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Dated: December 11, 2019

Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard BELL *et al.*

Application No.: 15/642,096

Confirmation No.: 7606

Filed: July 5, 2017

Art Unit: 1644

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

Examiner: James L. Rogers

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**AMENDMENT IN RESPONSE TO NON-FINAL
OFFICE ACTION UNDER 37 C.F.R. § 1.111**

Dear Sir:

In response to the Office Action dated June 11, 2019, please amend the above-identified U.S. patent application as follows:

Listing of Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

LISTING OF CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-51. (Canceled)

52. **(Previously presented)** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, and wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution.

53. **(Previously presented)** The method of claim 52, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

54. **(Previously presented)** The method of claim 53, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

55. **(Previously presented)** The method of claim 54, wherein the patient is treated with the antibody for at least 26 weeks.

56. **(Previously presented)** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution, and wherein the patient exhibits decreased lactate dehydrogenase levels.

57. **(Previously presented)** The method of claim 56, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

58. **(Previously presented)** The method of claim 57, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

59. **(Previously presented)** The method of claim 58, wherein the patient is treated with the antibody for at least 26 weeks.

REMARKS

Applicants acknowledges with appreciation the in-person interview with the Examiner and his supervisor on November 12, 2019, during which the following rejections were discussed.

Claims 52-59 are pending. *No new matter has been added.*

Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's indication that the Information Disclosure Statements submitted on August 22, 2017, March 28, 2018, April 27, 2018, and April 29, 2019 have been considered. Applicants submit herewith a Supplemental Information Disclosure Statement to make of record additional information for the Examiner's consideration.

Rejection of Claim 52-59 under 35 U.S.C. § 103(a)

Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen *et al.* (*N Engl J Med* 2004; 350: 552-9), in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660), and Bowdish *et al.* (US 2003/0232972).

In addition, claims 52-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.*, as applied to claim 52, and further in view of Bell *et al.* (US 2005/0191298).

A. **Rejection of Claim 52**

Claim 52 is directed to a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, and wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution.

The Examiner relies on Hillmen *et al.* for teaching a method of treating a paroxysmal nocturnal hemoglobinuria (PNH) patient by administering an effective amount of eculizumab. The Examiner relies on Evans *et al.* for teaching effective doses of eculizumab and that it is

within the skill of the art to determine the optimal dose. While the Examiner acknowledges that neither Hillmen *et al.* nor Evans *et al.* teach “a 300 mg single unit dosage as recited in the claims”, the Examiner asserts that it would have been obvious to modify the teachings of Hillmen *et al.* and Evans *et al.* to arrive at a 300 mg dosage.

Moreover, the Examiner alleges that one of ordinary skill in the art would have had a reasonable expectation of success in making a 10 mg /ml solution of the antibody in a sterile, preservative free solution in view of Wang, which the Examiner alleges teaches that eculizumab is highly soluble, including up to 30 mg per ml and can be formulated in a sterile, preservative free solution. While the Examiner acknowledges that neither Hillmen *et al.*, Evans *et al.*, nor Wang teach an antibody having the presently claimed heavy chain consisting of SEQ ID NO:2 and light chain consisting of SEQ ID NO:4, the Examiner nonetheless concludes that:

[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish’s TPO mimic amino acid sequence in Bowdish’s H chain published SEQ ID NO:67 which is 96% identical with currently claimed H chain SEQ ID NO:2 with Evan’s CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO:2 and to have combined that H chain sequence with Bowdish’s L chain SEQ ID NO: 68 that has 100% sequence identity to currently claimed L chain SEQ ID NO:4.

Applicant respectfully traverses the rejection. To establish a *prima facie case of obviousness*, it must be demonstrated that the presently claimed invention constitutes nothing more than a combination of known elements ***yielding a predictable result***, and that one of ordinary skill in the art would have had a ***clear reason to combine the elements***, as well as the technical ability to do so, based on the teachings and motivation provided by the prior art (see *KSR International Co. v. Teleflex Inc. et al.* 127 S. Ct. 1727 (2007) (“*KSR International Co.*”) and *Ecolab, Inc. v. FMC Corp.*, 569 F. 3d 1335 (Fed. Cir. 2009) (“*Ecolab, Inc.*”). The cited references fail to render the presently claimed invention obvious, at least because ***they provide no motivation, let alone a reasonable expectation of success***, in arriving at the claimed invention. Moreover, the secondary indicia of non-obviousness presented by Applicant herein (discussed below) provide clear, factually supported evidence, that the invention was non-obvious prior to the relevant filing date (see, *e.g.*, *Transocean Offshore Deepwater Drilling, Inc.*

v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1349 (Fed. Cir. 2012)), noting objective evidence of non-obviousness “may often be the most probative and cogent evidence in the record” and “may often establish that an invention appearing to have been obvious in light of the prior art was not”).

1. The Relevant Literature Prior to March 15, 2007 Repeatedly and Consistently Described “Eculizumab” as Having an IgG4 Heavy Chain Constant Region

Prior to March 15, 2007, the priority date of the present application, the unique amino acid sequence of the antibody in Soliris® (eculizumab) recited in the pending claims was not publicly known or disclosed in the prior art. In particular, while a person of ordinary skill in the art as of that date would have known that Alexion had designed and clinically tested an antibody named “eculizumab,” the person of ordinary skill in the art would not have known that “eculizumab” had the uniquely-engineered amino acid sequence claimed in the present application. That is because the literature as of March 15, 2007 – shown by at least eight publications listed in Table 1 below – consistently identified “eculizumab” as the antibody described in the “Thomas” publication (Thomas TC, *et al.*, Mol. Immunol., 1996;33:1389-1401), 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:

Table 1: References to “Eculizumab” as Thomas’s Humanized IgG4 Antibody

Exhibit	Statement Identifying “Eculizumab” as the IgG4 Humanized Antibody of Thomas
Hillmen 2004 (Hillmen, P., <i>et al.</i> , "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria," <i>N. Engl. J. Med.</i> 350:552-559 (2004)) at 553 – Phase II clinical trial for treatment of PNH	“ <i>Eculizumab</i> is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.” (Citing <i>Thomas</i> , Ref. No. 15)

Exhibit	Statement Identifying “Eculizumab” as the IgG4 Humanized Antibody of Thomas
Hill 2005 (Hill, A., <i>et al.</i> , "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria," <i>Blood</i> 106: 2559-2565 (2005)) at 2559 – 52-week extension of Hillmen 2004 Phase II clinical trial	“ <i>Eculizumab</i> is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.” (Citing <i>Thomas</i> , Ref. No. 9)
Hillmen 2006 (Hillmen, P., <i>et al.</i> , "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," <i>N. Engl. J. Med.</i> 355:1233-1243 (2006)) at 1234 – pivotal Phase III clinical trial for treatment of PNH,	“ <i>Eculizumab (Soliris, Alexion Pharmaceuticals)</i> is a humanized monoclonal antibody directed against the terminal complement protein C5.” (Citing <i>Thomas</i> , Ref. No. 13)
Hill 2007 (Hill, <i>et al.</i> , Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, <i>THE HEMATOLOGY JOURNAL</i> , 31-33, 2007) – post-Phase III case report for PNH patient	“ <i>Eculizumab</i> is a novel humanized monoclonal antibody directed against the complement protein C5.” (Citing <i>Thomas</i> , Ref. No. 6)
Bell (Bell, L. and Rother, R., "Method of Treating Hemolytic Disease," U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3, 2005; published September 1, 2005)) at [0052] –Phase II clinical studies described in Hillmen 2004 and Hill 2005	States that “[m]ethods for the preparation of h5G1.1-mAb” are described in <i>Thomas</i> , and that “[t]he antibody h5G1.1-mAb is currently undergoing clinical trials under the name <i>eculizumab</i> .”
Kaplan (Kaplan, M., "Eculizumab (Alexion)," <i>Curr. Opin. Investig. Drugs</i> 3: 1017-1023 (2002)) at 1018	States that “ <i>Eculizumab</i> (5G1.1), under development by Alexion Pharmaceuticals Inc. is a humanized C5 inhibitory monoclonal antibody (mAb),” and cites <i>Thomas</i> for the synthesis and complement-blocking activity of “intact humanized 5G1.1 antibody” or “humanized 5G1.1”

Exhibit	Statement Identifying “Eculizumab” as the IgG4 Humanized Antibody of Thomas
Brekke (Brekke, O. and Sandlie, I., "Therapeutic antibodies for human diseases at the dawn of the twenty-first century," <i>Nature Reviews Drug Discovery</i> 2: 52-62 (2003)) at 56	“ <i>Eculizumab</i> (5G1.1; Alexion Pharmaceuticals) <i>is</i> a humanized monoclonal antibody that prevents the cleavage of human complement component C5” (citing <i>Kaplan</i> , Ref. No. 31, which in turn cites to <i>Thomas</i>)
Pierangeli (Pierangeli, S., <i>et al.</i> , "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," <i>Arthritis & Rheumatism</i> 52: 2120-2124 (2005)) at 2123	Stating that “ <i>eculizumab</i> has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]” (citing to <i>Hillmen 2004</i> , Ref No. 18, which in turn cites to <i>Thomas</i>)

Looking at this literature, a person of ordinary skill in the art as of March 15, 2007 would have believed that Thomas’s IgG4 antibody was the **only** full-length humanized antibody shown to bind C5 and prevent its cleavage, that had been tested for safety and efficacy in treating PNH, and that had been submitted to the FDA for marketing approval.¹ In Thomas, a person of ordinary skill in the art would have seen the extensive work in rationally designing an “intact,” full-length anti-C5 humanized monoclonal antibody using an IgG4 isotype. In the published literature that followed Thomas, a person of ordinary skill in the art as of March 15, 2007 would have seen how researchers had fully established “eculizumab” – consistently identified as Thomas’s IgG4 antibody – to be safe and effective in treating PNH, applying for FDA and European approval for that antibody under the trade name Soliris®.

Contrary to the Examiner’s assertion, while Hillmen *et al.* discusses administering “eculizumab” for treating PNH, **nowhere** does this reference teach the structure of the antibody, let alone the uniquely-engineered heavy chain constant region amino acid sequence of SOLIRIS® (eculizumab) reflected in SEQ ID NO: 2. Instead, as noted above in Table 1, Hillmen *et al.* references Thomas to further describe “eculizumab,” which in turn taught an antibody with an

¹ Thomas also does not disclose the specific light chain amino acid sequence recited in SEQ ID NO: 4 of the present claims. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 at amino acid position 38, flanking light chain CDR1.

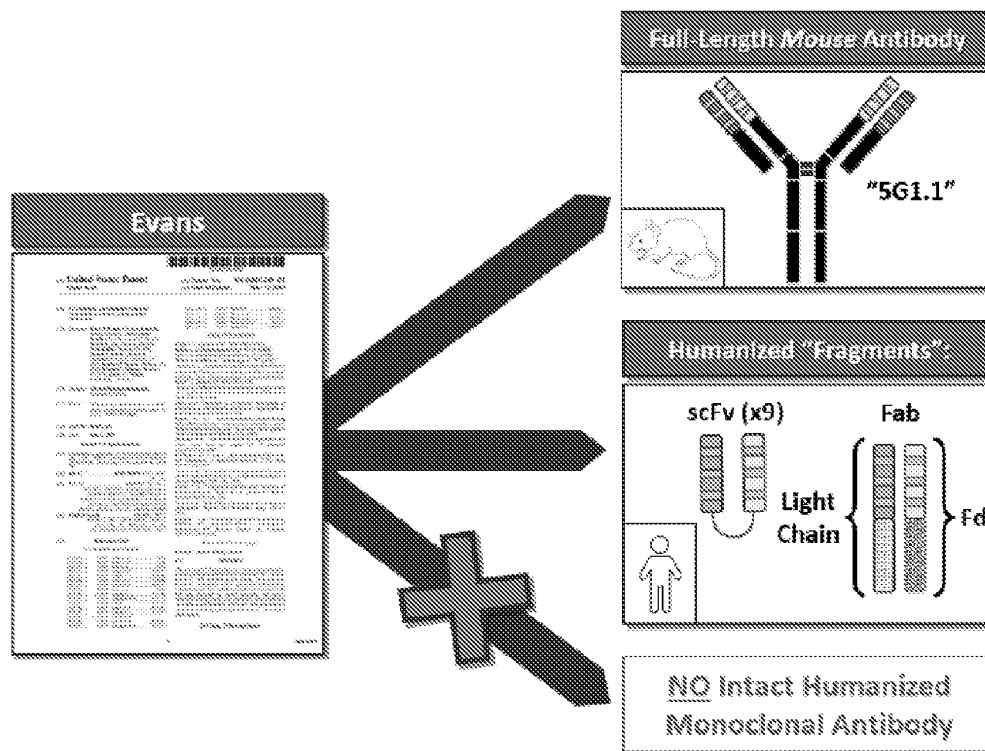
IgG4 heavy chain constant region having a very different amino acid sequence from the heavy chain constant region reflected in SEQ ID NO: 2. Accordingly, a person of ordinary skill in the art as of March 15, 2007 reading Hillmen *et al.* would have envisioned that the “eculizumab” antibody shown in that study to be safe and effective for treating PNH was the **IgG4** isotype antibody described in Thomas. Hillmen *et al.* clearly would have led a person of ordinary skill in the art in a direction divergent from the path that was taken by the present invention *i.e.*, towards the IgG4 antibody of Thomas, as opposed to the very different, uniquely-engineered antibody encompassed by the pending claims (see *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017)).

2. Evans *et al.* Does Not Disclose Any Full-Length Humanized Antibodies

Evans *et al.* fails to make up for the deficiencies of Hillmen. In contrast to Thomas and the literature regarding “eculizumab” that followed, a person of ordinary skill in the art would have understood that Evans *et al.* did **not** disclose “eculizumab.” Rather, a person of ordinary skill in the art would have understood that Evans *et al.* describes an earlier stage of research that predated the design of the intact, full-length humanized antibody “eculizumab” – because Evans *et al.* does not disclose any full-length humanized antibodies. At most, a person of ordinary skill in the art would have read Evans *et al.* as a precursor to the research that resulted in “eculizumab.” In fact, the only full-length antibody described in Evans *et al.* is the “5G1.1” mouse antibody, which Evans *et al.* obtained from the “5G1.1” hybridoma (Evans *et al.*, 19:47-49 and Figs. 18-19). Evans *et al.* further describes the researchers’ characterization of the “5G1.1” mouse antibody, including its binding affinity, in vitro activity blocking complement in hemolytic assays, and the sequencing and cloning of the variable regions of the “5G1.1 mouse antibody” (Evans *et al.*, Examples 7-10). But Evans *et al.* provides no such information for a full-length humanized antibody derived from the “5G1.1” mouse antibody – which a person of ordinary skill in the art would have understood would have a different amino acid sequence and different clinical properties from the mouse antibody, as attested to by Arturo Casadevall, an independent expert consultant, a Bloomberg Distinguished Professor of Molecular Microbiology & Immunology and Infectious Diseases at the Johns Hopkins Bloomberg School of Public

Health, and the Alfred and Jill Sommer Professor and Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health (see ¶126 of the Declaration of Arturo Casadevall; Appendix A).

To the extent Evans *et al.* describes “humanization” work based on the “5G1.1” mouse antibody, it was the development of recombinant “fragments” – scFv or Fab – that did not contain an intact heavy chain constant region, let alone the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the present application (see Example 11 of Evans *et al.* and ¶126 of the Declaration of Arturo Casadevall; Appendix A). For example, Evans *et al.* describes nine different humanized “scFv” fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region (Evans *et al.*, 43:6-14 and 43:62-45:4), and humanized “Fab” fragments that also lack the “Fc” portion (regions CH2 and CH3) of an intact antibody (Evans *et al.* 43:21-61 and ¶126 of the Declaration of Arturo Casadevall; Appendix A). Notably, the humanized Fab fragments of Evans *et al.* have different heavy chain sequences (“Fd,” Evans SEQ ID NOs: 11 and 12) from the non-prior art SEQ ID NO: 2 of the present application, including in the “CH1” constant region (¶12 of the Declaration of Arturo Casadevall; Appendix A). The following figure illustrates how a POSA would have understood what Evans *et al.* did disclose – a mouse antibody and humanized “fragments” – and what Evans *et al.* did not disclose, *i.e.*, an intact humanized monoclonal antibody:



In sum, nothing in Evans *et al.*, suggests or discloses constructing the uniquely-engineered heavy chain constant region set forth in SEQ ID NO: 2, and one of ordinary skill in the art as of March 15, 2007 would not have been motivated to make the heavy chain constant region set forth in SEQ ID NO:2, since they would have understood from the literature that the IgG4 isotype antibody of Thomas was clinically successful. Accordingly, like Hillmen *et al.*, Evans *et al.* would not have led one of ordinary skill in the art to make an antibody with the specific sequence encompassed by the pending claims.

3. A Person Skilled in the Art Would Have Had No Reason to Look to Bowdish *et al.*, and, Even Looking to Bowdish, a Person Skilled in the Art Would Not Have Combined Various Portions of Various Sequences to Arrive at the Claimed Sequence

Bowdish *et al.* concerns using an antibody – *any* antibody – as a “scaffold” to house a peptide (*e.g.*, the hormone thrombopoietin (“TPO”)), thereby providing greater stability and longer half-life for the peptide *in vivo*. The assays reported in Bowdish *et al.* have nothing to do with C5 binding or blocking complement-mediated lysis. Rather, Bowdish *et al.* assessed the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the “cMpl receptor”) – a biological interaction that is not part of the complement pathway and has nothing to do with cleavage of C5. Accordingly, one of ordinary skill in the art seeking a safe and effective anti-C5 antibody composition for the treatment PNH would not have looked to art, *e.g.*, Bowdish *et al.*, that teaches about something entirely different (see, *e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013)).

Importantly, like Evans *et al.*, Bowdish *et al.* fails to even mention “eculizumab.” There is no reason why a person of ordinary skill in the art as of March 15, 2007 would have set aside the literature’s clear teaching regarding the structure of the therapeutically successful “eculizumab” antibody and would have instead looked to Bowdish *et al.*, which addresses unrelated problems. None of the prior art references – including Hillmen *et al.*, Evans *et al.*, and Bell *et al.* – cited or pointed to Bowdish *et al.* in any manner.

Indeed, the term “5G1.1” in Bowdish *et al.*, would not have supplied any definitive information about the structure or sequence of “eculizumab.” As discussed above, the term “5G1.1” had been used in the literature to broadly refer to many different constructs such as, *e.g.*, the original mouse (“murine”) antibody identified by Alexion, and a wide variety of “humanized” constructs (also termed “h5G1.1”), including at least nine different variable region fragments (“scFv”) described in Evans *et al.*, as well as Thomas’s humanized IgG4 construct that the literature as of March 15, 2007 described as “eculizumab”. Thus, neither Bowdish *et al.*’s reference to using “5G1.1” as a scaffold for a TPO-mimetic peptide, nor Bowdish *et al.*’s citation to Evans *et al.*, would have explained to a person of ordinary skill in the art how Bowdish *et al.*’s

TPO-mimetic construct relates to the structure of “eculizumab,” let alone the complete unique sequence recited in the present claims.

Moreover, the only reference in Bowdish *et al.* to Evans *et al.* states: “Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated by reference herein.” However, Bowdish’s vague statement referencing the ’283 application for “[c]onstruction of 5G1.1,” without further explanation, is not effective to incorporate any specific material from Evans into Bowdish *et al.*, because it fails the requirement that “the host document . . . identify with **detailed particularity** what specific material it incorporates and **clearly indicate** where that material is found in various documents.” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Even if a person of ordinary skill in the art had attempted to make sense of Bowdish *et al.*’s reference to “[c]onstruction of 5G1.1 as described in [the ’283 application],” it would not have led them to a clear and unequivocal disclosure of the presently claimed invention. A person of ordinary skill in the art reading Bowdish *et al.*, would have understood that its incorporation was **limited** to the portion of the Evans *et al.* describing the “[c]onstruction of 5G1.1.”

In turn, a person of ordinary skill in the art looking to Evans *et al.* for “[c]onstruction of 5G1.1” would have been directed to Evans’s description of a **mouse** antibody – “the 5G1.1 antibody” or “the 5G1.1 mAb”, obtained from the original “5G1.1” hybridoma (see Evans *et al.* Example 7-10 and Figs. 18-19). For example, Evans *et al.* explains that “[a] particularly preferred antibody of the invention is **the 5G1.1 antibody** (5G1.1, **produced by the 5G1.1 hybridoma**, ATCC designation HB-11625),” and identifies Figs. 18 and 19 as disclosing the light chain and heavy chain variable regions of “**the antibody 5G1.1**.” In particular, nothing in Bowdish *et al.*’s reference to the “5G1.1” mouse antibody of Evans *et al.* would have indicated to a person of ordinary skill in the art that the “scaffold” antibody (whose sequence was not disclosed in Bowdish *et al.*) that was used to generate Bowdish *et al.*’s TPO-mimetic compound was the specific antibody consisting of SEQ ID NOs: 2 and 4, as recited in the pending claims.

Moreover, as the following figures illustrate, a comparison of the sequences for Evans’s “5G1.1” mouse antibody variable regions (Figs. 18-19) or the whole “5G1.1” mouse antibody with the sequences for Bowdish’s TPO-mimetic compound (Figs. 13A and 13B) would have

revealed a mismatch in amino acids beyond those that Bowdish *et al.* identified as the TPO-mimetic peptide insert (see ¶¶214-215 of the Declaration of Arturo Casadevall; Appendix A):

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Bowdish13A: QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGE
            ||||| ||||| ||||| ||| ||||| ||||| ||||| ||||| ||
Evans19: QVQLQQSGAEILMKPGASVKMSCKATGYIFSNYWIQWIKQRPGHGLEWIGE

Bowdish13A: ILPGSGSTEYTENFKDRVMTMRDTSSTVYMESSLRSEDATAVYYCARLP
            ||||| ||||| ||||| ||||| ||||| ||||| ||||| ||||| ||
Evans19: ILPGSGSTEYTENFKDKAAFTADTSSENTAYMQLSLTSSEDSAVYYCAR----

Bowdish13A: IEGPTLRQWLAARAP-----VWQGGLTVTVSS
            ||||| ||||| ||||| ||||| ||||| ||||| ||||| ||
Evans19: -----YTFGSSPNWYFDVWGAGITVTVSS

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Bowdish13B:  DIQMTQSPSSLSASVGRVTITCGASENTYGALNHWYQKPKGKAPKLLIYG
               ||||| ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
Evans18:      DIQMTQSPASLSASVGETVTITCGASENTYGALNHWYQKQKSPQLLIYG

Bowdish13B:  ATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLTNPPLTFGQ
               ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
Evans18:      ATNLADGMSSRFSGSGSGRQYYLKISLHPDDVATYYCQNVLTNPPLTFGA

Bowdish13B:  GTKVEIK
               ||| | |
Evans18:     GTKLEIK

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Top: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19

Bottom: Bowdish Fig. 13B compared to Evans Fig. 18

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Bowdish13A: -----QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
              ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: MEWTWVFLFLLSVIAGVHSQVQLQSGAELMKPGASVKMSCKATGYIFSN

Bowdish13A: YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVMTMTRDTSTSTVYM
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: YWIQWIKQRPGHGLEWIGRILPGSGSTEYTENFKDKAAFTALTSSNTAYM

Bowdish13A: ELSSLRSEDTAVYYCARLPPEGPTLRQWLAARAP-----VWQQTGLVTVS
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: QLSSLTSEDSAVYYCAR-----YFEGSSPNWYFDVWGAGTTVTVS

Bowdish13A: SASTKGFSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSG
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: SAKTTAPSVYPLAPVCGDTTGS SVTLGCLVKGYFPEPTLTWNSSGSLSSG

Bowdish13A: VHTFPAVLQSSGLYSLSVVTVPSSNFGTQTTCNVDHKPSNTKVDKTV
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: VHTFPAVLQSD--LYTLSSSVTVTSSTWFSQITCNVAFASSTKVDKKIE

Bowdish13A: RK--CCVECPP--CPAPP-VAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: PRGPTIKPCPECKCPAENLLGGPSVFI FPPKIKDVLMI SLSPIVTCVVVD

Bowdish13A: VSQEDPEVQFNWYVDGVEVHNAKTKFREEQFNSTYRVVSVLTVLHQDWLN
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: VSEDDPDVQLISWFVNNVVEVHTAQTQTHREDYNSTLRVVSALFIQHGDWMS

Bowdish13A: GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: GKEFKCKVNNKDLFAPFIERTISKPKGSVRAPQVYVLPPEEEMTEKKQVTL

Bowdish13A: TCLVKGFIYPSDIAVENESNGQPENNYKTTTPFVLDSDGSFFLYSKLTVDK
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: TCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK

Bowdish13A: RNQEGNVFSCSVMHEALHNHYTQKSLSLGLK
              ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
5G1.1HC: NWVERNSYSCSVVHEGLHNHHTTKSFRTPGK

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Bowdish Figure 13A (SEQ ID NO: 67) compared to heavy chain of 5G1.1 antibody from HB-11625

In view of the mismatch between the sequences of Bowdish *et al.* and the incorporated sequences of Evans *et al.*, a person of ordinary skill in the art as of March 15, 2007 would have found Bowdish *et al.*'s reference to Evans *et al.*, to be at most, ambiguous, and certainly would not have understood Bowdish *et al.* to clearly and unequivocally disclose an antibody consisting of SEQ ID NOS: 2 and 4 recited in the pending claims. In particular, nothing in Bowdish *et al.*'s reference to the "5G1.1" mouse antibody of Evans *et al.* would have indicated to a person of ordinary skill in the art that the "scaffold" antibody (whose sequence was not disclosed in Bowdish *et al.*) used to generate Bowdish *et al.*'s TPO-mimetic compound was the specific antibody consisting of SEQ ID NOs: 2 and 4 of the present application (see ¶¶162-163, 190 of the Declaration of Arturo Casadevall, Appendix A).

In sum, prior to March 15, 2007, no single document disclosed the entire amino acid sequence in eculizumab. Nor was eculizumab available to the public for testing or analysis prior to that date. If a person of ordinary skill in the art were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the present application claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed one of ordinary skill in the art to the 1996 Thomas publication for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring *IgG4* heavy chain constant region. The antibody encompassed by the pending claims has a very different, uniquely-engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

4. The Rejection Improperly Uses Hindsight Knowledge to Piece Together the Claimed Invention

Moreover, the Examiner's reliance on Bowdish *et al.* uses hindsight knowledge to reconstruct the sequences claimed in the present applications from bits and pieces of unrelated, prior art that teaches in an entirely different direction (*e.g.*, TPO-mimetics). Such hindsight-

driven analysis is always an improper basis for alleging obviousness. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against “slipping into use of hindsight” and “the temptation to read into the prior art the teachings of the invention in issue”); *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2017) (warning against “the distortion caused by hindsight bias” and “arguments reliant upon *ex post* reasoning”).

In particular, the Examiner uses hindsight to cobble together the sequence recited in the pending claims from Bowdish *et al.* (for portions of the claimed sequence, including its non-natural heavy chain constant region) and Evans *et al.* (for the variable region of the claimed sequence). However, the Examiner fails to show why one of ordinary skill in the art **without** hindsight would have selected Bowdish *et al.* and combined it with Evans *et al.* to obtain the antibody encompassed by the pending claims, or how they could have reasonably expected success in doing so. Specifically, the Examiner improperly uses the present application as a **reference point** for reconstructing the amino acid sequence of the claimed antibody **in hindsight**, from sequences selectively combined from Bowdish *et al.* and Evans. *et al.* However, a person of ordinary skill in the art could not have made any of these comparisons, because a person of ordinary skill in the art would not have had access to the sequence of the present application. But “working backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious.” *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

For example, in addition to the disclosure of a humanized scFv compounds, Evans *et al.*, also discloses many other sequences, including:

- Figures 18 and 19 (i.e., the variable regions of the mouse antibody that Bowdish *et al.*, references (with respect to the '283 application) for “[c]onstruction of 5G1.1” (see ¶¶214-15 of the Declaration of Arturo Casadevall; Appendix A);
- The “Fd” molecules of Evans *et al.*, SEQ ID NOs: 11, and 12, which a person of ordinary skill in the art would have understood were more “complete” fragments of a humanized antibody than an scFv, and provide sequences in the constant region (and for SEQ ID NO: 11, the variable region) that do not align with the presently

claimed sequences (see ¶¶ 129 and 158 of the Declaration of Arturo Casadevall; Appendix A); and

- The eight other humanized “scFv” molecules of Evans *et al.* (see ¶157 of the Declaration of Arturo Casadevall; Appendix A).

Even assuming the disclosures of Bowdish *et al.* and Evans *et al.* were fully combined, a person of ordinary skill in the art without hindsight would not have been directed to the complete amino acid sequence recited in the pending claims. Among other things, a person of ordinary skill in the art would not have reasonably assumed that “heavy chain CDR3” referenced in Bowdish *et al.* was the same as the heavy chain CDR3 described in Evans *et al.* for humanized scFv compounds, which are *not* full-length structures like the TPO-mimetic compound of Bowdish *et al.* (see ¶¶216-220 of the Declaration of Arturo Casadevall, enclosed herewith as Appendix A). Even if a person of ordinary skill in the art reading Bowdish *et al.* were to consider Evans *et al.* 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 (see ¶¶216-220 of the Declaration of Arturo Casadevall, enclosed herewith as Appendix A).

Critically, *nowhere* did Bowdish *et al.* even reference the word “eculizumab.” Nor did Bowdish *et al.* address the problem of the instant application – development of a monoclonal antibody that prevents C5 cleavage and is safe and effective for treating PNH. In fact, the Examiner disregards the art’s *actual* teachings about the structure and sequence of “eculizumab” in favor of a theory that improperly picks and chooses from unrelated art in hindsight.

5. Wang Does Not Disclose or Teach the Remaining Claim Limitations, and a Person Skilled in the Art Would Not Have Reasonably Expected the Claimed Composition to be Successful in Treating PNH

Finally, the Examiner relies on Wang for teaching that eculizumab is highly soluble, including at up to 30 mg per ml. Simply because an antibody may be soluble at a given concentration in a particular medium does not mean that it would be suitable in a pharmaceutical composition at that concentration. As explained in the enclosed Declaration by Dr. Trout (Appendix B), who is a Professor of Chemical Engineering at the Massachusetts Institute of

Technology (MIT) and the Director of the Society, Engineering and Ethics (SEE) Program at MIT, antibody formulation was an unpredictable field prior to March 15, 2007 and one of ordinary skill in the art could not have reasonably expected that any particular uncharacterized antibody would be capable of development into *any* pharmaceutical composition suitable for human therapeutic use, or treatment of PNH in particular, as required by the pending claims (see ¶¶39-54, 69 of the Declaration by Dr. Trout; Appendix B). Specifically, as attested to be Dr. Trout, “a person of ordinary skill in the art as of March 15, 2007 would have known that, even ‘[a]mong all the commercial antibody products,’ only ‘about half are stable enough to be formulated in a liquid form’ (which a solution is)” (¶71 of the Declaration by Dr. Trout; Appendix B).

Moreover, contrary to the Examiner’s suggestion, Wang does not disclose “a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution”, as presently claimed (see ¶80 of the Declaration by Dr. Trout; Appendix B). Specifically, Wang does not specifically teach eculizumab formulations of between 1 and 30 mg/ml, but rather discloses wide ranges, including 1-30 mg/ml, 40-200 mg/ml and 1-200 mg/ml that hypothetically might be used for nebulization of various unrelated “anti-C5” antibodies and derivative compounds (see Wang ¶¶[0067], [0130], [0170]-[0172], Fig. 10; and ¶¶82-83 of the Declaration by Dr. Trout; Appendix B). Regarding stability that a person skilled in the art would understand is needed for a pharmaceutical composition, Wang only contains a highly general, hypothetical statement that compositions of undefined anti-C5 antibodies “may be stable” over a wide concentration range of 1-200 mg/ml (Wang ¶ [0067]). A person skilled in the art would *not* have taken this vague, general statement from Wang as fact with respect to every specific antibody and concentration point, as attested in ¶84 of the Declaration by Dr. Trout (Appendix B). Accordingly, one of ordinary skill in the art, without the benefit of hindsight, would not have arrived at the dosage unit, concentration and volume recited in the pending claims (see, e.g., *KSR Int’l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007), wherein the Supreme Court emphasized that “[a] factfinder should be aware of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning”).

B. Rejection of Claims 52-59

Claims 52-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.*, as applied to claim 52, and further in view of Bell *et al.* The Examiner relies on Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.* for the reasons discussed above. The Examiner relies on Bell *et al.* for teaching treatment of PNH “using an anti-C5 antibody such as h5G1.1 mAb eculizumab”, that LDH is a known indicator of efficacy, and that treatment can continue for 64 weeks.

As discussed above, none of Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.*, either alone or in combination, render the present claims obvious. Bell *et al.* fails to cure the deficiencies of these references. Bell, like Hillmen *et al.*, would have reinforced one of ordinary skill in the art’s understanding as of March 15, 2007 that “eculizumab” was the IgG4 isotype antibody of Thomas, because Bell cited Thomas as describing “[m]ethods for the preparation of h5G1.1-mAb . . . under the tradename eculizumab”², and described positive Phase II clinical results for “eculizumab” in PNH patients. Bell thus would have further taught away from other antibody constructs that lacked such published reports of clinical safety and efficacy, such as the uniquely-engineered antibody defined by the claimed full length heavy and light chain sequences (*i.e.*, SEQ ID NOs: 2 and 4). Accordingly, given the consistent teaching as of March 15, 2007 that “eculizumab” was the IgG4 antibody of Thomas, one of ordinary skill in the art would not have found it obvious to use the very different, uniquely-engineered antibody encompassed by the pending claims, without the benefit of hindsight (see, *e.g.*, *KSR Int’l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007)).

Moreover, one of ordinary skill in the art without hindsight also would not have reasonably expected success in combining the Hillmen *et al.*, Evans *et al.*, Wang, Bowdish *et al.*, and Bell *et al.* references. Bell, like Hillmen, taught one of ordinary skill in the art as of March 15, 2007 that “eculizumab” had the **IgG4** constant region of Thomas; and nothing in Evans *et al.*, Wang, or Bowdish *et al.* would have given one of ordinary skill in the art a reasonable

² While paragraph [0052] of Bell also cited Evans for the disclosure of antibody fragments, one of ordinary skill in the art would have understood that Bell’s statements regarding the complete antibody “eculizumab” must refer to Thomas, not Evans, because Evans provided only antibody fragment sequences and no full-length humanized antibody sequence.

expectation that an antibody with a different, non-naturally occurring constant region – with no published reports indicating that such a constant region had even been tested in humans – would be safe and effective to block C5 cleavage and treat conditions such as PNH. One of ordinary skill in the art also would not have reasonably expected that substituting such a uniquely-engineered constant region would allow the antibody to retain the anti-C5 activity and therapeutic efficacy of “eculizumab” as reported in the literature. To the contrary, it was well-known as of 2007 that changes to the amino acid sequence of a monoclonal antibody (including in the heavy chain constant region) could significantly alter antibody properties including affinity, specificity, and immunogenicity, which could translate into unwanted clinical differences *in vivo*.

In sum, the cited references, alone or in combination, fail to render the presently claimed invention obvious, at least because they provide no motivation in arriving at the claimed method, let alone a reasonable expectation of success (see "*KSR International Co.*").

C. Secondary Considerations

It is well-established that objective indicia of non-obviousness (*e.g.*, evidence of copying, long-felt but unsolved needs, industry accolades, and commercial success) play a **critical role** in the analysis, and are "not just a cumulative or confirmatory part of the obvious calculus but constitute independent evidence" (see *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1365 (Fed Cir. 2008)). In fact, objective evidence of non-obviousness “may often be the most probative and cogent evidence in the record” and “may often establish that an invention appearing to have been obvious in light of the prior art was not” (see *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012)). Indeed, the Federal Circuit has clearly emphasized that "consideration of the objective indicia is part of the whole obviousness analysis, not just an afterthought," and "are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements" (see *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357, 1358 (Fed. Cir. 2013)).

There are two requirements for evidence of non-obviousness to be relevant. First, the evidence of non-obviousness must be commensurate in scope with the claimed invention (see *In*

re Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) citing *In re Tiffin*, 58 CCPA 1420, 448 F.2d 791, 792 (1971) and *In re Hiniker*, 150 F.3d 1362, 1369 (Fed. Cir. 1998)). Second, to be accorded substantial weight, there is fundamental requirement that there be a nexus between the merits of the claimed invention and the evidence of secondary considerations (see M.P.E.P. § 716.01(b), *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995), and *In re Kao* citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Moreover, there is a “presumption of a nexus” when a product is “coextensive” with a patent claim (see *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1372 (Fed. Cir. 2013)). Specifically, the Federal Circuit has held that “if the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.” (see *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000)).

In the present case, the strong evidence of secondary considerations (*e.g.*, copying, long-felt unresolved need, industry accolades, and commercial success) weigh significantly in favor of non-obviousness, as discussed in further detail below and in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Deepak Jain. Importantly, the factually supported evidence of non-obviousness presented herein is both commensurate with the scope of the claims *and* results from what is both claimed and novel. As discussed below, the presently claimed complete, full length, uniquely-engineered heavy chain sequence (which was not known in the prior art before the March 15, 2007 priority date of the present application), imparts significant therapeutic advantages which, in turn, directly relate to the merits of the invention (*i.e.*, the commercial success of the marketed product, Soliris® (eculizumab)). Therefore, the marketed product embodies the claimed features and is co-extensive with them, such that the required nexus between the merits of the claimed invention and the evidence of secondary indicia has been firmly established.

i. Long-Felt Need

Soliris® (eculizumab) has satisfied a long-felt, but previously unmet need, for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, which

has been referred to as the “most vicious acquired thrombophilic state known to medicine” (see, Fatimah Al-Ani *et al.*, *Ther. Clin. Risk Manag.* 2016; 12: 1161–1170; copy enclosed herewith as Appendix C). The unique anti-C5 therapeutic antibody, Soliris® (eculizumab), defined by the complete structure recited in the present claims (*i.e.*, SEQ ID NOs: 2 and 4) is not only the first FDA-approved anti-C5 antibody, but also the first FDA-approved treatment for PNH. In fact, in 2006, the FDA granted Soliris® (eculizumab) “Priority Review”³ status (*i.e.*, an FDA program to expedite the review process for drugs that are expected to have a particularly great impact on the treatment of a disease), demonstrating just how groundbreaking and transformative the FDA believed it could be for PNH patients.

Prior to FDA approval of Soliris® (eculizumab), patients with PNH had to suffer from debilitating symptoms, such as anemia, fatigue, thrombosis, hemoglobinuria, dyspnea, dysphagia, erectile dysfunction, hypertension and kidney problems for 10 to 15 years, with extremely limited treatment options (see <https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh>; enclosed herewith as Appendix E). In the absence of treatment, PNH resulted in a 5-year mortality rate of up to ~35% (see Appendix T). The “FDA approval of the orphan drug eculizumab in March 2007 marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria” (see Appendix I). Specifically, as attested by Dr. Peter Hillmen, “[e]culizumab has dramatically changed PNH...[u]ntil eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant” (see Appendix E).

Dr. Robert A. Brodsky similarly praised Soliris® (eculizumab) as a groundbreaking first-in-class treatment:

“We had very little to offer patients,” Robert A. Brodsky, MD, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, said in an interview. “I recently had a patient with PNH

³ “A *Priority Review* designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.” (FDA website, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review>; enclosed herewith as Appendix D).

present in absolute crisis. Several years ago the only thing we would have had to offer him was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this drug.” (see Appendix F).

In his own publication, Brodsky touts Soliris® (eculizumab) as being “highly effective in treating PNH” and states that “it has changed the natural history of the disease” (see Brodsky, *Blood*. 2014 Oct 30; 124(18): 2804–2811; enclosed herewith as Appendix F). Brodsky further states:

[t]he efficacy and safety of eculizumab has been demonstrated in 2 multinational phase 3 trials and a multinational extension study. The drug is highly effective in stopping intravascular hemolysis, eliminating or decreasing the need for red [blood] cell transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH. It has also been shown to improve renal function and to reduce prothrombotic and proinflammatory markers in PNH patients.

The literature is replete with similar testimonials and accolades (see, e.g., Fatimah Al-Ani *et al.*, stating that “[t]he advent of eculizumab has resulted in a dramatic improvement of the natural history of PNH patients with improvement in virtually every aspect of these patients’ lives”).

Importantly, Soliris® (eculizumab) has not only transformed the standard of care for PNH patients, but also significantly improved individual patient lives. Specifically, the cumulative survival rate increased from 66.8% before Soliris® (eculizumab) to 95.5% with Soliris® (eculizumab) (see Appendices U-W). Moreover, as evidenced by the enclosed testimonials from PNH patients (available at <https://alexion.com/patients/patient-stories>), treatment with Soliris® (eculizumab) has dramatically improved their quality of life and eliminated painful and debilitating symptoms that once plagued their lives and made day-to-day life challenging and unbearable (see Appendices G-J).

For example, prior to treatment with eculizumab, “Bill”, who was diagnosed with PNH in 1985, required hospitalizations and blood transfusions:

In addition to severe fatigue, Bill experienced stomach pain, kidney pain, dark urine, and dysphagia (difficulty swallowing). His symptoms made it difficult to eat and sleep. Soon, Bill became dependent on regular blood transfusions, which made day-to-day life all the more challenging... After years of managing his

symptoms as best he could with blood transfusions—and periodic hospitalizations—Bill learned about Soliris® (eculizumab), a then investigational therapy that was undergoing clinical trials. He successfully enrolled in one of the trials in 2005, and soon began to see improvements in his symptoms. Specifically, ***Bill was able to stop receiving blood transfusions*** (emphasis added; see Appendix G)

Similarly, when “Joe” was diagnosed with PNH, “he felt like his dreams were nearly shattered[,]... was worried that he would not have a future with his fiancée and was told he would never be able to compete in contact sports again.” Post-treatment with eculizumab, however, Joe “married his college sweetheart, welcomed the birth of two daughters, and is back in his routine” (see Appendix H).

“Victor” was equally devastated when he was diagnosed with PNH and “felt as if he had crawled into a cave”:

He was getting blood transfusions monthly, had little energy and was told he might only have 10 more years to live. The most difficult thing about having PNH was missing out on activities with friends and family, and the toll it took on him mentally. He became depressed. ‘People were doing things without me and I felt like I wasn’t a part of normal society,’ he says. ‘I didn’t want to talk to people.’

However, after being treated with eculizumab and receiving appropriate support, Victor’s life and outlook “radically changed” (see Appendix I).

When “Ruthie” was diagnosed with PNH in 1999, “she and her husband were scared to learn that PNH was a life-threatening illness that at the time had no approved treatments”:

Ruthie first learned about Soliris® (eculizumab) while it was in clinical trials, and began treatment shortly after it was approved by the U.S. FDA in 2007. Today, Ruthie continues to receive treatment, and has the energy to be an engaged and involved mother to three active kids. As her husband David notes, ‘In the beginning, we didn’t know how long Ruthie would be around, but today I’m excited for our children and for our future’ (see Appendix J).

Pursuant to M.P.E.P. § 716.04, the relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors.

First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967)... Second, the long-felt need must not have been satisfied by

another before the invention by applicant. *Newell Companies v. Kenney Mfg. Co.*, 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988)... Third, the invention must in fact satisfy the long-felt need. *In re Cavanagh*, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).

In the present case, it is clear that all three prongs have been met. Specifically, prior to eculizumab, there was a persistent need in the art for an effective treatment option, as physicians “had very little to offer patients” aside from palliative care (see Appendix E). This long-felt need was not satisfied until Soliris® (eculizumab) was introduced. The introduction of Soliris® (eculizumab) dramatically improved patient lives and satisfied a long-felt need for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, where prior existing treatment options had been limited and ineffective (see Appendices E-J). Importantly, it is the complete structure (*i.e.*, particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the therapeutically advantageous features that have made it the “gold” standard treatment and forever changed the standard of care for PNH patients. Accordingly, there is a direct nexus between the claimed invention and its ability to satisfy a long-felt, but previously unmet need.

ii. Copying

There are at least four instances of commercial copying (*i.e.*, biosimilar development) of Soliris® (eculizumab):

1. Amgen is developing a biosimilar eculizumab (“ABP 959”) for use in treating paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG) (see <https://www.amgenbiosimilars.com/products/our-pipeline/>; enclosed herewith as Appendix K).
2. Samsung Bioepis is developing a biosimilar eculizumab (“SB12”) and is currently recruiting for a clinical trial to compare “SB12 (Proposed Eculizumab Biosimilar) to Soliris in subjects with Paroxysmal Nocturnal Haemoglobinuria” (see

<https://www.samsungbioepis.com/en/product/product02.do>; enclosed herewith as Appendix L) and <https://www.clinicaltrials.gov/ct2/show/NCT04058158?cond=sb12&rank=1>; enclosed herewith as Appendix M).

3. Generium is developing a biosimilar eculizumab (“Elizaria®”), which launched in April 2019 in Russia (see <http://www.generium.ru/en/products/elizaria/>; enclosed herewith as Appendix N).
4. Biocad is developing a biosimilar of eculizumab (“BCD-148”), which was to be tested in a clinical trial alongside eculizumab in healthy volunteer study (see https://clinicaltrials.gov/ProvidedDocs/03/NCT04027803/Prot_000.pdf; enclosed herewith as Appendix O).

These companies are copying Soliris® (eculizumab) and developing biosimilars because the antibody as a whole (*i.e.*, the antibody’s complete sequence) renders it effective and advantageous in treating PNH, as claimed. Accordingly, there is a direct nexus between the claimed invention and copying by others.

iii. Industry Accolades

In 2008, Soliris® (eculizumab) received the Prix Galien USA Award for Best Biotechnology Product. The Prix Galien Award recognizes the technical, scientific and clinical research skills necessary to develop innovative medicines and “is considered the industry’s equivalent of the Nobel Prize, the highest accolade for biomedical research and innovation” (see <http://register.prix-galien-usa.com/registration/index>; Appendix P). The Prix Galien awards committee is made up of 11 individuals, including seven Nobel Laureates, founders of major biotechnology companies and editors of world-renowned biology journals. The candidates for the 2008 awards were selected from drugs approved during the past five years.

Soliris® received this prestigious award because it is a groundbreaking, first-in-line treatment that is effective in treating PNH patients. Again, it is the complete structure (*i.e.*, particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the features that has made it so exceptionally therapeutically effective and worthy of the Prix Galien USA Award. Accordingly,

there is a direct nexus between the claimed invention and its award-winning recognition.

iv. Commercial Success

Soliris® (eculizumab) is unquestionably a commercial success, having generated substantial sales in the relevant market. Soliris® (eculizumab) has been one of the twenty top selling biopharmaceutical products in recent history (see Table 3 of Gary Walsh, *Nature Biotechnology*, volume 36, pages 1136–1145 (2018); enclosed herewith as Appendix Q). As attested in the enclosed Declaration by Daniel Bazarko, the Senior Vice President and Chief Accounting Officer at Alexion (Appendix R), and as evidenced by the enclosed excerpts from Alexion's Forms 10-K for FY 2007-2019 (Appendix S), the annual net product sales for Soliris® have grown consistently since launch, including total U.S. sales of \$1 billion over each of the past three years, continuing to grow to over \$1.588 billion in 2018 (a 28.6% increase from 2017). Moreover, as also shown in Mr. Bazarko's Declaration, more than \$3.4 billion of Soliris' net product sales since its launch in 2007 is attributed to sales for PNH treatment. This astounding commercial success has a direct nexus to the methods of treating patients with Soliris® (eculizumab) (including PNH patients) by administering a unique anti-C5 antibody defined by a novel full-length sequence, which was not known or disclosed prior to the March 15, 2007 priority date of the present application. Specifically, the claimed complete sequence imparts Soliris® (eculizumab) with (*i.e.*, is coextensive with) efficacious and advantageous functional features (*e.g.*, binds to C5 with sufficient affinity and specificity to prevent cleavage of C5, while not activating complement and having no effector function) that have made it a groundbreaking blockbuster product. Accordingly, there is a direct nexus between the claimed invention and its commercial desirability.

D. Conclusion

In sum, the cited references, alone or in combination, fail to render the presently claimed invention obvious because they provide no motivation to arrive at the claimed invention, let alone a reasonable expectation of success (see "*KSR International Co.*"). Moreover, the factually supported evidence of secondary considerations weighs *significantly* in favor of non-obviousness

(see *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Importantly, the evidence of copying, long-felt unresolved need, industry accolades, and commercial success, associated with the use of eculizumab for treatment of PNH has a direct nexus to the novel features of the claimed invention (see *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)). Therefore, the provided evidence of secondary indicia must be considered in evaluating non-obviousness of the invention.

In view of the above, the presently claimed methods are patentable and Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Non-Statutory Double Patenting

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of US Patent 9,732,149, in view of Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of US Patent 9,718,880, in view of Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of US Patent 9,725,504, in view of Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of US Patent 9,409,980, in view of Evans *et al.* (US 6,355,245 B1), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of US Patent 9,415,102, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of US Patent 9,556,263, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of US Patent 9,352,035, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of US Patent 9,925,262, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Finally, claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of US Patent 10,239,937, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

While in no way acquiescing to the rejection, Applicants respectfully submit herewith a terminal disclaimer over US Patent 9,732,149, US Patent 9,718,880, US Patent 9,725,504, US Patent No: 9,409,980, US Patent No: 9,415,102, US Patent No: 9,556,263, US Patent No: 9,352,035, US Patent 9,925,262, and US Patent 10,239,937.

SUMMARY OF APPENDICES

A	Declaration by Arturo Casadevall
B	Declaration by Dr. Trout
C	Fatimah Al-Ani <i>et al.</i> , <i>Ther. Clin. Risk Manag.</i> 2016; 12: 1161–1170
D	FDA Priority Review (https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review)
E	https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh
F	Brodsky, <i>Blood</i> . 2014 Oct 30; 124(18): 2804–2811
G	Patient “Bill” (https://alexion.com/patients/patient-stories)
H	Patient “Joe” (https://alexion.com/patients/patient-stories)
I	Patient “Victor” (https://alexion.com/patients/patient-stories)
J	Patient “Ruthie” (https://alexion.com/patients/patient-stories)
K	Amgen (https://www.amgenbiosimilars.com/products/our-pipeline/)
L	Samsung Bioepis (https://www.samsungbioepis.com/en/product/product02.do)
M	Samsung Bioepis (https://www.clinicaltrials.gov/ct2/show/NCT04058158?cond=sb12&rank=1)
N	Generium (http://www.generium.ru/en/products/elizaria/)
O	Biocad (https://clinicaltrials.gov/ProvidedDocs/03/NCT04027803/Prot_000.pdf)
P	Prix Galien (http://register.prix-galien-usa.com/registration/index)
Q	Gary Walsh, <i>Nature Biotechnology</i> , volume 36, pages 1136–1145 (2018)
R	Declaration by Daniel Bazarko
S	Alexion’s Forms 10-K for FY 2007-2019
T	Hillmen, P., <i>et al.</i> , Natural history of paroxysmal nocturnal hemoglobinuria. <i>N. Engl. J. Med.</i> , 1995. 333(19): p. 1253-8.
U	Hillmen P, <i>et al. Br J Haematol.</i> 2013;162(1):62-73.
V	Hillmen P, <i>et al. Am J Hematol.</i> 2010;85(8):553-559.
W	Kelly RJ, <i>et al. Blood.</i> 2011;117(25):6786-6792.

CONCLUSION

Claims 52-59 are pending. *No new matter has been added.*

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 217-4630. Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 50-1196, under Order No. AXJ-114BUSCN5 from which the undersigned is authorized to draw.

Dated: December 11, 2019

Respectfully submitted,

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