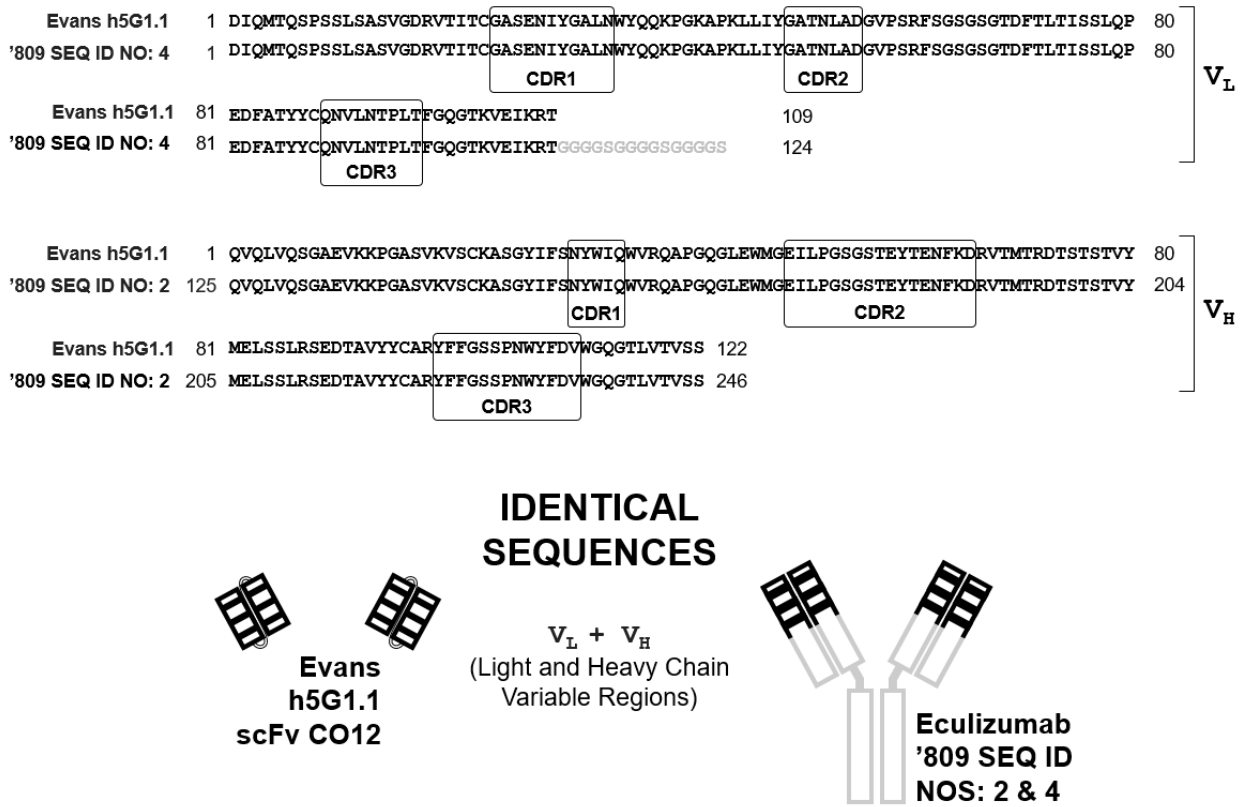
That starting heavy chain sequence is described as having the sequence of Figure 13A with a substituted heavy chain CDR3 ("HCDR3") domain reported by Evans, which is incorporated by reference. That original sequence is identical to SEQ ID NO:2 of claim 1.

Bowdish also teaches that its antibodies can be formulated as "pharmaceutical compositions," can be administered intravenously through known methods, and that such compositions "must be sterile" and that they can optionally include preservatives. (EX1004, [0148]-[0151]; EX1003, ¶85; EX1062, ¶¶35-36.)

2. Evans [EX1005]

Evans is a U.S. patent issued on March 12, 2002, based on application number 08/487,283. It is prior art under 35 U.S.C. §102(b). Evans is titled "C5-Specific Antibodies for the Treatment of Inflammatory Diseases." Example 11 provides eighteen constructs of "recombinant mAb-encoding DNAs." Of these, nine

constructs provide sequences for humanized 5G1.1 single-chain variable fragments (scFv), which correspond to V_H and V_L domains joined by a short peptide linker and starting with the "MA" leader sequence. (EX1005, 43:6-14, 43:61-45:4 (Example 11 (2) and (11)-(18)); EX1003, ¶¶87-88.) The nine constructs disclose CDR sequences within the variable regions of humanized 5G1.1, and Evans' CO12 scFv construct discloses the light and heavy chain variable domains of SEQ ID NOS:2 and 4 of claim 1:



(EX1005, 44:4-14 (Example 11, (12)); EX1003 ¶89.) All nine constructs disclose the identical heavy chain CDR3 sequence of SEQ ID NO:2 of claim 1. (EX1003, ¶88, Appendix A.)

Evans also teaches that its anti-C5 antibodies can be administered "in a variety of unit dosage forms," and that doses are typically from 1 to 100 mg per kg and preferably 5 to 50 mg per kg of patient weight. (EX1005, 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*., 18:29-43; EX1003, ¶90; EX1062, ¶¶37-38.)

3. Bell [EX1007]

Bell is a U.S. patent application published on September 1, 2005, and is thus prior art under 35 U.S.C. §102(b). Bell teaches that anti-C5 antibody known as "h5G1.1-mAb (eculizumab)" is a "particularly useful" treatment for PNH. (EX1007, [0012], [0052], [0081]-[0083], [0096], Fig. 3.) Bell also teaches that "[m]ethods for the preparation of" h5G1.1 "are described in" Evans (EX1005) and Thomas (EX1010), "the disclosures of which are incorporated [into Bell] in their entirety." (EX1007, [0052]; EX1003, ¶93; EX1062, ¶¶39-40.)

Bell teaches that formulations of its anti-C5 antibodies "suitable for injection" "must be sterile" and may or may not contain preservatives. (EX1007, [0062]; EX1003, ¶96; EX1062, ¶41.) Bell discloses human clinical studies in which eculizumab was administered intravenously at a dose of 600 mg every 7±1 days for four weeks, followed by a 900 mg dose one week later and then a 900 mg

maintenance dose every 14±2 days later. (EX1007, [0082]; *see also id.*, [0088]; EX1003, ¶¶92-93.)

Bell discloses that eculizumab is an effective treatment for PNH. (EX1007, [0081]-[0097], Figs. 1a, 1b, 3, 6a, 6b, 7-10; EX1003, ¶94; EX1062, ¶39.) Bell further teaches that when used as a treatment for PNH in a clinical trial, eculizumab resulted in an immediate (i.e., within one week of administration) and sustained decrease in the mean levels of lactate dehydrogenase (LDH). (EX1007, [0085], Fig. 1b.) The inclusion criteria for the Bell trial required that patients have received four or more transfusions in the 12 months prior to the study; at least four of the patients in the trial had platelet counts above 150,000 per microliter. (*Id.*, [0081], [0089], Claim 14; EX1003, ¶95.) Bell's trial also disclosed treatment with eculizumab for up to two years. (*Id.*, [0082], [0091]; EX1003, ¶94.)

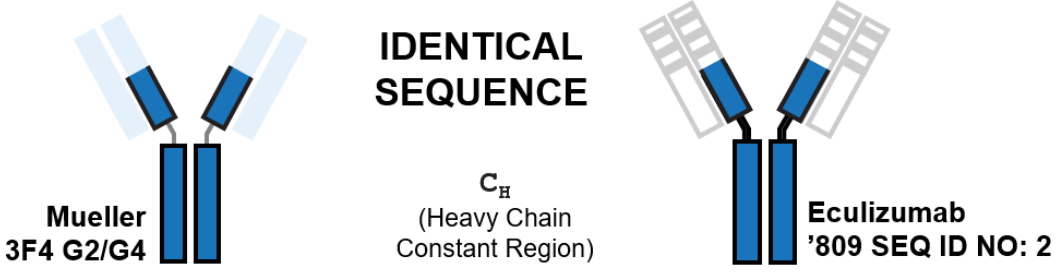
4. Tacken [EX1008]

Tacken is a journal article published on August 15, 2005, and is thus prior art under 35 U.S.C. §102(b). Tacken teaches that "h5G1.1-mAb" is "eculizamab [*sic*]." (EX1008, 011.) Tacken states that h5G1.1-mAb contains the "human hybrid IgG2/IgG4 constant domain," and further cites to the Mueller 1997 reference for these domains. (*Id.*; EX1003, ¶98.)

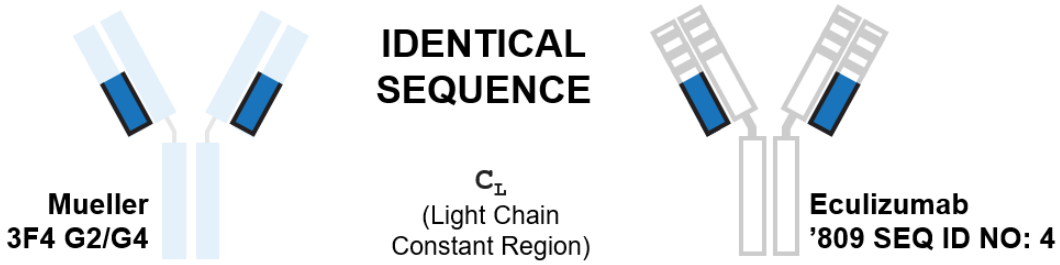
5. Mueller PCT [EX1009]

Mueller PCT, published on April 3, 1997, is the companion international patent application of the Mueller 1997 reference cited by Tacken. It is prior art under 35 U.S.C. §102(b). Mueller PCT discloses sequences for anti-pVCAM antibodies, including the full-length 3F4 HuG2/G4 antibody, which contains a hybrid IgG2/G4 heavy chain constant region with "the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4[.]" (EX1009, 8:23-26, 12:23-27; EX1003, ¶¶100-101.) Mueller PCT refers to antibodies with this IgG2/G4 constant region as "**HuG2/G4 mAb**." (EX1003, ¶102 (emphasis added).) Mueller PCT describes using "h5G1.1 CO12 **HuG2/G4 mAb**" and discloses the amino acid sequences for the constant regions of SEQ ID NOS:2 and 4 of claim 1:

Mueller 3F4 G2/G4 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
'809 SEQ ID NO: 2 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Mueller 3F4 G2/G4 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
'809 SEQ ID NO: 2 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Mueller 3F4 G2/G4 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
'809 SEQ ID NO: 2 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Mueller 3F4 G2/G4 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
'809 SEQ ID NO: 2 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Mueller 3F4 G2/G4 C_H	321	SLSLGK	326
'809 SEQ ID NO: 2 C_H	321	SLSLGK	326



Mueller 3F4 C_L	1	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH	80
'809 SEQ ID NO: 4 C_L	1	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH	80
Mueller 3F4 C_L	81	KVYACEVTHQGLSSPVTKSFNRGEC	105
'809 SEQ ID NO: 4 C_L	81	KVYACEVTHQGLSSPVTKSFNRGEC	105



(*Id.*, ¶¶100-104; EX1009, 054-55, 058-59.)

6. Wang [EX1044]

Wang is a U.S. patent application, published on December 8, 2005, and is thus prior art under 35 U.S.C. § 102(b). Wang describes various methods and compositions for formulation of antibodies, including eculizumab, that inhibit activation of the complement system. (EX1044, Abstract, [0004].) Wang's teachings identify the anti-C5 antibody eculizumab as a preferred embodiment, citing to Evans. (*Id.*, [0004], [0011], [0067].) Wang expressly teaches that eculizumab formulations "may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." (*Id.*, [0067].) Wang further provides specific examples disclosing that eculizumab can be effectively formulated in solutions with concentrations ranging from 1 mg/ml to 30 mg/ml while maintaining the integrity of the antibody. (*Id.*, Fig. 10, [0025], [0170]-[0173]; EX1003, ¶¶106-107; EX1062, ¶¶44-45.)

7. Hillmen [EX1011]

Hillmen is a New England Journal of Medicine manuscript, published on February 5, 2004, and is thus prior art under 35 U.S.C. § 102(b). Hillmen describes the results of the same eleven patient Phase 2 trial of eculizumab in PNH patients that is disclosed in Bell, and provides additional disclosures regarding the ability of eculizumab to confer transfusion avoidance on PNH patients. (EX1011, 007 (Table 1); EX1003, ¶109.)

8. Hill [EX1013]

Hill is a manuscript in the American Society of Hematology journal "Blood," published online on June 28, 2005, and is thus prior art under 35 U.S.C. § 102(b). Hill again describes the results of the same eleven patient Phase 2 trial of eculizumab in PNH patients that is disclosed in Bell and Hillmen, but provides additional details regarding the 52-week extension of the original 12 week study, and provides additional teachings about the lack of any anti-eculizumab antibodies detected in PNH patients in the trial. (EX1013, 013; EX1003, ¶111.)

9. Brown [EX1068]

Brown is a manuscript in the American Cancer Society journal "Cancer," published online on November 22, 2004, and is thus prior art under 35 U.S.C. § 102(b). Brown reports close correlation of quality of life data between the fatigue-

subscale of the "EORTC" and "FACIT-Fatigue" scales in its patient study. (EX1068, 002, 004; EX1003, ¶113.)

B. Overview of Proposed Grounds for IPR

Grounds 1-6 are based, at their core, on obviousness from combining Bell, Bowdish, and Evans in view of Tacken and Mueller PCT. (EX1003, ¶¶115-173; EX1062, ¶¶46-61.) A POSA would have been motivated to obtain the sequence of eculizumab (identical to SEQ ID NOS:2 and 4) by Bell, which teaches that eculizumab, also known as "h5G1.1," is a "particularly useful" antibody for treatment of PNH. Bell, like Bowdish, points to Evans for preparation of the h5G1.1 antibody. A POSA would have obtained SEQ ID NOS:2 and 4 from Bowdish and Evans. Bowdish provides the entire eculizumab amino acid sequence through SEQ ID NOS:67 and 69 and the incorporation by reference of the heavy chain CDR3 of Evans. Specifically, Bowdish provides the framework for the humanized IgG2/G4 eculizumab antibody and incorporates by reference the 13 amino acid heavy chain CDR3 for humanized 5G1.1 that Evans discloses to complete the eculizumab sequence. And Bowdish discloses the exact light chain of SEQ ID NO:4 outright. Thus, Bowdish and Evans as a single integrated document disclose the full sequence of Bowdish's 5G1.1 antibody, the exact antibody sequence recited in challenged claim 1 (SEQ ID NOS:2 and 4), as a pharmaceutical composition. Tacken and Mueller PCT provide additional guidance to a POSA to confirm that Bowdish's

5G1.1 antibody is Alexion's "potential product," known both as h5G1.1 and eculizamab (*sic*), which contains the IgG2/IgG4 constant region reported in the Mueller 1997 reference (also disclosed in Mueller PCT). With this guidance, a POSA would have understood that the starting sequence used by Bowdish, having the heavy chain CDR3 of Evans, was eculizumab (SEQ ID NOS:2 and 4). With the obviousness of using the claimed sequences to treat PNH established, the remaining dependent claims of the '809 patent are shown to be obvious over the Wang, Hillmen, Hill, and Brown references.

Grounds 7-12 are based on obviousness in combining Bell, Evans, and Mueller PCT in view of Tacken. (EX1003, ¶¶174-188; EX1062, ¶¶46-61.) Bell teaches that eculizumab, also known as "h5G1.1," is a "particularly useful" antibody for treatment of PNH. Bell points to Evans for the complete variable region sequences of eculizumab under the name "humanized 5G1.1," which corresponds to the variable regions of SEQ ID NOS:2 and 4. Bell and Evans are combined with Mueller PCT, which teaches the constant regions of SEQ ID NOS:2 and 4. The combination of Evans and Mueller PCT is directed by Tacken, which confirms the constant region of eculizumab is the IgG2/G4 type taught by Mueller PCT. In addition, Mueller PCT's disclosure of "h5G1.1 CO12 HuG2/G4" specifically teaches a POSA to combine with the CO12 variable domain from Evans, resulting in an antibody as a pharmaceutical composition that is a 100% match for SEQ ID

NOS:2 and 4 as recited in challenged claim 1. As with Grounds 1-6, the remaining dependent claims of the '809 patent are shown to be obvious over the Wang, Hillmen, Hill, and Brown references in the same fashion.

This petition is supported by the declaration of Dr. Jeffrey Ravetch, M.D., Ph.D., a renowned expert in antibody structure, modification of antibody domains, and development of therapeutic antibodies for a variety of human diseases (EX1003, ¶¶1-14, 19-20); and Dr. Cindy Ippoliti, Pharm.D., a skilled pharmaceutical scientist with over 30 years of experience in the administration of therapeutic antibody drugs to patients (EX1062, ¶¶1-9, 17-18).

C. Ground 1: Claims 1-3, 6-14, and 17 Are Obvious Over Bell, Bowdish, and Evans in view of Tacken and Mueller PCT

1. Claim 1

Bell teaches that eculizumab, also referred to as h5G1.1, had been successful in the treatment of PNH. Bell discloses that a "[p]articularly useful" treatment for PNH is the anti-C5 antibody known as "h5G1.1-mAb (eculizumab)." (EX1007, [0012], [0052], [0082]; EX1003, ¶115.) As Bell explains, by 2005 "[t]he antibody h5G1.1" carried the "tradename eculizumab." (EX1007, [0052].) Bell discloses human clinical trial evidence that eculizumab is an effective treatment for PNH. (*Id.*, [0003], [0012], [0081]-[0097], Figs. 1a, 1b, 3, 6a, 6b, 7-10.) Each of Bell, Bowdish, and Evans discloses intravenous administration of anti-C5 antibodies. (*See id.*,

[0060], [0082]; EX1004, [0148]-[0151]; EX1005, 18:29-43; EX1003, ¶116; EX1062, ¶48.)

These definitive clinical data would have more than motivated a POSA to obtain the structure of eculizumab. (EX1003, ¶117.) Although Bell's disclosure does not include the exact amino sequence of eculizumab, Bell teaches that the antibody h5G1.1 *is* eculizumab, and that "methods for the preparation of" h5G1.1 "are described in" Evans (EX1005) and Thomas (EX1010), both of which are incorporated into Bell in their entirety. (EX1007, [0052].) Based on Bell's reference to Evans for h5G1.1, and Evans' disclosure of humanized scFv sequences (discussed below), a POSA would have understood that Evans contains the variable region sequences for eculizumab. And as discussed further below, a POSA would not have wrongly concluded from Bell's citation to Thomas that the eculizumab disclosed in Bell would have an IgG4 isotype as discussed in the Thomas reference. (*See infra* VIII.C.1.b; EX1003, ¶¶118, 136.)

(a) Bowdish and the Incorporated Evans Reference Provide the Complete Sequence of h5G1.1

Bowdish is an Alexion patent publication that, through incorporation by reference of Evans, discloses both SEQ ID NOS:2 and 4, as claimed in the '809 patent. Bowdish's SEQ ID NO:69 discloses the light chain sequence of SEQ ID NO:4 in claim 1 of the '809 patent, exactly. (EX1004, Fig. 13B; EX1003, ¶¶119-120.)

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Bowdish SEQ ID NO: 69   1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  80
'809 SEQ ID NO: 4       1 ----------------------DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  58
                                                          CDR1                    CDR2

Bowdish SEQ ID NO: 69  81 PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN 160
'809 SEQ ID NO: 4      59 PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN 138
                                                  CDR3

Bowdish SEQ ID NO: 69 161 FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
'809 SEQ ID NO: 4     139 FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
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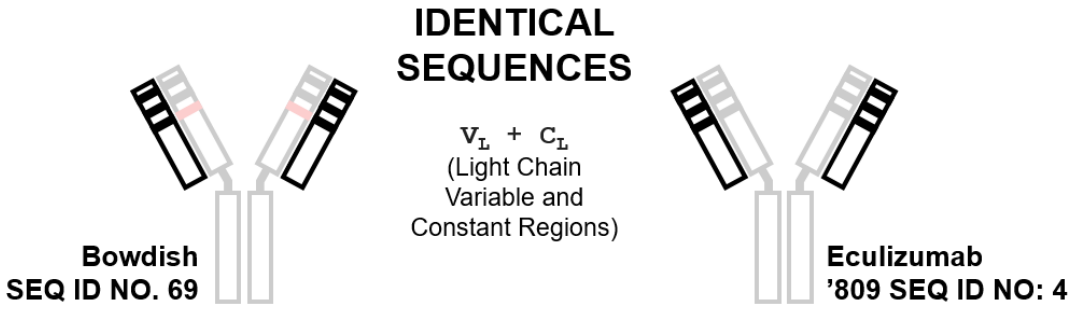
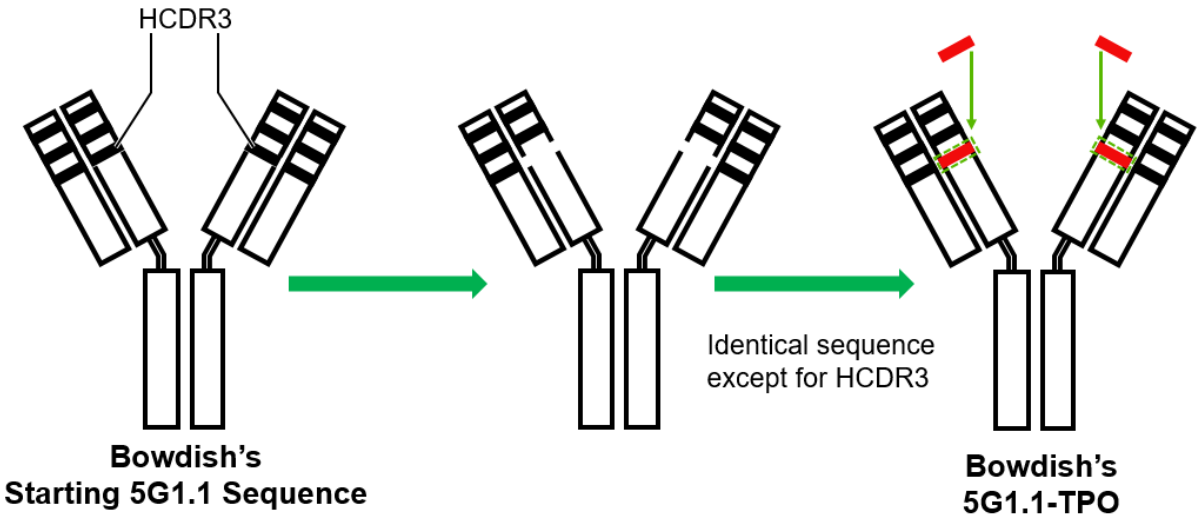
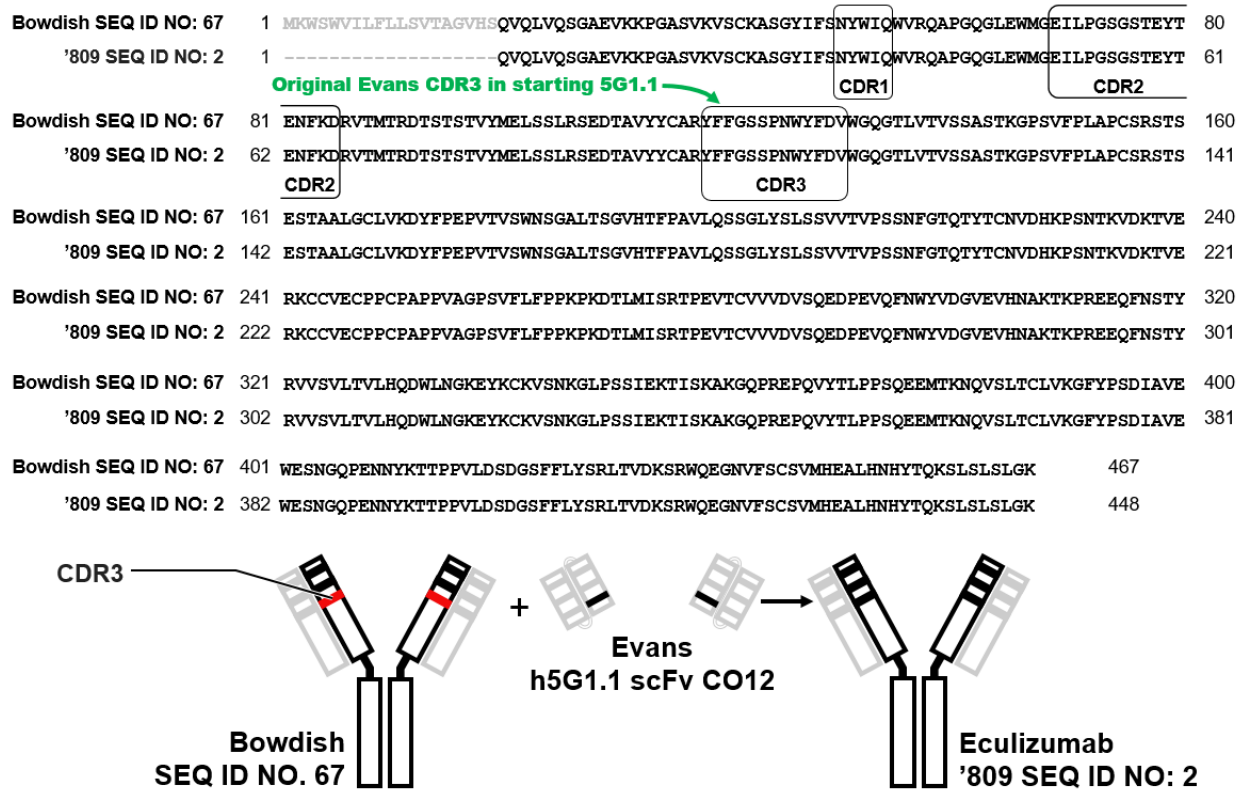


In addition, Bowdish explains that it created SEQ ID NO:67 from a starting heavy chain sequence that is identical to SEQ ID NO:2. Bowdish's SEQ ID NO:67 discloses all elements of the heavy chain sequence of SEQ ID NO:2 in claim 1, with the exception of the 13 amino acid "native CDR3" of "5G1.1" within SEQ ID NO:2. (EX1004, Fig. 13A, [0191]; EX1003, ¶121.) Bowdish explains that the "native CDR3" has been replaced with a TPO mimetic peptide and identifies the sequence of that peptide. (*Id.*) Critically, Bowdish identifies the Evans U.S. Application Ser. No. 08/487,283 (published in 2002 as Evans patent '245 (*see* EX1005, Cover)) as disclosing the "native CDR3" and incorporates the Evans application by reference. (*See* EX1004, [0191]; EX1003, ¶121.) Accordingly, Bowdish identifies the heavy

chain sequence that had the "native CDR3" before it was replaced with the TPO peptide's HCDR3.



In other words, the original heavy chain of Bowdish's 5G1.1 antibody contained Evans' "native CDR3," YFFGSSPNWYFDV, before it was replaced with the TPO mimetic peptide, LPIEGPTLRQWLAARAPV, as shown in SEQ ID NO:67. (EX1003, ¶122; EX1004, [0191]; EX1005, Fig. 19, 43:6-14, 43:61-45:4.) Accordingly, the original heavy chain has the identical sequence as SEQ ID NO:2 of claim 1.



(EX1003, ¶122.) There can be no doubt that the 5G1.1 sequences taught in Evans encode antibodies that bind C5. (EX1005, Cover (Title), 7:60-64, 9:44-45, Fig. 8, Claim 19; *see also* EX1022, 16:10-12; EX1003, ¶123.) Bowdish's disclosure thus teaches the antibody sequence recited in claim 1, indeed, as the Board previously concluded, "Bowdish discloses a substantial portion of the anti-C5 antibody 5G1.1 and points to Evans as evidencing the remaining amino acid sequence." (EX1024, 045.)

A POSA following Bowdish's incorporation of Evans would have no difficulty immediately identifying the sequence Bowdish refers to as "the native CDR3." Evans' Example 11 teaches the construction of recombinant antibodies

using the heavy and light chain CDRs of the 5G1.1 antibody. (EX1005, 42:56-45:33; EX1003, ¶123.) In all, Evans' Example 11 provides eighteen constructs of "recombinant mAb-encoding DNAs." Of these, nine provide humanized single-chain variable domain structures ("scFvs") which correspond to the V_H and V_L domains of an antibody joined by a short peptide linker and starting with the "MA" leader sequence. (EX1005, 42:56-45:33; EX1003, ¶¶123-125.) Importantly, the *identical* HCDR3 sequence is used in *every one* of these examples. (EX1005, 9:65-10:20, 42:56-45:33, 143:22-144:14, Figs. 18-19, Claim 19; EX1003, ¶126, Appendix A.) This is not surprising, since the CDR regions determine binding to target (here, C5), and are a fundamental component of the uniqueness of a particular antibody such as 5G1.1. (EX1003, ¶126.)

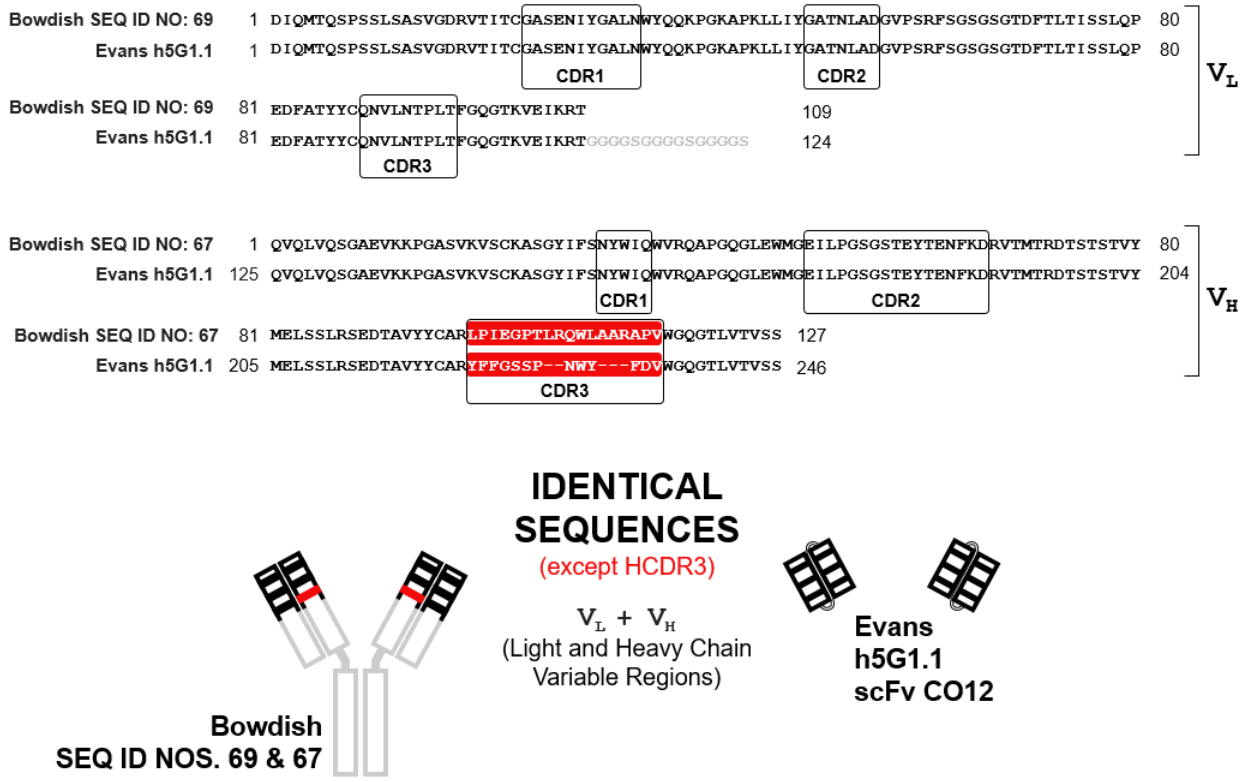
Bowdish's express incorporation by reference of Evans is operative to bring the entire disclosure of Evans within Bowdish "as if it were explicitly contained therein." *See Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906 (Fed. Cir. 2018). The disclosure in Bowdish specifically incorporates Evans for "[c]onstruction of 5G1.1." (EX1004, [0191].) That is, Bowdish identifies specifically what material from Evans is being incorporated, and expressly incorporates those teachings without qualification. Accordingly, Bowdish and Evans must be treated as an integrated single reference. *Paice*, 881 F.3d at 906-07.

The disclosure of Bowdish and Evans as a single integrated document is also enabling. It does not matter whether either of the Bowdish or Evans inventors, on their own, actually made the assembled sequence of eculizumab. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380-81 (Fed. Cir. 2003) ("A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter."). It only matters that the Bowdish and Evans integrated document discloses sufficient information to make eculizumab. *Id; see also Novo Nordisk Pharms., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347, 1356 (Fed. Cir. 2005) (reference disclosed production of hGH protein in an enabling manner which, in combination with "standard recombinant DNA techniques" known to a POSA, could be used to produce the protein.). (*See also* EX1003, ¶127.)

Further, a POSA looking to obtain the amino acid sequences for h5G1.1 (eculizumab) would have easily found Bowdish and considered it to be analogous art to Bell, and to the field of the challenged patent, because it provides express teachings about the structure of the antibody "5G1.1," identifies "Alexion Pharmaceuticals" as the inventors' addressee, and cites to the same Evans patent as does Bell for the structure of 5G1.1. (EX1004, Cover, [0191]; EX1003, ¶128; *see supra* VIII.A.3.) These links are more than sufficient to meet the standard for

analogous art. *See Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000-01 (Fed. Cir. 2016); *In re GPAC Inc*., 57 F.3d 1573, 1577-79 (Fed. Cir. 1995).

Although Bowdish calls its antibody framework "5G1.1," a POSA would have understood that it is referring to h5G1.1 based on a comparison of Bowdish's and Evans' variable region sequences. (EX1003, ¶129.) 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* EX1004, Figs. 13A & 13B.) A routine comparison of these sequences with Evans' constructs in Example 11 would have quickly revealed that Evans' SEQ ID NO:20 is identical to the variable regions in Bowdish's SEQ ID NOS:69 and 67, except for the HCDR3 sequence:



(EX1003, ¶129.) Evans' SEQ ID NO:20 is designated "***humanized***" 5G1.1 scFv. Further, since Bowdish used an "anti-human IgG" in a binding assay to detect 5G1.1, it would have been evident to a POSA that Bowdish discloses humanized 5G1.1. (*Id.*, ¶¶81, 130; EX1004, [0192].) Thus, a POSA would have understood that Bowdish's antibody framework sequences in SEQ ID NOS:67 and 69, including the constant region sequences, are indeed humanized 5G1.1 (*i.e.*, h5G1.1). (EX1003, ¶130.)

(b) Tacken and Mueller PCT Confirm that Bowdish's 5G1.1 Is Eculizumab

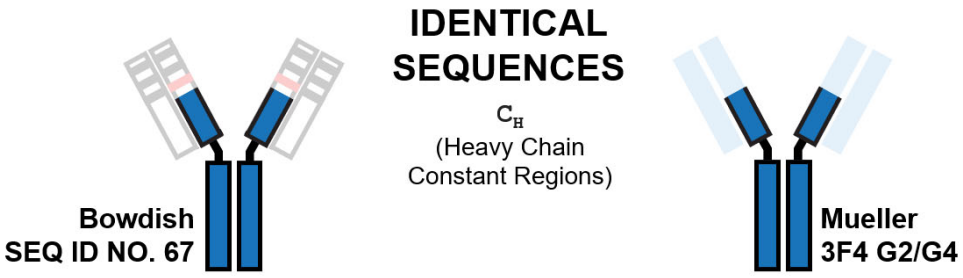
The Tacken reference would have further confirmed that Bowdish contains the desired constant regions of eculizumab. First, Tacken is yet another reference

that equates h5G1.1 with eculizumab. (EX1008, 010; *see supra* VIII.A.4.) Second and critically, Tacken teaches that eculizumab contains an IgG2/IgG4 constant region that is "the same" as that disclosed in Tacken's reference 17, which is the Mueller 1997 article.

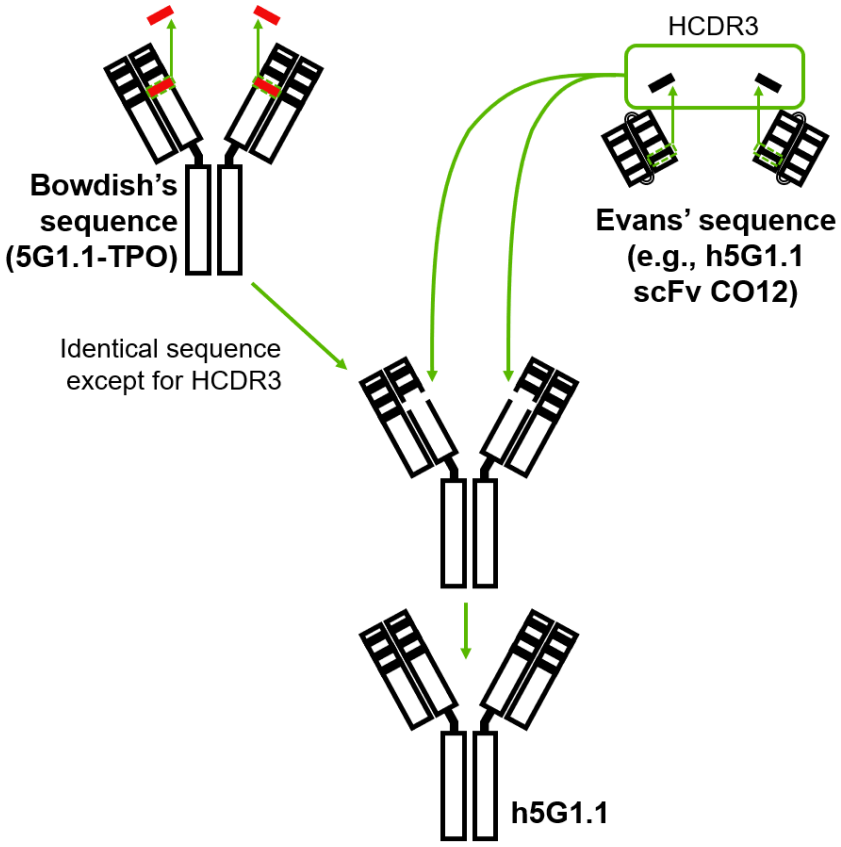
> **Recombinant antibodies**
>
> The humanized antihuman DC-SIGN antibody hD1V1G2/G4 (hD1) was generated by complementarity determining region (CDR) grafting of AZN-D1 hypervariable domains into human framework regions. The humanized variable heavy and variable light regions were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively. This construct was cloned into a mammalian expression vector and the final construct transfected into NSO cells. Stable transfectants were obtained using glutamate synthetase (GS) selection (Lonza Biologics, Portsmouth, NH). Supernatants containing hD1 were purified over a protein A column. An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(EX1008, 011 (citing EX1006); EX1003, ¶131.) Mueller PCT, the companion patent application for Mueller 1997, expressly discloses the full amino acid sequence for the IgG2/IgG4 constant domain heavy chain used in the "h5G1.1 HuG2/G4" antibody. (EX1009, 014, 058-59, 097; EX1003, ¶132.) 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:

Bowdish SEQ ID NO: 67	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Mueller 3F4 G2/G4 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Bowdish SEQ ID NO: 67	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Mueller 3F4 G2/G4 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Bowdish SEQ ID NO: 67	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Mueller 3F4 G2/G4 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Bowdish SEQ ID NO: 67	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Mueller 3F4 G2/G4 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Bowdish SEQ ID NO: 67	321	SLSLGK	326
Mueller 3F4 G2/G4 C_H	321	SLSLGK	326



(EX1003, ¶¶132-133.) Just as easily, a POSA in March 2007 would have readily confirmed that Bowdish's starting 5G1.1 antibody had the desired IgG2/G4 constant regions as opposed to pure IgG2 or IgG4 constant regions by running Bowdish's 5G1.1 antibody through a protein sequence search. (*Id.*, ¶134; *see also* EX1033, 005; EX1037, 005.) With this confirmation in hand, a POSA would have known to swap back into Bowdish's SEQ ID NO:67 the thirteen amino acid heavy chain CDR3 disclosed throughout Evans – as shown below:



(EX1003, ¶134.)

Tacken, like Bowdish, is analogous art to Bell and to the field of the challenged patent. Tacken is from the same field of study (humanized antibodies, including eculizumab) and is pertinent to the issue of the structure of eculizumab, which Tacken expressly identifies and describes as an anti-C5 antibody and Alexion's "potential product." (EX1008, 010-11; EX1003, ¶135.) A POSA seeking the sequence of eculizumab would have relied on Tacken, and its clear teaching from 2005 that eculizumab has an IgG2/IgG4 constant domain. (EX1003, ¶135.) A POSA reading Tacken would also have understood that Thomas—which was

published in 1996 and pre-dates Mueller PCT—discloses only an IgG4 isoform of 5G1.1, and was thus not eculizumab. (EX1010, 013; EX1003, ¶¶118, 136.) Moreover, Mueller PCT is analogous art to Bell, Bowdish, Evans, and Tacken, and to the field of the challenged patent, because like those references it is concerned with recombinant antibodies, expressly recites 5G1.1, is associated with Alexion, and has Alexion scientist Mark Evans identified as an inventor on both Evans and Mueller PCT. (EX1009, Cover, 12:19-27; EX1005, Cover; EX1003, ¶137.)

The teachings of the prior art cited in this Ground provide a direct route to the sequence of eculizumab that renders challenged claim 1 obvious. A POSA would have been strongly motivated by Bell to obtain the sequence of eculizumab. Indeed, Bell is just one of many references in the prior art which taught that eculizumab was a useful treatment for PNH. (*See* EX1011; EX1013; EX1012; EX1014; EX1015; EX1003, ¶138.) A POSA further would have been informed by Tacken as to important details regarding the structure of eculizumab, and from the combined teaching of Bowdish and Evans, a POSA could immediately confirm the correctness of the constant region against the teachings of Mueller PCT. (EX1003, ¶138.)

A POSA also would have had a reasonable expectation of success in assembling SEQ ID NOS:2 and 4 recited in challenged claim 1, since the prior art already confirmed each of the details necessary to create the heavy and light chains of the antibody. A POSA would have understood how to make an anti-C5 antibody

with SEQ ID NOS:2 and 4 using the teachings of Bowdish and Evans and standard, well-known molecular biology methods. (EX1004, [0069]-[0070], [0131]; EX1005, 45:24-33; EX1003, ¶139.)

2. Claim 2

Formulating a "pharmaceutical composition" in a "single unit dosage form" limitation adds nothing of patentable significance. Bowdish expressly discloses its anti-C5 antibodies as pharmaceutical compositions. (EX1004, [0148]-[0151]; EX1003, ¶140; EX1062, ¶49.) Bell discloses that its antibodies can be administered "in a variety of unit dosage forms." (EX1007, [0058].) A POSA would have known that single-use dosage units are the most convenient and appropriate for use in contexts such as intravenous infusion in which sterility must be maintained (and is considered compromised when a vial is opened). (EX1003, ¶141; EX1062, ¶¶25, 50; EX1055-1060.)

3. Claim 3

Claim 3 requires that claim 2's dosage form be a 300 mg dosage. Bell's report of the eculizumab clinical trial in PNH patients employed a dosing regimen with two phases: an initial 600 mg dose followed by a 900 mg dose, with all doses delivered by intravenous infusion. (EX1007, [0082].) Given Bell's express disclosure of a dosage regimen having 600 and 900 mg phases, a 300 mg unit dosage form would have been obvious. 300 is the highest common factor of 600 and 900, and thus the

most convenient unit dose to use without the need to manufacture vials of differing quantities, and without causing unnecessary waste of costly antibody treatments. A POSA aware of Bell's teachings would have been motivated to choose a 300 mg single-use dosage form above all other options given these considerations. (EX1003, ¶142; EX1062, ¶51.)

4. Claim 6

Claim 6 specifies that the claimed patient is "anemic." In the clinical trial disclosed by Bell, the pre-treatment hemoglobin value for patients was 10.0 ± 0.4 g/dl. (EX1007, Fig. 1A.) Per American Society of Hematology guidelines, anemia is defined as a hemoglobin value of less than 14 g/dl in a man or less than 12 g/dl in a woman. (EX1064, 008; EX1003, ¶143.) A POSA would have recognized that the patients in Bell's PNH trial were anemic prior to treatment. Moreover, Bell expressly taught that symptoms of PNH, which include anemia, are "eliminated or decreased" by administration of anti-C5 antibodies such as eculizumab. (EX1007, [0037]; *see also id.*, [0014], [0066], [0076]-[0077]; EX1003, ¶143.)

5. Claim 7

Claim 7 requires that the antibody be administered "at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment." This is disclosed by Bell, which teaches a dosing regimen with 600 and 900 mg dose phases. Based on the CDC (Centers for Disease Control) disclosure that the average body weight

for adult females and males in the U.S. as of 2005 was 74 kg and 87 kg, respectively, patients in Bell's study necessarily received doses ranging from 6.9 mg/kg to 12.2 mg/kg, fully within the range recited by claim 7. (EX1065, 061; EX1003, ¶144; EX1062, ¶58.)

The limitation of claim 7 is also expressly disclosed by Evans, which teaches that doses of its anti-C5 antibodies are typically from 1 to 100 mg per kg and "preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment." (EX1005, 17:60-18:13.) A POSA would thus have been motivated to administer doses in the claimed range, and had a reasonable expectation of success, in light of these express teachings and Bell's disclosure that such doses successfully treated PNH. (EX1003, ¶145; EX1062, ¶59.)

6. Claim 8

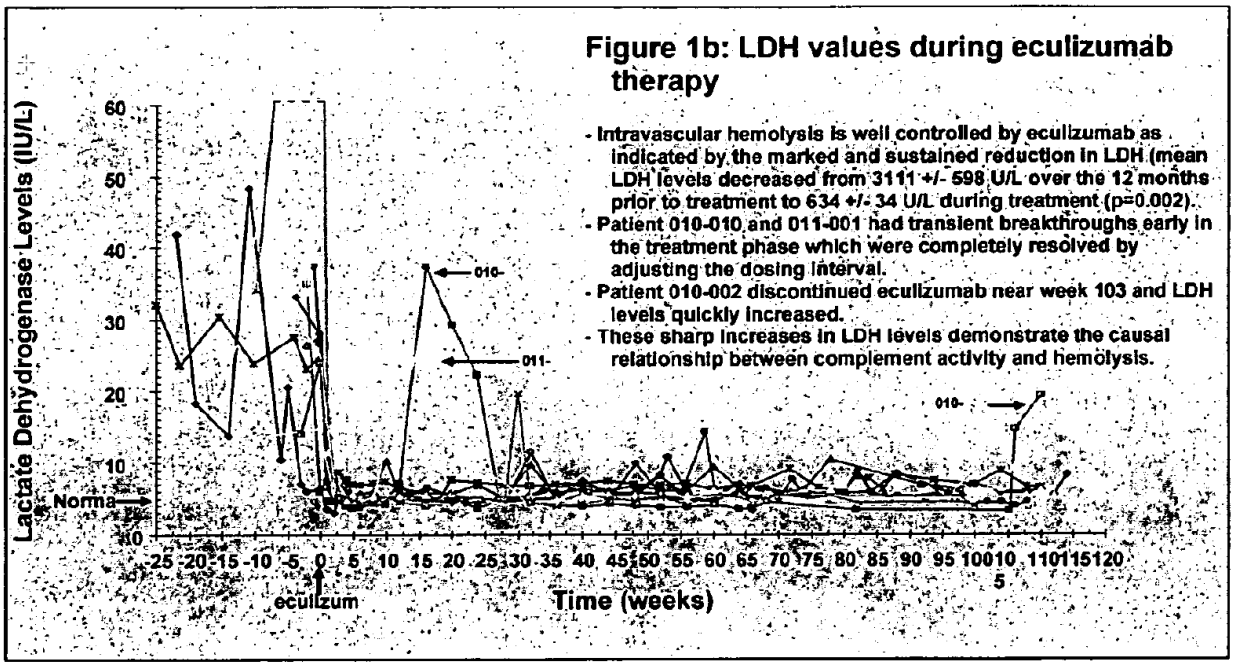
Claim 8 recites the same dosing regimen disclosed by Bell, namely "600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days." Bell teaches this eculizumab dosing regimen, exactly.

> **[0082]** Over the course of four weeks, each of 11 patients received a weekly 600 mg intravenous infusion of anti-C5 antibody for approximately thirty minutes. The specific anti-C5 antibody used in the study was eculizumab. Patients received 900 mg of eculizumab 1 week later then 900 mg on a bi-weekly basis.

(EX1007, [0082].) Bell also teaches that two patients received the maintenance dose every 12 days. (*Id.*, [0088].) A POSA would have been motivated to use, and would have expected success in, the exact dosing regimen for PNH that Bell had already disclosed. (EX1003, ¶¶146-147.)

7. Claims 9-11

Claims 9-11 require that the patient exhibits "decreased [LDH] levels" (Claim 9) that is "immediate and sustained" (Claim 10) or "occurs within one week of administration" (Claim 11). Bell expressly discloses that eculizumab therapy decreased LDH levels in PNH patients by more than 80%, and that this decrease was "marked and sustained." (EX1007, [0085], Figs. 1a-1b; EX1003, ¶¶148-149.)



A POSA would have recognized from Bell's disclosure that LDH values in PNH patients treated with eculizumab immediately and markedly decreased to near-normal levels, and then remained low for the duration of eculizumab treatment. (EX1003, ¶149.) Bell's disclosure as shown in the above figure is further verified by both Hillmen and Hillmen 2003, which describe the same results from the same eleven patient Phase 2 PNH study that are disclosed in this figure. (*See supra* V.C.) These manuscripts confirm that the eculizumab caused an immediate and sustained decrease in LDH levels that "began after a single dose of eculizumab in all patients." (EX1011, 005 (Fig. 2), 006; EX1003, ¶150.) Similarly, Hillmen 2003 states that "dramatic improvement in the biochemical parameters of hemolysis occurring in all patients within a week of starting therapy persists. Mean LDH decreased from 3111 +/- 598 U/L … to 670 +/- 69 U/L over 6 months following treatment[.]" (EX1017, 002; EX1003, ¶150.)

8. Claim 12

Claim 12 requires that the PNH patient "has received at least four transfusions in the twelve months prior to administration of the antibody." This is expressly disclosed by Bell's description of its PNH clinical trial. (EX1007, [0081] ("Patients were defined as transfusion dependent with a history of four or more transfusions within twelve months."); EX1003, ¶151.)

9. Claims 13 and 14

Claim 13 requires that the PNH patient "has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody." Claim 14 recites the same thing, but depends from claim 12. This limitation is expressly disclosed by Bell, which teaches that at least four of the eleven PNH patients in the study were "non-thrombocytopenic," with platelet counts greater than 150,000 per microliter before the study began, and that these patients became transfusion-independent after receiving the antibody treatment. (EX1007, [0089]; EX1003, ¶152.)

10. Claim 17

Claim 17 requires that the patient exhibit an improved quality of life score on either "EORTC" or "FACIT" scales. This is expressly taught by Bell: "Overall improvements [based on EORTC] were observed in global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, fatigue, pain, dyspnea and insomnia." (EX1007, [0095], Fig. 9; EX1003, ¶153.)

D. Ground 2: Claim 15 Is Obvious Over Bell, Bowdish, Evans, and Hillmen in view of Tacken and Mueller PCT

Claim 15 depends from claim 1 and requires that the patient "has about a 51% likelihood of transfusion avoidance" after treatment. This is expressly disclosed by the Hillmen report of the same eleven patient clinical trial disclosed in Bell.

Hillmen's Table 1 shows that six of eleven patients, or about 54%, required zero transfusions after 3 months of treatment.

Table 1. Transfusion Rates, Hemoglobin Levels, and Reticulocyte Counts 12 Months before and after 3 Months of Eculizumab Treatment.

Patient No.	12 Mo before Eculizumab Treatment				After 3 Mo of Eculizumab Treatment			
	Transfusions		Hemoglobin	Reticulocytes	Transfusions		Hemoglobin	Reticulocytes
	no. of units	*rate**	*g/dl*	*×10⁻³/mm³*	*no. of units*	*rate†*	*g/dl*	*×10⁻³/mm³*
1	22	1.8	10.3	77.5	2	0.7	10.0	100.7
2	23	1.9	8.3	200.0	8	2.9	8.8	182.6
3	20	1.6	10.1	169.5	0	0.0	10.7	175.9
4	28	2.3	9.3	282.0	0	0.0	9.4	333.3
5	12	1.0	11.9	96.3	2	0.7	10.6	121.8
6	14	1.2	9.8	346.8	0	0.0	10.6	259.0
7	34	2.8	12.8	100.6	0	0.0	13.5	166.8
8	21	1.7	9.5	164.5	0	0.0	9.8	239.6
9	55	4.5	10.7	138.0	3	1.1	11.4	285.8
10	41	3.4	8.5	108.7	5	1.8	8.8	140.1
11	14	1.2	8.5	91.4	0	0.0	10.0	97.4
Median‡		1.8				0.0		
Mean		2.1	10.0	161.4		0.6	10.3	191.2

* The rate (in units per month) was calculated as (number of units ÷ 365 days) × 30.
† The rate (in units per month) was calculated as (number of units ÷ 84 days) × 30.
‡ P=0.003 for the change in the median rate of transfusion by the Wilcoxon signed-rank test.

(EX1011, 007 (Table 1); EX1003, ¶154.) As explained by the '809 patent, incidence of transfusion avoidance was a co-primary endpoint of the Phase 2 eculizumab study, and 51% of patient cohort achieved this endpoint. (EX1001, 21:5-10, 21:31-34, 23:59-65.) Hillmen also confirmed the same result, in which a little more than half the patient group achieved transfusion avoidance, years earlier in the Phase 2 trial as reported in Hillmen, shown above. The same was also disclosed in the prior art Hillmen 2006 reference discussing the Phase 3 trial. (EX1014, 006; EX1003, ¶155.)

E. Ground 3: Claim 16 Is Obvious Over Bell, Bowdish, Evans, and Hill in view of Tacken and Mueller PCT

Claim 16 depends from claim 1 and requires the patient have a less than 3% likelihood of developing antibodies to the anti-C5 antibody. This was expressly taught by Hill, which disclosed that after 12 months of eculizumab treatment in the Phase 2 study, "[i]n no patients were antibodies against eculizumab detected." (EX1013, 013; EX1003, ¶156.)

F. Ground 4: Claims 4-5, 18-26, and 29 Are Obvious Over Bell, Bowdish, Evans, and Wang in view of Tacken and Mueller PCT

1. Claim 4

Claim 4 depends from claim 3 addressed in Ground 1 and specifies a dosage form of 300 mg in 30 mL at 10 mg/ml of a sterile, preservative-free solution. This is obvious in view of the teachings of Wang. For convenience in handling and addition to IV bags for infusion, antibody therapies by 2007 were commonly supplied in a liquid solution that could easily be drawn into a syringe. (EX1003, ¶157; EX1062, ¶53.) Based on simple arithmetic, 30 ml of a 10 mg/ml solution provides a 300 mg total dose of antibody, which as explained above would be considered desirable by a POSA. (*See supra* VIII.C.3; EX1003, ¶¶142, 157; EX1062, ¶51.) A POSA would also know that eculizumab could be successfully and stably formulated in an aqueous solution at concentrations in the range of 1 to 30 mg/ml based on the express teachings of Wang, and thus eculizumab could be

formulated at 10 mg/ml. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173]; EX1003, ¶157; EX1062, ¶53.) A POSA would also have known that 10 mg/ml was well within the known range of concentrations of a large number of FDA-approved antibody pharmaceutical compositions. (EX1003, ¶157; EX1062, ¶54; EX1061, 014 (Table 1).)

Each of Bell, Bowdish, and Evans teaches that formulations of anti-C5 antibodies such as eculizumab "must be sterile." (EX1007, [0062]; EX1004, [0150]; EX1005, 18:29-43.) Each of Bell, Bowdish, and Evans also teaches that use of a preservative is optional, and thus can be omitted from the formulation – express disclosure sufficient to teach the negative claim limitation of "preservative free." (*Id.*) *See Upsher-Smith Lab'ys, Inc. v. PamLab, L.L.C.*, 412 F.3d 1319, 1320-21 (Fed. Cir. 2005) ("[A] prior art composition that 'optionally includes' an ingredient anticipates a claim for the same composition that expressly excludes that ingredient[.]").

These disclosures specific for eculizumab accord with the conventional teachings of the prior art for antibody pharmaceutical compositions in general. For example, several widely-prescribed FDA-approved antibodies (approved before 2007) were provided in sterile, preservative free formulations. (EX1003, ¶¶158-159; EX1062, ¶¶55-56; EX1055, 002; EX1056, 002, 013; EX1057, 001; EX1058, 001-02; EX1059, 001; EX1060, 001.)

A POSA would have been motivated to prepare pharmaceutical compositions matching the limitations of the challenged claims based on the teachings of the prior art. For example, each of Bell, Bowdish, and Evans expressly teach formulations and compositions matching the limitations as discussed above. Further, a POSA would have looked to Wang for its additional express disclosures about formulation methods and compositions that specifically pertain to eculizumab. (EX1044, [0004], [0011], [0067]; EX1003, ¶160; EX1062, ¶53.)

A POSA would also have had a reasonable expectation of success in arriving at pharmaceutical compositions having the characteristics recited in the challenged claims, because the prior art discloses these characteristics specifically in the context of eculizumab. (EX1003, ¶161.) Further, a POSA would have had a reasonable expectation of success in preparing a stable, non-aggregated pharmaceutical composition of eculizumab at a concentration of 10 mg/ml based on the Wang reference, which teaches stable eculizumab formulations at concentrations as high as 30 mg/ml. (EX1003, ¶161; EX1061, 009.) Collectively, such dose form and formulation limitations are nothing more than "the predictable use of prior art elements according to their established functions," and therefore add nothing of patentable significance. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007); *see also W. Union Co. v. MoneyGram Payment Sys., Inc*., 626 F.3d 1361, 1371-72 (Fed. Cir. 2010).

2. Claim 5

Claim 5 depends from claim 3 (addressed in Ground 1) and recites that "the antibody is diluted to a concentration of 5 mg/mL prior to administration." This limitation is of no patentable weight. It was (and remains) commonplace for IV drugs to be diluted prior to administration, indeed even today "ready to use" IV formulations are uncommon. As discussed above, drugs for IV infusion supplied in solution are drawn by syringe and added to an IV bag for infusion; this step necessarily involves dilution. Moreover, dilution specifically to a final concentration of 5 mg/ml is closely in line with the concentration of a number of recombinant antibodies already approved by 2007. (EX1003, ¶162; EX1062, ¶57; EX1061, 014 (Table 1).) Indeed, even as of 1997 the prescribing information for Rituxan required that the antibody be diluted to a final concentration of 1 to 4 mg/ml in an IV infusion bag for administration. (EX1060, 002; EX1003, ¶162; EX1062, ¶57.)

A POSA would have been motivated to prepare formulations of eculizumab for administration by IV infusion, and would have found it obvious to dilute the antibody in the process to a concentration range that was directly in line with concentrations of several other approved therapeutic antibodies, and would have had a reasonable expectation of success in obtaining and using eculizumab for IV infusion at a final concentration of 5 mg/ml. (EX1003, ¶163; EX1062, ¶57.)

3. Claim 18

Claim 18 trivially requires that the PNH patient be treated "for at least 26 weeks." Bell expressly discloses this, teaching that all eleven of its patients continued on study for a total of 64 weeks, and ten of eleven continued in an extension study for two years. (EX1007, [0082]; EX1003, ¶164.)

4. Claim 19

Claim 19 has the same limitation that the patient be anemic as does Claim 6, and is invalid for the same reasons. (*See supra* VIII.C.4; EX1003, ¶¶143, 165.)

5. Claim 20

Claim 20 has the same dosage level limitations as claim 7, and is invalid for the same reasons. (*See supra* VIII.C.5; EX1003, ¶¶144-145, 166.)

6. Claim 21

Claim 21 has the same dosing regimen limitations as claim 8, and is invalid for the same reasons. (*See supra* VIII.C.6; EX1003, ¶¶146-147, 167.)

7. Claims 22-24

Claims 22-24 have the same limitations relating to reduction of LDH levels as claims 9-11, and are invalid for the same reasons. (*See supra* VIII.C.7; EX1003, ¶¶148-150, 168.)

8. Claim 25

Claim 25 has the same pre-treatment transfusion limitations as claim 12, and is invalid for the same reasons. (*See supra* VIII.C.8; EX1003, ¶¶151, 169.)

9. Claim 26

Claim 26 has the same pre-treatment platelet level limitations as claim 13, and is invalid for the same reasons. (*See supra* VIII.C.9; EX1003, ¶¶152, 170.)

10. Claim 29

Claim 29 has the same EORTC quality of life limitations as claim 17, and is invalid for the same reasons. (*See supra* VIII.C.10; EX1003, ¶¶153, 171.)

G. Ground 5: Claim 27 Is Obvious Over Bell, Bowdish, Evans, Wang, and Hillmen in view of Tacken and Mueller PCT

Claim 27, depending from claim 5, has the same limitations regarding likelihood of transfusion avoidance as claim 15. As discussed above, this result was disclosed by Hillmen, and thus claim 27 is invalid for the same reasons. (*See supra* VIII.D+VIII.F.2; EX1003, ¶¶154-155, 172.)

H. Ground 6: Claim 28 Is Obvious Over Bell, Bowdish, Evans, Wang, and Brown in view of Tacken and Mueller PCT

Claim 28, like claim 17, depends from claim 5 and requires an improvement in quality of life scores, however claim 28 specifies the FACIT-Fatigue scale. As noted above, Bell expressly discloses improvement of quality of life on the EORTC scale. (*See supra* VIII.C.10+VIII.F.2.) Bell does not expressly report results on the FACIT-Fatigue scale, but a POSA would have had a reasonable expectation of success in achieving the claimed result on the FACIT-Fatigue scale, because of the well-known correlation between the two scales. For example, Brown reports close

correlation of quality of life data between the fatigue-subscale of the "EORTC" and "FACIT-Fatigue" scales in its patient study. (EX1068, 002, 004; EX1003, ¶¶153, 173.)

I. Ground 7: Claims 1-3, 6-14, and 17 Are Obvious Over Bell, Evans, and Mueller PCT in view of Tacken

1. Claim 1

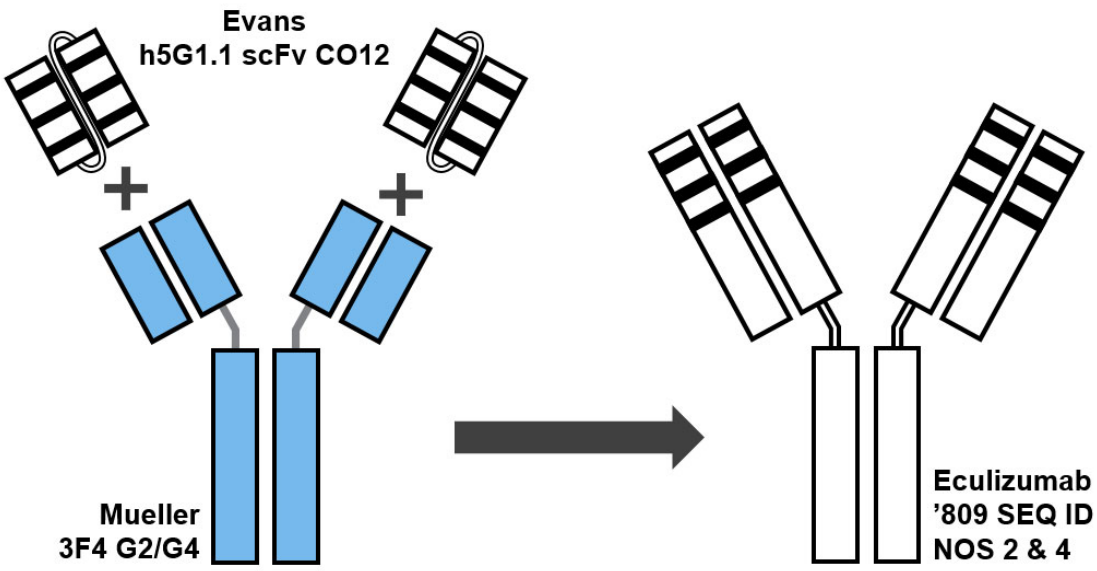
A POSA would also have been directed by Bell and Tacken to Evans and Mueller PCT to use an antibody with SEQ ID NOS:2 and 4 to treat PNH. As explained in Ground 1, a POSA would have been strongly motivated by Bell to obtain the amino acid sequence of the anti-C5 antibody eculizumab as a method of treatment for PNH by IV administration—the subject matter of claim 1. (*See supra* VIII.C.1.) Bell points directly to Evans and Thomas for this information and incorporates both by reference. (*Id.*) As discussed above, a POSA would not have concluded that eculizumab was an IgG4 antibody from this reference to Thomas in view of the later teachings of Tacken and Mueller PCT. (*See supra* VIII.C.) A POSA examining Evans, entitled "C5-specific Antibodies for the Treatment of Inflammatory Diseases" would readily understand that it teaches the critical CDR sequences for the heavy and light chains of the original mouse antibody 5G1.1, which binds C5, as well as variable domain sequences for humanized forms of 5G1.1. (EX1005, 1:1-3, 9:65-10:20, 42:56-45:23, 143:22-144:14, Figs. 18-19, Claim 19; EX1003, ¶¶174-176.)

Evans' Example 11 teaches the construction of recombinant antibodies using the heavy and light chain CDRs of the 5G1.1 antibody. (EX1005, 42:56-45:33; EX1003, ¶175; *see supra* VIII.D.) In all, Evans' Example 11 provides eighteen "recombinant mAb-encoding DNAs" constructs. Of these, nine provide humanized single-chain variable domain structures ("scFv") which correspond to the V_H and V_L domains of an antibody joined by a short peptide linker. (EX1005, 42:56-45:33; EX1003, ¶175.) Evans then explains that "one each of the various L1, L2, and L3 CDRs" and "one each of the various H1, H2, and H3 CDRs" disclosed in Example 11, assembled into "matched pairs of the variable regions (e.g., a V_L and a V_H region) … may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies *of the invention*." (EX1005, 45:5-33 (emphasis added); EX1003, ¶¶175-176.)

A POSA would have been motivated to build antibodies using *each* of the sequences labeled "5G1.1." Even if Evans does not identify the specific sequence used in eculizumab by name, it explains that *each* of the nine disclosed sequences include V_H and V_L domains with the CDRs of 5G1.1. (EX1005, 42:56-45:33; EX1003, ¶¶176-177.) Bell points to Evans for its teaching of the structure of 5G1.1, thus a POSA would have known to try any of these sequences. *See Merck & Co. v. Biocraft Lab'ys, Inc.,* 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [asserted prior art] discloses a multitude of effective combinations does not render any particular

formulation less obvious."). When, as here, there are a "finite number of identified, predictable solutions," a POSA has good reason to pursue them and the resulting combinations are obvious ones. *See KSR*, 550 U.S. at 421.

Even if a POSA wished to prioritize among the nine constructs providing a humanized V_H and V_L disclosed in Evans' Example 11 to choose, Mueller PCT would have guided POSA to the sequence in part 12 of Example 11, identified as "CO12." (*See* EX1005, 44:4-14; EX1009, 014.) The only G2/G4 hybrid discussed in Mueller PCT is referred to as "h5G1.1 **CO12** HuG2/G4," thus a POSA would have been particularly motivated to assemble a full length G2/G4 antibody using the variable region employed in the CO12 example of Evans. (EX1009, 014; EX1003, ¶178.) This assembly with the constant G2/G4 regions of Mueller PCT and variable regions of Evans results in the claimed sequences:



(EX1003, ¶178.) The resulting antibody is a perfect match to SEQ ID NOS:2 and 4 recited in claim 1, which corresponds to eculizumab. (*Id.*, ¶179):

```
Evans + Mueller   1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  80
'809 SEQ ID NO: 2 1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  80
                                  ← Evans | Mueller →
Evans + Mueller  81 MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS|ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT 160
'809 SEQ ID NO: 2 81 MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT 160

Evans + Mueller 161 VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
'809 SEQ ID NO: 2 161 VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Evans + Mueller 241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY 320
'809 SEQ ID NO: 2 241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY 320

Evans + Mueller 321 KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD 400
'809 SEQ ID NO: 2 321 KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD 400

Evans + Mueller 401 SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448
'809 SEQ ID NO: 2 401 SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448
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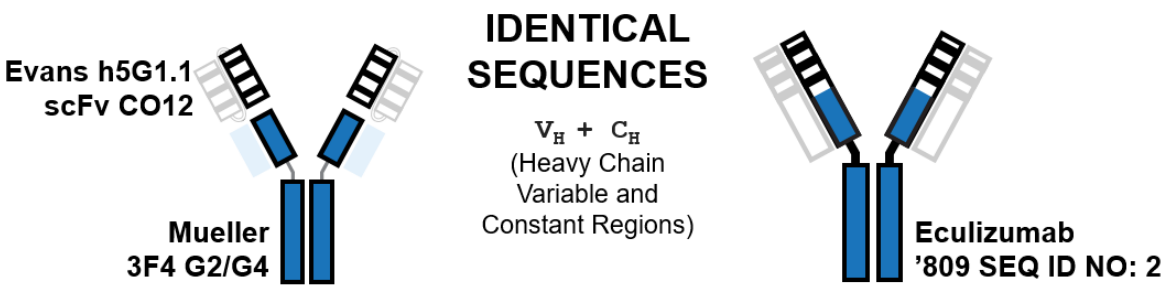
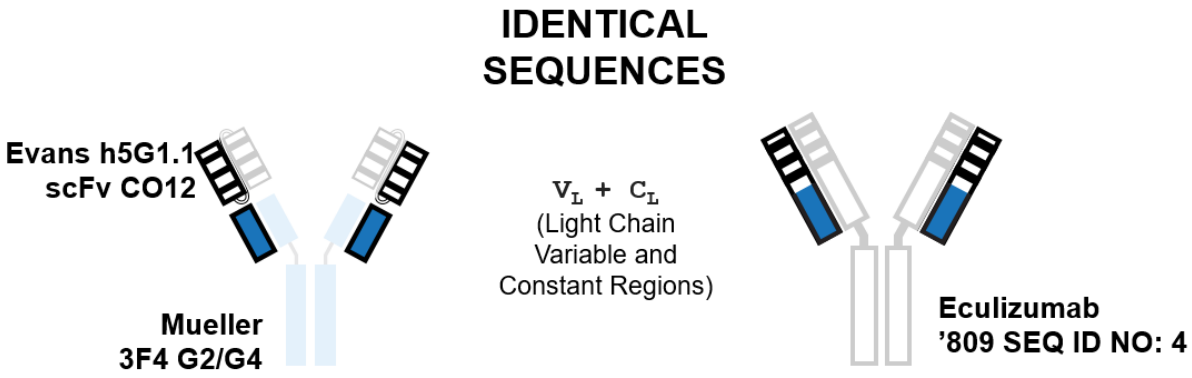


Evans + Mueller	1	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP	80
'809 SEQ ID NO: 4	1	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP	80
		← Evans | Mueller →	
Evans + Mueller	81	EDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
'809 SEQ ID NO: 4	81	EDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Evans + Mueller	161	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	214
'809 SEQ ID NO: 4	161	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	214



Also as explained in Ground 1, Tacken specifically teaches that eculizumab has an IgG2/IgG4 constant region, and refers to the Mueller 1997 reference for this point. (*See supra* VIII.C.1.) A POSA would thus have been motivated by the express teachings of Tacken to create an antibody using the variable domain for 5G1.1 disclosed in Evans and the constant region discussed in Mueller 1997 and expressly taught in Mueller PCT. (*See id.*) Indeed, the same disclosure in Evans providing instructions for how to combine 5G1.1 variable regions with constant region domains to form a full-length antibody *expressly* suggests that it is "[p]articularly preferred" to use "a mixture of constant domains from IgGs of various subtypes" – exactly like the IgG2/IgG4 disclosure of Tacken and Mueller PCT. (EX1005, 45:29-33; EX1003, ¶180.)

Although these disclosures provided ample motivation for a POSA to use Evans and Mueller PCT to use the antibody having the sequences recited in claim 1 for treatment of PNH, the art provides still further motivation. The Mueller 1997 reference associated with Mueller PCT provides *general* motivation to convert IgG4 isotype antibodies to the "HuG2/G4 design" in any human antibody intended for therapeutic use "where elimination of FcR binding and C activation may be desirable." (EX1006, 016; EX1003, ¶181.) A POSA would have immediately recognized these benefits as useful in the context of a therapeutic antibody intended for use to block part of the complement system, and arrived at an antibody that is an IgG2/IgG4 hybrid sequence like the constant region of SEQ ID NO:2 of claim 1. (EX1003, ¶181.) Thus, a POSA would have been motivated to use the humanized 5G1.1 variable domains of Evans and combine them with constant regions from Mueller PCT to make the antibody of claim 1. (*Id*.) Still other disclosures in the prior art similarly taught that antibodies with hybrid IgG2/IgG4 constant regions conferred benefits such as reduced inflammation and activation of the complement system. (EX1021; EX1003, ¶181.)

The same disclosures would also have provided a POSA with a reasonable expectation of success, since a POSA would know from Tacken that such assemblies had already been made to form eculizumab, which had itself already been validated as a PNH treatment as shown in Bell and other studies. *See KSR*, 550 U.S. at 416

("combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"); (EX1003, ¶182).

2. Claims 2-3, 6-14, and 17

These dependent claims add trivial and uninventive limitations that do nothing to rescue the obviousness of the invalid method of treatment claim recited in claim 1. As explained above in connection with Ground 1, these conventional limitations were all disclosed in the same prior art relied on for obviousness of claim 1, and are thus invalid for the same reasons as explained above when combined with the references used in Ground 7. (*See supra* VIII.C.2-10; EX1003, ¶¶140-153, 183.)

J. Ground 8: Claim 15 Is Obvious Over Bell, Evans, Mueller PCT, and Hillmen in view of Tacken

Claim 15 adds nothing of patentable significance to the obvious method of claim 1, and is unpatentable in view of the Ground 7 combination, further in view of Hillmen, for the same reasons discussed above. (*See supra* VIII.D; EX1003, ¶184.)

K. Ground 9: Claim 16 Is Obvious Over Bell, Evans, Mueller PCT, and Hill in view of Tacken

Claim 16 adds nothing of patentable significance to the obvious method of claim 1, and is unpatentable in view of the Ground 7 combination, further in view of Hill, for the same reasons discussed above. (*See supra* VIII.E; EX1003, ¶185.)

L. Ground 10: Claims 4-5, 18-26, and 29 Are Obvious Over Bell, Evans, Mueller PCT, and Wang in view of Tacken

These dependent claims add trivial and uninventive limitations that do nothing to rescue the obviousness of the invalid method of treatment claim recited in claim 1. As explained above in connection with Ground 4, these conventional limitations were all disclosed in the same prior art relied on for obviousness of claim 1, and are thus invalid for the same reasons as explained above when combined with the references used in Ground 7, further in view of Wang. (*See supra* VIII.F.1-10; EX1003, ¶¶157-171, 186.)

M. Ground 11: Claim 27 Is Obvious Over Bell, Evans, Mueller PCT, Wang, and Hillmen in view of Tacken

Claim 27 adds nothing of patentable significance to the obvious method of claim 5, and is unpatentable in view of the Ground 10 combination, further in view of Hillmen, for the same reasons discussed above. (*See supra* VIII.G; EX1003, ¶187.)

N. Ground 12: Claim 28 Is Obvious Over Bell, Evans, Mueller PCT, Wang, and Brown in view of Tacken

Claim 28 adds nothing of patentable significance to the obvious method of claim 5, and is unpatentable in view of the Ground 10 combination, further in view of Brown, for the same reasons discussed above. (*See supra* VIII.H; EX1003, ¶188.)

IX. NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

There are no secondary considerations that would weigh against the strong case of obviousness set forth in this petition. (EX1003, ¶¶189-194; EX1062, ¶62.) Secondary considerations must be tied to what is *novel* in the claim, indeed any secondary considerations evidence that is not "both claimed *and* novel in the claim" cannot be said to have a nexus to the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis modified).

To the extent Alexion will argue that secondary considerations evidence can be derived from commercial success of its drug Soliris (the brand name of eculizumab), any such evidence must fail as evidence of nonobviousness because the use of eculizumab as a treatment for PNH was *indisputably* in the prior art and thus not novel in the claim. Several prior art publications expressly disclosed the utility of eculizumab as a treatment for PNH, including the Bell, Hillmen, and Hill references. (*See supra* V.C & VIII.A.) *See 7 Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) ("if the feature that creates the commercial success was known in the prior art, the success is not pertinent."). Similarly, the fact that eculizumab was not commercially approved as a treatment for PNH until March 2007 is of no moment to the secondary considerations analysis, because the use of eculizumab as a PNH therapy is undisputed prior art to the '809 patent. *See Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330-31 (Fed. Cir. 2017) (finding the

fact that Patent Owner's drug was the first to receive FDA commercial marketing approval for solid oral treatment for multiple sclerosis was not probative of nonobviousness when "[t]he treatment of multiple sclerosis with a solid oral composition … was indisputably known in the prior art."); (*see also* EX1024, 056-57).

There is also no presumption of nexus, because any evidence based on Soliris sales must be due to the claimed invention specifically, not Alexion's other efforts such as marketing, *and* not contributions from the prior art. *See, e.g., Prometheus Lab'ys v. Roxane Lab'ys*, 805 F.3d 1092, 1101 (Fed. Cir. 2015); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). Moreover, as explained above, Alexion has long identified the prior art Evans patent, not the challenged '809 patent, with the invention of eculizumab, and indeed sought to apply patent term extension under 35 U.S.C. § 156 for Soliris to the Evans patent. (*See supra* V.E.) Given the extensive disclosures of methods of treating PNH with eculizumab having the sequence disclosed in the prior art, Alexion cannot establish that commercial success based on Soliris's product launch in 2007 is relevant. (EX1003, ¶¶189-190.)

Similarly, Alexion cannot argue that the methods of treating PNH in the challenged claims solved a long-felt and art-recognized need, as required, because prior art published two to three years before the priority date of the '809 disclosed eculizumab as a treatment for PNH. Thus, judged against the priority date, as it must

be, it cannot be said that as of March 2007 the long-felt need addressed by Soliris still existed. *See Nike, Inc. v. Adidas AG*, 955 F.3d 45, 55 (Fed. Cir. 2020) (finding no long-felt need existed because "other methods of minimizing waste … had existed before the date of the invention"); *Celgene Corp. v. Peter*, 931 F.3d 1342, 1352 (Fed. Cir. 2019) (finding no long-felt need existed because "[Patent Owner] did not show that the prior art methods of controlling the distribution of hazardous drugs … were insufficient to meet any need to control distribution of thalidomide."). (EX1003, ¶191.)

Nor is there any competent evidence of industry praise. Any industry recognition following the launch of Soliris as a beneficial therapy for the rare disease PNH has no nexus with anything inventive in the challenged claims. As with the considerations of commercial success and long-felt need, by March 2007 there was nothing *novel* about the use of eculizumab to treat PNH. Further, any prizes awarded to Alexion relating to the use of Soliris as a PNH treatment have no nexus because there is nothing to suggest that the prize was awarded due to anything other than the previously known methods of treating PNH with eculizumab. *See S. Ala. Med. Sci. Found. v. Gnosis S.P.A.*, 808 F.3d 823, 827 (Fed. Cir. 2015) (praise lacked nexus because it was directed to a method of treatment already known in the prior art); *see also Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020). (EX1003, ¶192.)

Finally, Alexion cannot rely on Petitioner's intent to develop a biosimilar of Soliris as evidence of "copying," because the biosimilar statutes and regulations *require* that any biosimilar of Soliris be "highly similar to the reference product." *See* 42 U.S.C. §262(i)(2); *see also Adapt Pharma Operations Ltd. v. Teva Pharm. USA*, 25 F.4th 1354, 1374 (Fed. Cir. 2022) ("evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." (citation omitted)). (EX1003, ¶193.)

Petitioner reserves the right to rebut any evidence of secondary considerations that Alexion asserts in this proceeding.

X. THE BOARD SHOULD REACH THE MERITS OF THE PETITION

No basis exists under either § 314(a) or § 325(d) for discretionary denial, as explained below.

A. § 314(a)

The '809 patent has never been asserted in any litigation.

B. § 325(d)

The Board assesses § 325(d) issues under the two-part *Advanced Bionics* framework: (1) whether the same or substantially the same art was previously presented to the Office, and if so (2) whether Petitioner has demonstrated that the Examiner 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 as to §III.C.5, first paragraph). Examples of "material error" could be "misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims" or misapplying the law in a material way. *Id.* at 8-9 n.9.

This Petition should be instituted in light of the *Advanced Bionics* framework and the art and arguments presented during prosecution of the '809 patent and its parent '189 patent. Part (1) of the framework is not satisfied because the Examiner did not consider critical arguments and combinations of art relied on in this Petition. To the extent certain art or arguments were considered, Part (2) is satisfied because the Examiner materially erred by overlooking specific teachings of the prior art, accepting without challenge Alexion's incorrect characterizations of the art; and by misapplying the law with respect to secondary considerations for non-obviousness.

1. Evaluation of Art and Arguments During '809 Prosecution

Part (1) of the *Advanced Bionics* framework is not satisfied because the arguments and evidence presented herein were not before the Examiner during '809 prosecution, and therefore, do not constitute "the same or substantially the same prior art or arguments" under §325(d). During '809 prosecution, the Examiner rejected the claims for obviousness-type double patenting over various patents in view of Hillmen, Evans and Wang. (EX1002, 634-37.) Although these references

were cited by the Examiner, this Petition presents them in a different light. For example, for Evans, the Examiner concluded that it "lacks at least the constant region" of the claimed antibody. (*Id.*, 1878.) But the Petitioner combines Evans with references—such as Tacken, Mueller PCT, and Bowdish—that teach exactly those constant regions, including the IgG2/IgG4 constant domain of eculizumab. The Examiner did not evaluate the obviousness combinations or the arguments presented in this Petition with respect to Hillmen, Evans and Wang.

Part (1) also does not apply to Brown because it is a new reference that was not identified anywhere during '809 prosecution. Grounds 6 and 12 rely on Brown's disclosure regarding the correlation between the "EORTC" and "FACIT-Fatigue" scales. (EX1068, 002, 004.)

Further, 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. (EX1002, 113, 118, 153, 169.) The Board has consistently found that when a reference is not the basis of rejection, and merely cited in an IDS, it weighs "strongly against" exercising discretionary denial. *See, e.g., CODE200, UAB v. Bright Data Ltd.*, IPR2022-00353, Paper 8 at 10 (PTAB July 1, 2022). This is particularly true where there is a credible showing of Examiner error. *See Whitewater W. Indus., Ltd. v. Am. Wave Machs., Inc.,* IPR2022-01034, Paper 8 at 34-35 (PTAB Nov. 22, 2022); *Advanced Energy Indus.*

Inc. v. Reno Techs. Inc., IPR2021-01397, Paper 7 at 7-8 (PTAB Feb. 16, 2022); *Samsung Elecs., Co. v. G+ Commc'ns, LLC,* IPR2022-01598, Paper 10 at 13 (PTAB Apr. 4, 2023).

Part (2) of *Advanced Bionics* is also satisfied with respect to Bell, Bowdish, Tacken and Mueller PCT because the Examiner materially erred in overlooking specific disclosures, such as (1) Tacken, which discloses that eculizumab contains the IgG2/G4 constant domain, (2) Mueller PCT which discloses that sequence, and (3) Bowdish, which discloses the sequence for antibody 5G1.1, including the complete sequence for IgG2/G4 constant domain. (*See supra* VIII.C.) They are also enabling prior art for Bell. Thus, the prosecution history reflects a significant gap in Examiner's evaluation of art and arguments regarding the known sequence of eculizumab, that is recited in claims 1-29. (EX1003, ¶196.) Similarly, the Examiner erred in not appreciating Hill's disclosure regarding lack of anti-eculizumab antibodies that renders claim 16 obvious. (*Id*., ¶197.)

Further, though the Examiner cited Wang in the rejections, the Examiner erred in overlooking Wang's disclosures regarding the claimed formulations, as evidenced by the lack of any discussion regarding Wang in the Notice of Allowance. *See Advanced Bionics*, Paper 6 at 10 ("[I]f the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).");

Apple, Inc. v. Koss Co., IPR2021-00381, Paper 15 at 26, 28-29 (PTAB July 2, 2021) ("*Koss*") (finding examiner erred in evaluating prior art reference that was not discussed substantively in the Notice of Allowance). (EX1003, ¶198.)

2. Evaluation of Art and Argument During Prosecution of '189 Parent Patent

The prosecution record of the '189 patent also does not preclude institution of this Petition because the Examiner materially erred in his evaluation of the asserted art and arguments during '189 prosecution for at least the following reasons (*Id.,* ¶195):

(a) Error 1: The Examiner Overlooked Tacken and Mueller PCT

First, the Examiner materially erred in not appreciating the significance of Tacken or Mueller PCT during prosecution. Both Tacken and Mueller PCT were cited in Amgen's three IPR petitions, all of which were submitted in an IDS during '189 prosecution. (EX1032, 048 (Nos. 4-6).) Tacken and Mueller PCT were also separately identified in an IDS. (*Id.*, 027, 038.) As described above, Tacken expressly teaches that eculizumab contains the IgG2/G4 constant region, and Mueller PCT discloses that sequence. (*See supra* VIII.C.) But the Examiner did not appreciate Tacken's or Mueller PCT's disclosure, as evidenced by his failure to address either reference in the Office Action or Reasons for Allowance. (EX1034; EX1035; EX1003, ¶199.) *See Apple Inc. v. Seven Networks, LLC*, IPR2020-00285,

Paper 10 at 28–31 (PTAB July 28, 2020) (granting institution because the Examiner did not provide a reason for allowance that addressed the art or arguments presented in an IPR petition listed in an IDS); *RTI Surgical, Inc. v. LifeNet Health,* IPR2019-00573, Paper 20 at 26-27 (PTAB Aug. 12, 2019) (granting institution because the Examiner did not issue a rejection based on art that was cited in an IPR petition listed in an IDS).

It is not surprising that the Examiner overlooked Tacken and its teachings because Alexion mischaracterized the literature regarding the sequence of eculizumab. (EX1003, ¶200.) In its Response to an Office Action, Alexion stated:

> [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-isotype humanized antibody, because the pertinent literature ***consistently and unambiguously*** said so[.]

(EX1036, 006 (emphasis added).) Alexion went on to list several references that purportedly referred to eculizumab as an IgG4 antibody.[4] But Alexion failed to

[4] Alexion listed Kaplan 2002 among these references, but its characterization of that article is incorrect. Kaplan expressly refers to Evans for the composition of eculizumab.

provide a complete account of the literature, including the Tacken article, published in 2005 by its own employees. (EX1003, ¶201.) Given Tacken's 2005 disclosure that eculizumab contains IgG2/G4 isotype, and the clear link from Tacken's disclosures to the work of Mueller regarding the IgG2/G4 isotype, a POSA would have found it unambiguous that eculizumab has Mueller PCT's IgG2/G4 constant region, not the IgG4 constant region described by Thomas in 1996. (*See supra* VIII.C.) But, as a result of Alexion's inaccurate statements regarding the literature as of the priority date, the Examiner overlooked these critical disclosures of Tacken and Mueller PCT. (*See also* EX1003, ¶201.)

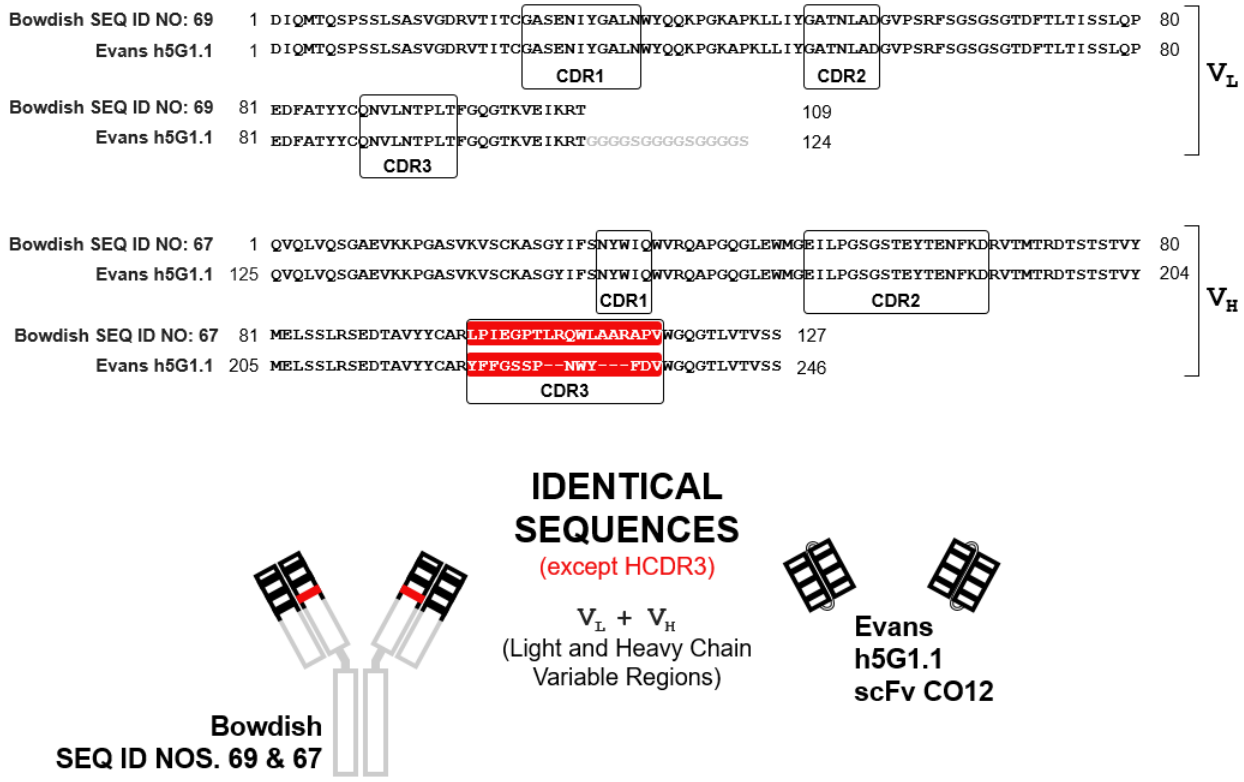
(b) Error 2: The Examiner Erred in Evaluating Bowdish and Evans

Second, the Examiner erred in evaluating Bowdish and Evans by relying on Alexion's misleading comparison of Bowdish's IgG2/G4 TPO-mimetic compound, which is a humanized antibody, with Evans' *mouse* 5G1.1 sequence. *See Liquidia Techs., Inc. v. United Therapeutics Corp.,* IPR2020-00770, Paper 7 at 14-15 (PTAB Oct. 13, 2020) (although the examiner rejected the claims based on the same art that was cited in IPR filings listed in an IDS, the Board declined to deny institution because the "examiner erred in relying on the applicant's argument … to allow the challenged claims."). During prosecution, Alexion provided an alignment of Evans' 5G1.1 *mouse* antibody variable regions with Bowdish's sequence rather than using Evans' 5G1.1 *humanized* variable region. This, unsurprisingly, revealed a mismatch

in the sequences. (EX1036, 014.) The Examiner was persuaded by Alexion's comparison, as evidenced by the Reason for Allowance:

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

(EX1035, 006-07; EX1003, ¶202.) In fact, a comparison of Evans' *humanized* sequence with Bowdish's sequence—which is the correct, apples to apples, comparison for the humanized 5G1.1 antibody that a POSA would make—would have shown the Examiner that there is no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert, as shown below:



(EX1003, ¶203.) Indeed, a proper comparison would have shown the Examiner that the starting variable region sequence used by Bowdish is identical to the Evans sequence, and that Bowdish swapped out the HCDR3 region of Evans for the TPO mimetic peptide. Thus, a POSA could reconstruct *humanized* 5G1.1 by reversing this step. (*See id*.) Tellingly, Alexion did not share any such alignments with the Examiner during prosecution, even though they plainly could have.

Alexion also misled the Examiner that Bowdish's "[c]onstruction of 5G1.1" would have directed a POSA only to Evans' mouse antibody in Examples 7-10 (EX1036, 013.) Alexion's argument conveniently ignores the express description of other examples in Evans. Specifically, 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[.]" (*Id*., 42:59-62 (emphasis added).) Evans also discloses "CDR sequences that are useful in the **construction** of the humanized antibodies of the invention[.]" (*Id*., 8:50-54 (emphasis added).) By comparison, Alexion focused the Examiner on 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*., 37:34-39:30.) This misdirection by Alexion is relevant because a POSA considering Bowdish's "construction of 5G1.1" for assembly of a full-length antibody by recombinant means would have referred to Evans' construction of the humanized 5G1.1 scFv constructs detailed in Example 11, not Example 7. (*See also supra* VIII.C; EX1003, ¶204.)

Further, the Examiner misapprehended Evans by relying on Alexion's mischaracterization that Evans discloses "multiple options" for heavy chain CDR3 sequence. In its Response, Alexion argued that even if a POSA were to consider Evans "for its disclosure of heavy chain CDR3 sequences, Evans et al. allows for multiple options, and nothing in Bowdish et al. or Evans et al. indicates which, if any, were used in the 'scaffold' antibody used to produce Bowdish et al.'s TPO-

mimetic peptide[.]" (EX1036, 018 (citation omitted).) This is a blatant misrepresentation of Evans — 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, ¶205, Appendix A.) Alexion's misinformation regarding Evans' unique HCDR3 sequence for h5G1.1 misled the Examiner into allowing the claims during prosecution.

(c) Error 3: The Examiner Misapplied the Law in Evaluation of Secondary Considerations

Third, the Examiner materially erred by misapplying the law in evaluating the evidence of secondary considerations submitted by Alexion during prosecution. *Advanced Bionics*, Paper 6 at 8-9 n.9 ("An example of a material error … may include an error of law[.]"). In the statement of Reasons for Allowance, the Examiner noted that "some of the secondary considerations are evidence of nonobviousness, particularly the invention as claimed satisfies a long felt need and that there is objective evidence of copying." (EX1035, 007.) However, Alexion's arguments for these secondary considerations are insufficient evidence of non-obviousness as a matter of law.

The Examiner erred in accepting Alexion's evidence for long-felt need. Alexion derived its evidence of long-felt need from the success of its drug Soliris (eculizumab). (EX1036, 024-26.) But as described above, eculizumab as a PNH therapy was indisputably in the prior art. (*See supra* IX; EX1003, ¶¶191, 206.)

For copying, the Examiner also misapplied the law in accepting Alexion's evidence. Alexion submitted four separate biosimilars as its evidence of copying. (EX1036, 026-27.) However, with biosimilars, as with Hatch-Waxman/ANDA cases, evidence of copying is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval. *See, e.g.*, *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1374 (Fed. Cir. 2022) (holding that copying in ANDA context is not probative of nonobviousness). "Copying" by biosimilar applicants is entitled to no weight as a secondary consideration of nonobviousness. (*See supra* IX.) The Examiner therefore erred in considering development of biosimilars as evidence of copying. (EX1003, ¶¶193, 206.)

(d) Error 4: The Examiner Erred in Evaluating Wang

Fourth, the Examiner erred in evaluating Wang, which unequivocally teaches and renders obvious the claimed eculizumab formulation. Although the Examiner cited Wang in a rejection, its pertinent disclosures were not discussed substantively in the Notice of Allowance. *Koss*, Paper 15 at 26, 28-29. This is not surprising given Alexion's mischaracterization that Wang's formulations are about "unrelated 'anti-C5 antibodies'" (EX1036, 018-19) when in fact Wang expressly discloses that "eculizumab" is a "preferred embodiment" for its anti-C5 antibodies, and specifically teaches the 1-30 mg/ml concentration in the context of "eculizumab" formulations. (EX1044, [0004], [0170]-[0173].) Wang even calls out "eculizumab"

as an "embodiment" for antibodies that are "stable" in a formulation of 1-200 mg/ml. (*Id.*, [0067].) Alexion's mischaracterizations of Wang evidently led the Examiner to err and fail to appreciate the strength of its teachings as prior art. (EX1003, ¶¶207-208.)

XI. CONCLUSION

Petitioner respectfully requests institution of IPR based on the grounds set forth and described above.

Dated: June 16, 2023

Respectfully submitted,

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue NW
Suite 700
Washington, DC 20004
Tel: (650) 843-5505
Fax: (650) 849-7400

By: / Michelle S. Rhyu /
Michelle S. Rhyu
Reg. No. 41,268
Counsel for Petitioner

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this petition complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i) because it contains 13,785 words, according to the word-processing system used to prepare this petition, excluding the parts of this petition that are exempted by 37 C.F.R. § 42.24(a) (including the table of contents, a table of authorities, mandatory notices, a certificate of service or this certificate word count, appendix of exhibits, and claim listings).

DATED: June 16, 2023

COOLEY LLP
ATTN: Patent Docketing
1299 Pennsylvania Avenue NW
Suite 700
Washington, D.C. 20004
Tel: (650) 843-5505
Fax: (650) 849-7400

/ Michelle S. Rhyu /
Michelle S. Rhyu
Reg. No. 41,268

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. Sections 42.6 and 42.105, that a complete copy of the attached **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,703,809 B2,** including all exhibits (**Nos. 1001-1068**) and related documents, are being served via Federal Express on the June 16, 2023, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon Patent Owner by serving the correspondence address of record with the USPTO as follows:

NELSON MULLINS RILEY & SCARBOROUGH LLP,
One Financial Center, Ste. 3500
Boston, MA 02111

DATED: June 16, 2023

/ Michelle S. Rhyu /
Michelle S. Rhyu
Reg. No. 41,268
COOLEY LLP
1299 Pennsylvania Ave. NW, Suite 700
Washington, D.C. 20004
Tel: (650) 843-5505