IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS
Patent Owner.

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Case IPR2019-00740
U.S. Patent No. 9,718,880

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**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,718,880**

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## I. Statement of Precise Relief Requested and Reasons Therefor (37 C.F.R. §42.22(a)).

Amgen Inc. petitions for *Inter Partes* Review, seeking cancellation of claims 1-3 of U.S. Patent No 9,718,880 ("'880 patent"; AMG1001), assigned to Alexion Pharmaceuticals, Inc. The challenged claims are unpatentable under 35 U.S.C. §§ 102 and/or 103. This Petition is supported by the declaration of Dr. Joseph Balthasar (AMG1002), an expert in the development and evaluation of therapeutic monoclonal antibodies. AMG1002, ¶¶1-10. Because the petition demonstrates a reasonable likelihood that claims 1-3 are unpatentable, institution is warranted.

## II. Introduction.

The challenged claims encompass methods of treating paroxysmal nocturnal hemoglobinuria ("PNH") using a humanized anti-C5 antibody having a specified sequence. During prosecution of the '880 patent, Alexion asserted—incorrectly, yet repeatedly—that the claimed sequence "was not disclosed in the prior art; nor was it available to the public." AMG1016, 179-180; *see also* 720( "[n]either eculizumab nor its complete sequence, including the sequence of its unique, non-naturally occurring, protein engineered heavy chain, was in the public domain prior to the March 15, 2007 effective filing date of the present application."). Indeed, Alexion's argument that the claimed sequence was not publicly known was the only stated basis for withdrawing the rejections and issuing a notice of allowance:

"none of the applied references in the rejections recite using an antibody [with the claimed sequence]." *Id*., 762. But, as shown herein, long before the '880 patent's alleged priority date Alexion repeatedly published using pharmaceutical compositions for intravenous infusion of the monoclonal anti-C5 antibody eculizumab to treat a patient suffering from PNH. AMG1002, ¶¶29-43.

Alexion admitted that it performed at least 17 clinical trials treating PNH with a humanized anti-C5 antibody ("eculizumab"), and that the antibody used in those trials had the claimed amino acid sequence. *Id.* 735-737. Thus, by Alexion's admission, prior art publications of those trials necessarily disclose the claimed sequence, providing an inherent disclosure of the claimed sequence. In addition, Alexion's own prior art publications of the sequence and structure of a humanized anti-C5 antibody, were such that the skilled artisan could and would have made and used an antibody formulation as claimed, with a reasonable expectation of success. The challenged claims, therefore, offer nothing novel or inventive.

## III. Summary.

Eculizumab (Soliris®) is a monoclonal antibody that binds complement protein C5 and inhibits C5 cleavage. Alexion obtained U.S. Patent No. 6,355,245 ("Evans"), which is prior art to the '880 patent, on March 12, 2002. Alexion contends that Evans "claims the approved product" (Soliris®; eculizumab), and

provides both written description and enablement support for claims directed to eculizumab. AMG1009, 4; AMG1010, 2; AMG1049, 838-839.

The FDA approved Soliris® for treatment of patients with PNH on March 16, 2007. AMG1009, 2. Exactly *one day* before receiving FDA approval, Alexion filed PCT Application No. PCT/US2007/006606[1] ("the '606 application") and began prosecuting a chain of new patents directed to eculizumab. This was no coincidence.

To secure new eculizumab patents from the '606 application, Alexion repeatedly told the USPTO that eculizumab's amino acid sequence—specifically its IgG2/IgG4 heavy chain constant region—was not available in the prior art. But Alexion did not inform the UPSTO that it had been repeatedly publishing on eculizumab, its amino acid sequence—including its engineered IgG2/IgG4 heavy chain—years, and its use in intravenous formulations for treating PNH before March 15, 2007. Indeed, Alexion proudly boasted about widespread knowledge of the IgG2/IgG4 constant region in the art when it suited Alexion's interests, but remained silent about it to the USPTO. AMG1049, 838-839. Alexion's carefully timed pursuit of the '606 application one day before product approval improperly

[1] The '880 patent claims priority to the '606 application.

seeks to ensnare and monopolize that which is already in the public domain, through Alexion's own publications nonetheless.

Well before March 15, 2007, artisans were aware that eculizumab was safe and effective for treating PNH. Alexion itself admitted, prior to that date, that eculizumab was administered via intravenous infusion to patients in at least 17 different clinical trials, many of which were published (summarized below in Table 1). AMG1014, 735-737. Alexion also admitted that the eculizumab used in these trials has the claimed amino acid sequence. *Id* Thus, by Alexion's admission, the humanized anti-C5 antibody administered in these published trials (eculizumab) necessarily has the claimed sequence.

In addition, and contrary to Alexion's misrepresentation, the amino acid sequence and structure of eculizumab *were* known in the art, and a skilled artisan would have had ample reasons, guidance, and direction to make and use eculizumab as claimed, rendering the challenged claims obvious. Indeed, it was Alexion who placed the claimed amino acid sequence into the public domain, yet failed to inform the examiner of this.

For example, Alexion's patent application publication US 2003/0232972 A1 ("Bowdish"), *not* raised by the examiner during prosecution, published in 2003, used eculizumab as the starter "scaffold" antibody for creating a recombinant thrombopoietin (TPO) peptide-antibody, and provided the full eculizumab amino

acid sequence except for the heavy chain CDR3 ("HCDR3") sequence that it had replaced with the TPO peptide. AMG1006, ¶¶[0191]-[0193], Figs. 13A-13B, and SEQ ID NOs. 67 and 69. But the missing HCDR3 sequence was taught in Evans.

Bowdish explicitly incorporated by reference Evans[2] (another Alexion patent) for making eculizumab: "[c]onstruction of 5G1.1 [i.e., eculizumab] is described in U.S. Application Ser. No. 08/487,283, incorporated herein by reference."[3] *Id*., ¶[0191]. As Dr. Balthasar explains, the skilled artisan would have readily identified the heavy chain CDR3 sequences in Evans, thereby obtaining the complete amino acid sequence of the claimed antibody. *See* AMG1002, ¶¶55-56.

The claimed amino acid sequence was also taught in the art through the combination of Evans and another Alexion publication, WO 97/11971 ("Mueller"; AMG1008). In addition to disclosing its heavy chain CDR3 sequence, Evans taught the amino acid sequences of eculizumab's light and heavy chain variable regions. AMG1007, 44:4-13; AMG1002, ¶¶56, 146. With the heavy and light chain variable region sequences in hand, the artisan would have needed only to

[2] Alexion patent application publication US 2005/0191298 A1 ("Bell") also explicitly incorporates by reference Evans for preparing eculizumab. AMG1005, ¶[0052].

[3] Evans issued from U.S. Application No. 08/487,283. AMG1007, face.

identify the sequences for the light and heavy chain constant regions—information found in Evans (light chain) and Mueller (both the light and heavy chains).

Notably, Alexion *never* provided Mueller to the examiner. Published in 1997, Mueller taught methods of creating recombinant antibodies with chimeric IgG2/IgG4 constant regions that were known not to activate the complement system. AMG1008, 7:28-31, 8:23-26, 12:27-32. Mueller further described using eculizumab—a humanized anti-C5 antibody with the same IgG2/IgG4 constant region as the experimental antibody—as a control antibody, and provided amino acid sequences of its IgG2/IgG4 heavy chain constant region and light chain constant region. *Id*., 12:35-37, Fig. 15, 52-53, 58-61; AMG1002, ¶¶57-59, 166. Dr. Balthasar explains that a skilled artisan also would have readily obtained the complete amino acid sequence of the humanized anti-C5 antibody that results from the combination of Evans and Mueller; a sequence that Alexion now claims to be novel. *See* AMG1002, ¶¶170-175.

Alexion admittedly placed methods of treating PNH using a pharmaceutical composition comprising a humanized anti-C5 antibody, as claimed, squarely in the prior art, and it's numerous prior art publications of eculizumab clinical trials results would have given the artisan ample reason to formulate eculizumab to treat PNH. The prior art also supplied sufficient information about the sequence and structure of eculizumab such that the artisan could and would have made and used

a humanized anti-C5 antibody, as claimed, with a reasonable expectation of success. The challenged claims, therefore, offer nothing novel or inventive over what was well known in the art to a POSA before March 15, 2007.

The examiner was not aware that eculizumab's amino acid sequence was already in the prior art. The Board here has the benefit of a more complete record, and should take the opportunity to correct the examiner's error by determining that claims 1-3 of the '880 patent are unpatentable as anticipated and obvious.

## IV. The '880 patent and its prosecution history.

The '880 patent issued on August 1, 2017, from U.S. Appl. No. 15/148,839, filed on May 6, 2016, and claims a priority date of March 15, 2007.[4] Its claims recite:

> 1. A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

[4] Petitioner does not concede that the '880 patent is entitled to any of its claimed priority dates.

> 2. A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

EX1001, 39:1-16.

During prosecution, the examiner initially rejected Alexion's claims as obvious over Hillmen, which disclosed methods of using infusions of eculizumab for treating PNH, in view of Evans, which teaches "effective" doses of "antibody 5G1.1, which is the same as eculizumab," which "may be formulated in a pharmaceutically effective carrier such [as] saline, which is considered to be a "preservative free solution," and Wang, which "teaches that eculizumab is highly soluble, including at up to 30 mg per ml," and that eculizumab can be formulated in a sterile, preservative-free solution, AMG1016, 120-121.

In response, Alexion asserted—incorrectly—that "the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public;" that Hillmen "fails to teach any part of the sequence;" and Evans "fails to teach or

in any way suggest the unique, non-naturally occurring, protein-engineered full heavy chain of eculizumab." *Id*., 179-180.

In a final rejection, the examiner relied upon Thomas, for a teaching of the claimed sequence. *Id*. 598-599. Again, Alexion's response was that "[n]either eculizumab nor its complete sequence, including the sequence of its unique, non-naturally occurring, protein engineered heavy chain, was in the public domain prior to the March 15, 2007 effective filing date of the present application. *Id*., 720. Indeed, Alexion's argument that eculizumab's amino acid sequence was not publicly known was the only stated basis for withdrawing the rejections and issuing a notice of allowance: "none of the applied references in the rejection recite using an antibody [with the claimed sequence]." *Id*., 762.

As shown herein, the examiner was misled. And Alexion has repeatedly made these same misleading arguments to obtain additional eculizumab patents related to the '880 patent[5] that claim subject matter already in the public domain. For example, when prosecuting U.S. 9,732,149 (claiming eculizumab), Alexion

[5] Prosecution of parent applications is considered part of the file history of the child application. *Omega Eng'g, Inc., v. Raytek Corp.*, 334 F.3d 1314, 1333 (Fed. Cir. 2003); *see also*, *Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004).

argued that "[n]either eculizumab nor its complete sequence … was in the public domain prior to the March 15, 2007 effective filing date." AMG1015, 709-712. And when prosecuting U.S. 9,725,504 (claiming methods of using eculizumab formulations), Alexion argued that "the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public." AMG1014, 586-588.

Meanwhile, Alexion was saying the exact opposite in a European opposition proceeding over an eculizumab-related EP patent being challenged for sufficiency of disclosure. There—contrary to what it was telling the USPTO—Alexion stated that "the sequence for eculizumab was publicly available prior to the [February 3, 2004] priority and filing date" and "a sequence for eculizumab was submitted to Chemical Abstract Services (CAS) and entered into their STN database on 14 February 1999…."[6] AMG1017, 277, 291(¶5.1.2). And during prosecution of related U.S. Application No. 11/127,438, Alexion argued that its provisional applications provided written description for claims to "eculizumab" and an

[6] Alexion later tried to take this statement back during prosecution of a different European application, arguing that the eculizumab sequence information submitted in February 1999 had unintentional errors in it and therefore was not a public disclosure of the true eculizumab amino acid sequence, notwithstanding Alexion's intent to disclose it to the public. AMG1054, 247-254, 292-293.

antibody containing a "mutated Fc portion" because the provisional applications incorporated by reference the Evans prior art:

> Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are *described in U.S. Patent No. 6,355,245*, the disclosures of which are incorporated herein in their entirely [*sic*] by this reference … Applicant submits that *h5G1.1* … [was] *well-known to one of ordinary skill in the art as eculizumab* … at the time of filing of priority applications.

AMG1049, 838-839 (emphasis added).[7] Alexion cannot have it both ways. Indeed, the European Opposition Division has already revoked at least two of Alexion's European eculizumab-related patents. AMG1017, 368-378; AMG1027, 2667-2685.

## V. State of the art before March 15, 2007.

### A. Humanized monoclonal antibodies were well-known.

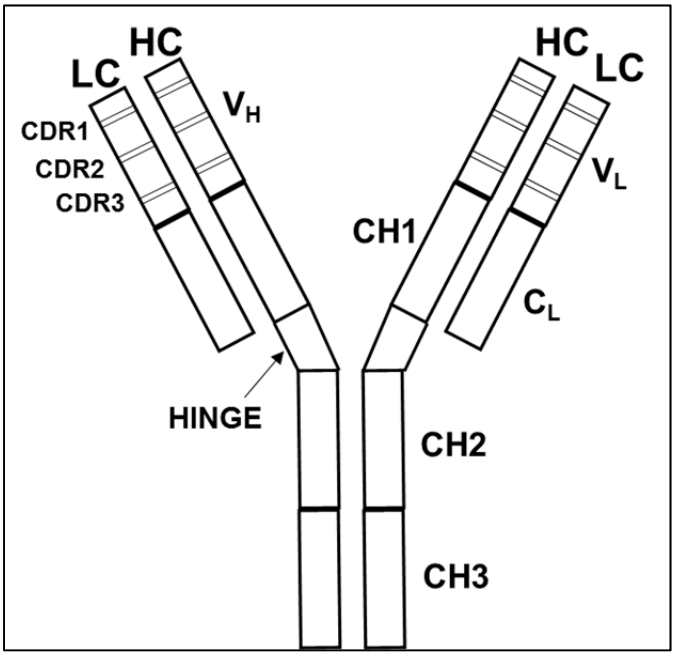
Before March 15, 2007, the structure of humanized monoclonal antibodies was well understood in the art. AMG1002, ¶¶22-28. Antibodies in general were known to be Y-shaped proteins made up of two identical "heavy chain"

[7] Unless otherwise stated, emphasis has been added throughout this Petition.

polypeptides and two identical "light chain" polypeptides. AMG1018, 7. The art taught that these heavy and light chains comprise a **variable region**—denoted as $V_L$ (for the light chain) and $V_H$ (for the heavy chain)—and a **constant region**—denoted as $C_L$ (for the light chain) and $C_H$ (for the heavy chain). AMG1018, 11-12.

The $V_L$ and $V_H$ regions each contain three "complementarity-determining regions" ("CDRs") which provide the antibody with its antigen-binding specificity. *Id.* The term "humanized" refers to an antibody having a human framework into which CDR regions from a non-human monoclonal antibody (*e.g.*, mouse) are inserted. AMG1007, 5:57-67.

This diagram depicts the basic antibody structure:




*See* AMG1002, ¶26.

### B. The prior art taught that eculizumab is a humanized anti-C5 monoclonal antibody (h5G1.1) containing a hybrid IgG2/IgG4 constant region.

Before March 15, 2007, artisans knew that "eculizumab" was more than just a name; it was a known humanized anti- C5 monoclonal antibody derived from the mouse monoclonal antibody "5G1.1," and was frequently referred to as "h5G1.1" or "h5G1.1-mAb." *See* AMG1005, ¶[0052] ("[t]he antibody *h5G1.1-mAb* is currently undergoing clinical trials under the trade name *eculizumab*."); AMG1034, 1279 ("*h5G1.1-mAb*" is synonymous with "*5G1.1, eculizumab*, Alexion Pharmaceuticals."); and AMG1002, ¶¶44-46.[8] Moreover, Alexion has admitted that "*h5G1.1* … [was] well-known to one of ordinary skill in the art *as eculizumab*…." AMG1049, 838.

The prior art also taught structural aspects of eculizumab, including that eculizumab contains a hybrid IgG2/IgG4 constant region. AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶¶47-50. For example, Tacken explicitly described using "h5G1.1-mAb (5G1.1, *eculizumab*; Alexion Pharmaceuticals)"

[8] *See also*, AMG1019, 56 ("*Eculizumab (5G1.1*; Alexion Pharmaceuticals) is a humanized monoclonal antibody."); AMG1020, 2123 ("*Eculizumab (5G1.1)*, the humanized anti-C5 mAb."); AMG1021, 1017 ("*Synonyms 5G1.1, h5G1.1*, C5 complement inhibitor (Alexion), h5G 1.1 scFv").

containing an "*IgG2/IgG4 constant region*." AMG1034, 1279. Likewise, when prosecuting a related application, Alexion told the USPTO that "it was well-known to one of ordinary skill in the art at the time of filing of priority applications [in 2002] that eculizumab has a G2/G4 Fc portion, *i.e.*, a mutated Fc portion."[9] AMG1049, 838-839. It was also well known before March 15, 2007, that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system. AMG1032, 11, 19, 28; AMG1031 ("Mueller II"), 451; AMG1002, ¶¶48, 56.

**C. The art taught eculizumab's amino acid sequence.**

Before March 15, 2007, the art taught eculizumab's amino acid sequence. AMG1002, ¶¶51-60. In 2003, Bowdish described a peptide-antibody recombinant protein using eculizumab as the starter antibody and TPO-mimetic as the agonistic

[9] A POSA would have readily distinguished another "humanized 5G1.1" published in Thomas et al. from eculizumab because Thomas' antibody, was an "IgG4 isotype" called "h5G1.1 HuG4," and not an IgG2/IgG4 isotype. The artisan would have been able to readily distinguish eculizumab from them based on whether a hybrid IgG2/IgG4 constant region was present. AMG1023, 1389, 1396; AMG1002, ¶49.

peptide inserted in place of eculizumab's heavy chain CDR3 sequence. AMG1006, ¶¶[0191]-[0193]. Bowdish provided the full amino acid sequence for the TPO-mimetic-eculizumab antibody, and thus taught eculizumab's amino acid sequence with the exception of its heavy chain CDR3 sequence (HCDR3).[10] *Id*, Figures 13A-13B (SEQ ID NOs: 67 and 69); AMG1002, ¶¶51-53. But that HCDR3 sequence was also known in the art from Evans. Indeed, Bowdish cites and incorporates by reference Evans for making eculizumab. AMG1006, ¶[0191] ("[c]onstruction of 5G1.1 is described in [Evans], incorporated herein by reference.")[11].

Evans disclosed all six CDR regions of the original mouse 5G1.1 antibody, which are underlined in the sequences in Evans' Figures 18 and 19. AMG1007, 9:65-10:20, Figures 18-19. As Dr. Balthasar confirms, a POSA would have had a reason to replace the TPO mimetic from Bowdish's TPO-eculizumab antibody with Evans' HCDR3 to generate eculizumab for use in treating PNH. AMG1002, ¶¶149-152. When combined, the "scaffold" sequences in Bowdish and eculizumab

[10] As Dr. Balthasar explains, a skilled artisan would have understood that the italicized portions of the sequences in Bowdish's Figures 13A-13B are "leader sequences" that are cleaved off during antibody maturation. AMG1002, ¶53; AMG1006, Figs. 13A-13B; AMG1045, 582.

[11] *See* note 5.

HCDR3 in Evans together form a humanized anti-C5 antibody having the claimed sequence. AMG1002, ¶¶140-148.

Another Alexion publication, Mueller, also provided complementary pieces of the eculizumab amino acid sequence, along with direction and guidance for making and using the antibody. AMG1002, ¶¶57-60. Mueller published in 1997 and disclosed the amino acid sequence of eculizumab's hybrid IgG2/IgG4 constant region and eculizumab's light chain constant region. AMG1008, 52-53, 58-61; AMG1002, ¶¶57-60. Mueller taught methods of developing recombinant antibodies to reduce immune-mediated organ transplant rejection, including antibodies comprising a hybrid IgG2/IgG4 constant region. *Id*., 8:23-26, 12:27-30. Mueller described using eculizumab (referred to as "h5G1.1 CO12 HuG2/G4 mAb") as a control antibody that shares that same hybrid IgG2/IgG4 constant region as the experimental antibodies. *Id*., 12:35-37, Figure 15. In these disclosures, Mueller provided the amino acid sequence of the hybrid IgG2/IgG4 constant region used in its antibodies—*i.e.*, the amino acid sequence of eculizumab's hybrid IgG2/IgG4 constant region. *Id*., 58-61; AMG1002, ¶¶57-60.

Dr. Balthasar's Figure 10 below schematically shows which portions of eculizumab were disclosed in the prior art.[12]

[12] Green represents eculizumab sequences disclosed in the reference; blue

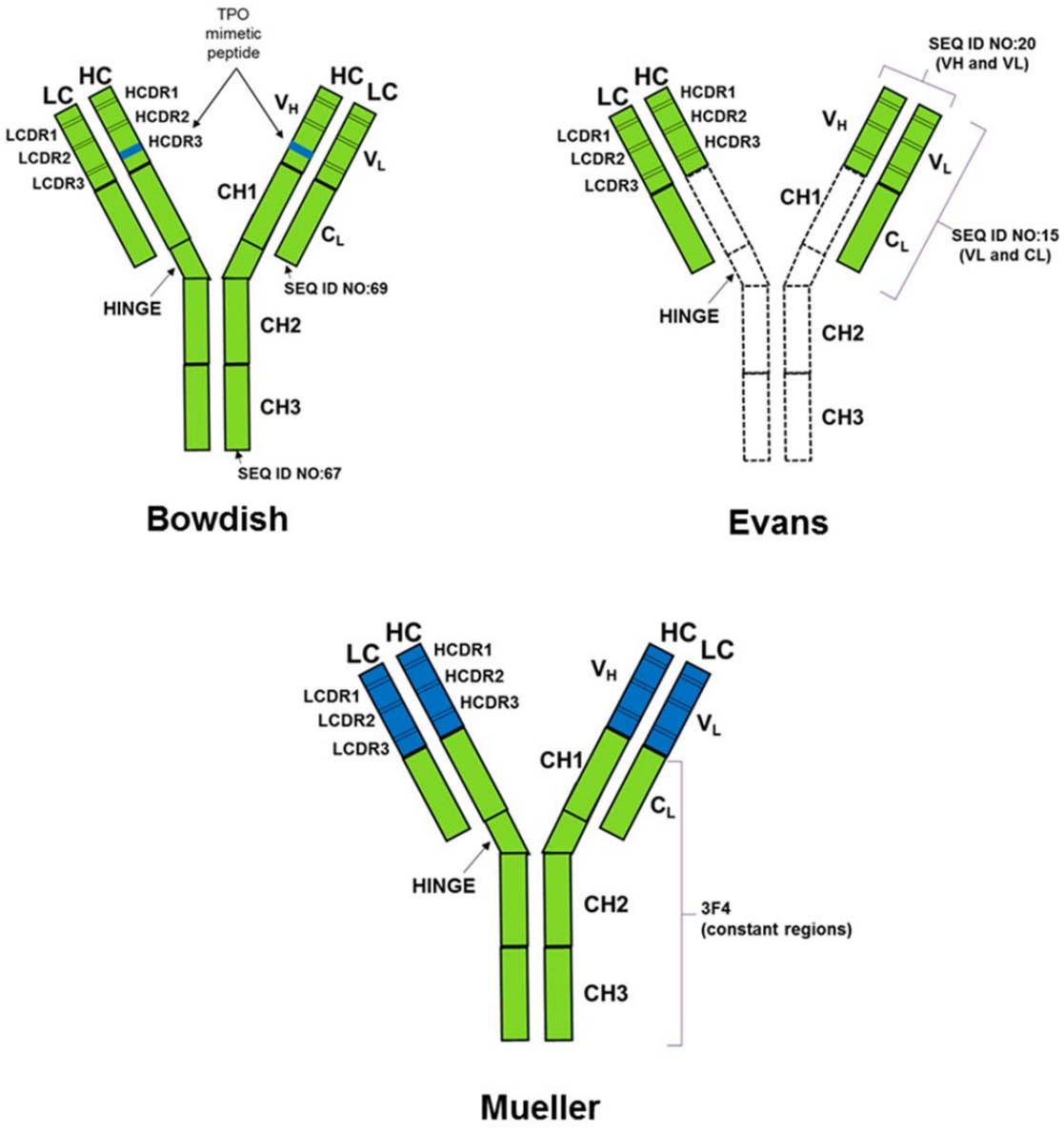



**Figure 10.**

*See* AMG1002, ¶¶60.

Though different portions of eculizumab's amino acid sequence were taught

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represents non-eculizumab sequences in each reference. AMG1002, ¶60.

in different references, the POSA is presumed to be knowledgeable of all the pertinent art—*i.e.*, all the portions of eculizumab and its general structure. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

**D. Eculizumab was a known, effective treatment for PNH.**

Eculizumab was already a well-known antibody used to treat PNH; a pathological condition that results from complement system dysregulation. AMG1023, 1389. Alexion itself acknowledged that there were at least "17 different clinical studies using eculizumab that occurred prior to March 16, 2007." AMG1016, 734(¶3). Indeed, numerous Alexion publications described clinical studies using eculizumab for successfully treating PNH. AMG1004, Abstract, 554; AMG1042, Abstract; AMG1047, Abstract, 2560; AMG1011, Abstract; AMG1005, ¶¶[0081]-[0096]; AMG1012, Abstract, 1235; AMG1013, Abstract. Each of the publications described intravenous infusion of eculizumab in weekly 600 mg doses for four weeks followed by a 900 mg dose one week later, then biweekly 900 mg maintenance doses (summarized below).

Thus, the art taught not only that eculizumab was safe and effective for treating PNH, but also taught an effective dosing regimen and pharmaceutical composition.

**Table 1 – Clinical Trials Using Eculizumab to Treat PNH**

| **Study** | **Alexion Study Number** [13] | **Dosing Regimen** | **Outcome** |
|---|---|---|---|
| Hillmen (AMG1004)<br><br>Phase 2 Pilot Study[14]<br><br>11 patients | C02-001 | "infusions of 600 mg of eculizumab weekly for four weeks, followed one week later by a 900-mg dose and then by a dose of 900 mg every other week through week 12"<br><br>AMG1004, 554. | "safe and well tolerated in patients with PNH"<br><br>"improvement in the quality of life in patients with PNH"<br><br>AMG1004, Abstract. |
| Hill '05 (AMG1047)<br><br>Phase 2 Pilot Study Extension #1<br><br>11 patients | E02-001 | "maintenance dose of 900 mg intravenously every 14 days" for 52 weeks (64 weeks total)<br><br>AMG1047, 2560. | "sustained reductions in hemolysis and blood transfusions and continued improvement in quality of life."<br><br>AMG1047, 2565. |
| Hill '04 (AMG1011) | X03-001 | "10 of the 11 patients from the initial 3 month study have continued to | "eculizumab is well tolerated and has persisting efficacy … as |

[13] Study numbers as identified in Alexion's statements made to the USPTO during prosecution. *See, e.g.*, AMG1014, 757, 765.

[14] Alexion also disclosed results from what appears to be the same pilot study in an Abstract published by Hillmen et al. in 2003. AMG1042 ("Hillmen '03").

**Table 1 – Clinical Trials Using Eculizumab to Treat PNH**

| Study | Alexion Study Number [13] | Dosing Regimen | Outcome |
|---|---|---|---|
| Phase 2 Pilot Study Extension #2<br><br>10 patients | | receive 900 mg eculizumab every other week for 2 years."<br><br>AMG1011, Abstract. | well as improvement in the symptoms of PNH, for over 2 years of therapy."<br><br>AMG1011, Abstract. |
| Bell (AMG1005)<br><br>Summary of Pilot Study and Extensions<br><br>11 patients | N/A | "weekly 600 mg intravenous infusion of [eculizumab] … Patients received 900 mg of eculizumab 1 week later then 900 mg on a bi-weekly basis."<br><br>AMG1005, ¶[0082]. | "reduction in adverse symptoms associated with PNH"<br><br>AMG1005, ¶[0096]. |
| Hillmen '06 (AMG1012)<br><br>Phase 3 "TRIUMPH" study<br><br>87 patients | C04-001 | "infusions of 600 mg of eculizumab or placebo every week (±2 days) for 4 weeks, followed 1 week (±2 days) later by 900 mg of eculizumab or placebo, and then by a maintenance dose of 900 mg of eculizumab or placebo every 2 weeks (±2 days) through week 26."<br><br>AMG1012, 1235. | "Eculizumab is an effective therapy for PNH."<br><br>AMG1012, 1233. |
| Young (AMG1013) | C04-002 | "Eculizumab was dosed as follows: 600 mg IV every 7 days x 4; 900 | "eculizumab treatment markedly reduces intravascular hemolysis, |

**Table 1 – Clinical Trials Using Eculizumab to Treat PNH**

| Study | Alexion Study Number [13] | Dosing Regimen | Outcome |
|---|---|---|---|
| Phase 3 "SHEPHERD" study<br><br>97 patients | | mg 7 days later; and then 900 mg every 14±2 days."<br><br>AMG1013, Abstract. | thereby providing clinical benefit to treated [PNH] patients."<br><br>AMG1013, Abstract. |

## VI. Person of ordinary skill in art.

A person of ordinary skill in the art (POSA) is a hypothetical person, presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. *KSR Int'l. Co. v. Teleflex Inc.*, 550 US 398, 421 (2007); *Standard Oil*, 774 F.2d at 454. A POSA in the field of the '880 patent had 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. AMG1002, ¶21. A POSA also had knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same. *Id.* 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 field. *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 and a formulation chemist may have been part of a team. *Id*.

## VII. Claim construction.

Claims must be given their ordinary and customary meaning in light of the specification—"the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-1313 (Fed. Cir. 2015) (en banc); *see also*, 37 C.F.R. §42.100(b); 83 Fed. Reg. 51340, 51358 (Oct. 11, 2018).

The meaning of all claim terms in the '880 patent are plain on their face and require no further construction. AMG1002, ¶64. Amgen reserves the right to rebut any claim construction arguments Alexion might raise.

## VIII. Identification of the challenge (37 C.F.R. §42.104(b)).

Amgen requests IPR based on the grounds summarized below.

| Ground | 35 U.S.C. Section (pre-AIA) | Claims | References |
|---|---|---|---|
| 1 | §102(b) | 2 | Hillmen |
| 2 | §102(b) | 2 | Hill '05 |
| 3 | §103(a) | 1, 3 | Hillmen, Bell, and Wang |

| | | | |
|---|---|---|---|
| 4 | §103(a) | 1, 3 | Hill '05, Bell, and Wang |
| 5 | §103(a) | 1-3 | Bell, Bowdish, Evans, and Wang |
| 6 | §103(a) | 1-3 | Bell, Evans, Mueller, and Wang |

- Hillmen et al., *N. Engl. J. Med.* 350(6):552-559 (2004) ("**Hillmen")** published February 5, 2004. AMG1004, 552.

- Hill et al., *Blood* 106(7):2559-2565 (2005) ("**Hill '05**") published October 1, 2005. AMG1047, 2559.

- US 2005/0191298 A1 ("**Bell**"), published September 1, 2005. AMG1005, face.

- US 2005/0271660 A1 ("**Wang**") published December 8, 2005. AMG1028, face.

- US 2003/0232972 A1 ("**Bowdish**"), published December 18, 2003. AMG1006, face .

- U.S. Patent No. 6,355,245 ("**Evans**'), issued March 12, 2002. AMG1007, face.

- WO 97/11971 ("**Mueller**"), published April 3, 1997. AMG1008, face.

These references are prior art under 35 U.S.C. §102(b) because each

published more than one year before March 15, 2007, the '880 patent's earliest claimed priority date.

## IX. The same or substantially the same prior art or arguments were not previously presented to the Office.

The arguments and evidence presented herein were not before the examiner during prosecution and, therefore, do not constitute "the same or substantially the same prior art or arguments" under 35 U.S.C. §325(d).

As discussed in §III.B, the examiner rejected Alexion's claims as obvious over combinations of Hillmen, Evans, Wang and Thomas during prosecution. Thomas was the only reference relied upon for eculizumab sequence information. AMG1016, 596-602. And, the examiner allowed the '880 patent claims mistakenly believing—because of Alexion's mischaracterization of the art—that the sequence and structure of eculizumab were not already known. *Id*., 762-763.

Though Hillmen, Evans, and Wang were referenced by the examiner during prosecution, this Petition presents them in a different light, along with new references—Bell, Bowdish, and Mueller—which teach the IgG2/IgG4 constant domain missing from the art combination raised during prosecution.

Bell and a parent application to Bowdish (US 2003/0049683 A1) was cited but not relied upon during prosecution, and Mueller was not cited at all. Thus, the art combinations here, which were not raised by the examiner during prosecution,

provide the complete sequence of eculizumab, thereby teaching the very thing the examiner mistakenly concluded was missing from the prior art. Consequently, this Petition is not the same/substantially the same as or cumulative of any previous arguments and § 325(d) does not preclude instituting this Petition.

## X. Ground 1: Hillmen anticipates claim 2.

Hillmen anticipates claim 2. A reference anticipates when it discloses each and every claim limitation "either expressly or inherently." *In re Crish*, 393 F.3d 1253, 1256 (Fed. Cir. 2004). "Under the principles of inherency, if the prior art necessarily … includes[] the claimed limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1363 (Fed. Cir. 1999). Dr. Balthasar confirms that Hillmen discloses all the limitations of claim 2, either expressly or inherently, and is enabling. AMG1002, ¶¶73-81.

### A. Hillmen explicitly disclosed every element of claim 2, except for eculizumab's amino acid sequence.

Dr. Balthasar confirms that Hillmen disclosed all the limitations of claim 2, either expressly or inherently. AMG1002, ¶¶74-76. Hillmen expressly disclosed a "pharmaceutical composition comprising an antibody that binds C5" as claimed because Hillmen disclosed administering infusion of *eculizumab* formulations to patients, and eculizumab was a known antibody that binds C5. AMG1004, Abstract. For example, Hillmen disclosed that "patients with PNH received

*infusions* of *eculizumab*…." *Id*. Hillmen further described eculizumab as an "*antibody against terminal complement protein C5*." *Id*.

### B. Alexion admitted that Hillmen's eculizumab necessarily has the claimed sequence.

Hillmen's antibody necessarily "comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" because Alexion admitted that Hillmen's eculizumab possesses those very amino acid sequences.

During prosecution, Alexion submitted a list of eculizumab clinical studies—including Hillmen's Phase 2 Pilot Study (Study "C02-001")—and stated that "the antibody (eculizumab) used in each of the studies … *contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4*." AMG1014, 767(¶6); *see also, id.*, 765 (study number "C02-001"). This admission is binding on Alexion. *See, e.g., Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996); *Tyler Refrigeration v. Kysar Indus. Corp*., 777 F.2d 687, 690 (Fed. Cir. 1985).

The FDA Medical Review in Alexion's approval package for Soliris® confirmed that "Study C02-001" was published in "Hillmen, P et al. … NEJM. 2004; 350:552-558" (i.e., Hillmen). AMG1024, 109. Similarly, Australia's Pharmaceutical Benefits Advisory Committee ("PBAC") produced a public summary document for Soliris® showing that clinical trial "C02-001 (Pilot Study)" was published in "N Engl J Med 2004, 350:552-559." AMG1025, 2.

Because Alexion's admission confirms that the "eculizumab" disclosed in Hillmen necessarily comprised a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4, Hillmen inherently discloses the claimed sequences.

Despite admitting to the Office that the eculizumab disclosed in Hillmen necessarily comprised a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4, Alexion misleadingly argued during prosecution that its contribution over the art was the specific amino acid sequence of eculizumab. AMG1014, 586-587, 738-744. However, as *Crish* makes clear, "just as the discovery of properties of a known material does not make it novel, *the identification and characterization of a prior art material also does not make it novel*." *Crish*, 393 F.3d at 1258. There is "[a] long line of cases confirm[ing] that one cannot establish novelty by claiming a known material by its properties." *Id*.

In *Crish*, the applicant claimed an hINV promoter region based on its nucleotide sequence. The court stated that the pertinent inquiry for its anticipation analysis is "whether the claimed [invention] was new," and determined that:

> The promoter region of hINV *was not new* … hINV was *known and used years before* … The only arguable contribution to the art that Crish's application makes is the identification of the nucleotide sequence of the promoter region of hINV. However, just as the discovery

> of properties of a known material does not make it novel, *the identification and characterization of a prior art material also does not make it novel*.

*Id*.; *see also, Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999 ("the discovery of a previously unappreciated property of a prior art composition … does not render the old composition patentably new to the discoverer."); *Abbott Labs. v. Baxter Pharms.*, 471 F. 3d 1363, 1368 (Fed. Cir. 2006) (lack of knowledge of a compound's property is "wholly irrelevant to the question of whether the [a patent] claims something 'new' over the disclosure of the [prior art].").

This precedent is squarely applicable here and compels finding anticipation. The '880 patent's mere claim to a composition comprising an amino acid sequence that Alexion admits was a property of a prior art compound (eculizumab) contributes nothing over the prior art..

**C. Hillmen's disclosure is enabling.**

Hillmen also provided an enabling disclosure of the claimed pharmaceutical composition. An anticipatory publication "must be capable, *when taken in conjunction with the knowledge of those skilled in the art* to which it pertains, of placing that invention in the possession of the public." *In re Donohue*, 632 F.2d 123, 125 (CCPA 1980) ("*Donohue I*"); *see also*, *In re Donohue*, 766 F.2d 531, 533

(Fed. Cir. 1985) ("*Donohue II*") (public possession "is effected if one of ordinary skill in the art could have *combined the publication's description* of the invention *with his own knowledge* to make the claimed invention."); and *Elan Pharms. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003).

To determine whether experimentation would be undue, one must examine "(1) the quantity of experimentation; (2) the amount of direction or guidance present; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims." *Impax Labs. v. Aventis Pharms.*, 545 F.3d 1312, 1314-1315 (Fed. Cir. 2008) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Applying these factors, Dr. Balthasar explains that Hillmen, coupled with the general knowledge in the art, would have enabled a POSA to possess a pharmaceutical composition comprising eculizumab having the claimed sequences. AMG1002, ¶¶77-80.

The alleged invention claim 2 are directed to a pharmaceutical composition comprising an antibody (eculizumab). This antibody was expressly disclosed in Hillmen; and Alexion admitted that Hillmen's eculizumab had the claimed sequences. AMG1004, Abstract, 553-554; AMG1016, 737(¶6), 736; AMG1024, 109; AMG1025, 2. And the general knowledge in the prior art was replete with disclosures, direction, and guidance about eculizumab's structure and its amino

acid sequence. AMG1002, ¶78.

Dr. Balthasar's Figure 10 above illustrates the art disclosing eculizumab amino acid sequences. *See* §IV, *supra*; AMG1002, ¶60. Dr. Balthasar explains two independent ways in which a POSA would have obtained eculizumab's amino acid sequence:

(1) A POSA would have known that **Bowdish** disclosed the entire amino acid sequence of eculizumab with the exception of the heavy chain CDR3 region, and that **Evans** disclosed the eculizumab heavy chain CDR3 region (the missing piece from Bowdish). AMG1006, ¶¶[0191]-[0193], Figure 13A-13B (SEQ ID NOs:67 and 69); AMG1007, 44:4-13 (SEQ ID NO:20); AMG1002, ¶78.

(2) A POSA also would have known that **Evans** disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, and **Mueller** disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab. AMG1007, 44:4-13 (SEQ ID NO:20); AMG1008, 52-53, 58-61; AMG1002, ¶78.

And given the high level of skill in the relevant field, the POSA would have readily obtained eculizumab's sequences as claimed from the art using only routine experimentation.

Armed with the general knowledge in the relevant field, a POSA reading

Hillmen would not have "needed to experiment unduly to gain possession of the invention." *Impax*, 545 F.3d at 1315-1316; AMG1002, ¶79. Here, just as in *In re Donohue*, "the primary reference named a composition falling within the scope of the claims and indicated that it had previously been made and tested; additional references showed that a method of making this composition would have been within the knowledge of one of ordinary skill in the art." *Donohue I* at 126.

The law compels finding anticipation here. The claimed antibody was not new—Hillmen taught administering a pharmaceutical composition comprising eculizumab. Under *Crish*, simply adding the amino acid sequence of an already known antibody to the claims does not confer novelty. Moreover, Alexion's admission that Hillmen's eculizumab inherently possesses the claimed sequences is binding under *Vitronics.* And under *Donohue I* and *Donohue II*, Hillmen is enabling in view of the multiple publications of eculizumab's sequence in the art and pharmaceutical compositions that were standard and well-known in the art, particularly for intravenous therapeutic antibody compositions. AMG1002, ¶80. Accordingly, Hillmen anticipates claim 2.

## XI. Ground 2: Hill '05 anticipates claim 2.

Dr. Balthasar confirms that Hill '05 disclosed a pharmaceutical composition comprising eculizumab—a known antibody that necessarily possesses the claimed amino acid sequences— and is enabling. AMG1002, ¶¶82-92. Thus, Hill '05

anticipates claim 2. *In re Crish*, 393 F.3d 1253, 1256 (Fed. Cir. 2004).

### A. Hill '05 explicitly disclosed every element of claim 2, except for eculizumab's amino acid sequence.

Hill '05 disclosed administering eculizumab formulations to patients over a one-year extension period, concluding that "[r]esults of this 1-year extension study showed that eculizumab therapy continues to be safe and well tolerated in PNH patients." AMG1047, 2565.

Hill '05 disclosed "an antibody that binds C5" as claimed because Hill '05 disclosed administering *eculizumab* formulations to patients, and eculizumab was a known antibody that binds C5. *Id*, Abstract, 2560. For example, Hill '05 disclosed that patients in the extension study received a "maintenance dose of *eculizumab*," and "this maintenance dose of 900 mg intravenously every 14 days was continued throughout the extension study period." *Id*. Hill '05 further described eculizumab as an "a *humanized monoclonal antibody* that specifically targets the *complement protein C5*." *Id*, 2559.

### B. Hill '05's eculizumab necessarily has the claimed sequence.

Hill '05 also disclosed the claimed antibody that "comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" because as already discussed above, Alexion admitted that the eculizumab used in Hill '05's trial—which was already in the public domain—necessarily possesses the

claimed amino acid sequence. AMG1002, ¶¶83-87.

Hill '05 is an Alexion publication describing results from a one-year extension study involving the same 11 patients enrolled in the Hillmen Phase 2 Pilot Study. *Id*, 2559-2560. In the list of eculizumab clinical studies Alexion submitted to the USPTO during prosecution, Alexion also included Hill '05's extension study (Study number "E02-001") when affirmatively stating that "the antibody (eculizumab) used in each of the studies … *contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4*." AMG1016, 737(¶6); *see also, id.*, 735 (study number "E02-001"). Again, Alexion's admission is binding. *Vitronics* 90 F.3d at 1583; *Tyler Refrigeration*, 777 F.2d at 690.

Hill '05 explicitly confirms that it is an extension study of Hillmen's Phase 2 Pilot Study, stating "[w]e previously reported the outcome of an open-label study of eculizumab in patients with PNH [*citing Hillmen*] … Here we report the results of a 1-year follow-up study designed to assess the long-term efficacy and safety of eculizumab in patients with PNH." AMG1047, 2559. Hill '05 also disclosed that "[t]he acute-phase study was an initial 12-week, open-label trial of eculizumab in 11 patients with PNH and has been previously described in detail [*citing Hillmen*] … The current study was an open-label *extension of that acute-phase study*." *Id*, 2560. This is consistent with Alexion's admission to the USPTO that study number E02-001 (Hill '05) is entitled "Extension Study in Patients … who Previously

Participated in Study C02-001 [Hillmen]." AMG1016, 735.

Because Alexion's admission confirms that the "eculizumab" disclosed in Hill '05 necessarily comprised a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4, as claimed, Hill '05 inherently discloses an antibody comprising the claimed sequences. AMG1002, ¶¶83-87. And, as discussed above, merely claiming the amino acid sequence of a known antibody—as the '880 patent claims—does not confer novelty. *Crish*, 393 F.3d at 1258; *Atlas Powder*, 190 F.3d at 1347; *Abbott Labs.*, 471 F.3d at 1368.

**C. Hill '05's disclosure is enabling.**

Hill '05 is enabling for the same reasons discussed above in Ground 1. AMG1002, ¶¶88-92. The alleged invention and claim 2 are directed to a pharmaceutical composition comprising an antibody (eculizumab) that was expressly disclosed in Hill '05. AMG1047, Abstract, 2559-2560. And as already discussed, the general knowledge in the prior art had ample disclosures, direction, and guidance on eculizumab and its amino acid sequence. AMG1002, ¶89. *See* §IV, *supra*.

Again, Dr. Balthasar explains two independent ways in which a POSA would have obtained eculizumab's amino acid sequence: (1) from the "5G1.1" scaffold sequences in **Bowdish** and the HCDR3 sequence in **Evans** (AMG1006, ¶¶[0191]-[0193], Figure 13A-13B (SEQ ID NOs:67 and 69); AMG1007, 44:4-13

(SEQ ID NO:20)); or (2) from the heavy and light chain variable region sequences in **Evans** and the heavy and light chain constant domain sequences in **Mueller** (AMG1007, 44:4-13 (SEQ ID NO:20); AMG1008, 52-53, 58-61). AMG1002, ¶89. Given the high level of skill in the relevant field, the POSA would have readily obtained eculizumab's sequences as claimed from the art using only routine experimentation. *Impax*, 545 F.3d at 1315-1316; AMG1002, ¶90. And formulation preparation techniques were standard and well-known in the art, particularly for intravenous therapeutic antibody formulations. AMG1002, ¶91; AMG1056-1076.

As in Ground 1, the law also compels finding anticipation in Ground 2. The claimed antibody was not new because Hill '05 taught administering a pharmaceutical composition comprising eculizumab. Later claiming the amino acid sequence of a known antibody does not make what was already publicly known now novel. *Crish*, 393 F.3d at 1258; *Atlas Powder,* 190 F.3d at 1347; *Abbott Labs.*, 471 F. 3d at 1368. Moreover, Alexion is bound by its admission that Hill '05's eculizumab inherently possesses the claimed sequences. *Vitronics*, 90 F.3d at 1583; *Tyler Refrigeration*, 777 F.2d at 690. And a POSA taking Hill '05's disclosure in conjunction with the knowledge of skill in the art would have been able to possess the claimed pharmaceutical composition without undue experimentation. *Donohue I*, 632 F.2d at 125; *Donohue II*, 766 F.2d at 533. Under *Donohue I* and *Donohue II*, Hill '05 is enabling in view of the multiple publications of eculizumab's sequence

in the art and pharmaceutical compositions that were standard and well-known in the art, particularly for intravenous therapeutic antibody compositions. AMG1002, ¶¶89-91.

## XII. Ground 3: claims 1 and 3 would have been obvious over Hillmen, Bell, and Wang.

As already discussed, Hillmen disclosed a pharmaceutical composition comprising eculizumab (an anti-C5 antibody) having the claimed sequences either expressly or inherently. *See* § IX.

Claims 1 and 3 further require that the pharmaceutical composition is "a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody [ or anti-C5 antibody] solution." AMG1001, 39:2-8 and 13-16. Those additional limitations were taught in Bell and Wang. And, a POSA would have had reason to combine Bell and Wang with Hillmen to arrive at claims 1 and 3, with a reasonable expectation of success. AMG1002, ¶¶93-109.

Like Hillmen, Bell taught methods of treating a patient suffering from PNH using a pharmaceutical composition comprising eculizumab. AMG1005, ¶¶[0012], [0052], [0081]-[0096]. Indeed, Bell disclosed a Phase 2 Pilot Study involving 11 PNH patients treated with eculizumab over a period of 12 weeks—identical to that disclosed in Hillmen. *Compare* AMG1005, ¶¶[0081]-[0082] *with* AMG1004, Abstract and 553-554. As Dr. Balthasar explains, Bell and Hillmen shared the

following identical features:

- antibody (eculizumab);
- patient pool (6 male, 5 female);
- administration route (IV);
- dosing regimens;[15] and
- resulting data.

AMG1002, ¶¶40, 111; AMG1005, ¶¶[0081]-[0096].[16] Given the substantial overlap, a POSA would have had ample reason to combine Hillmen and Bell, with

[15] 600 mg eculizumab weekly for four weeks, followed by a 900 mg dose, then 900 mg eculizumab every other week through week 12.

[16] Because the clinical study taught in Bell is the same C02-001 study disclosed in Hillmen, which discloses the eculizumab amino acid sequences of SEQ ID NOs: 2 and 4, Bell, too, therefore anticipates claim 2 for the same reasons discussed above for Hillmen. AMG1016, 737(¶6); *see also, id.*, 735 (study number "C02-001"); AMG1005, ¶[0082]; AMG1002, ¶94, n6. Hill '05, Hill '04, Hillmen '06, and Young '06 also anticipate claim 2 for the same reasons. AMG1016, 737(¶6), 735 (study numbers E02-001, X03-001, C04-001, and C04-002, respectively); AMG1047, 2559-2560; AMG1011, Abstract; AMG1012, 1235; AMG1013, Abstract.

a reasonable expectation of success at achieving the claimed subject matter.

Wang taught therapeutic antibody formulations, and explicitly taught formulating "*eculizumab* as the antibody therapeutic." AMG1028, ¶[0004]. With all three references explicitly teaching aspects of eculizumab, a POSA would have had ample reason to combine Hillmen, Bell, and Wang with a reasonable expectation of success at achieving the claimed subject matter. No objective indicia of nonobviousness support patentability. *See* §XV.

**Bell taught "sterile, preservative-free"**: Bell explains that its eculizumab formulations "*must be sterile* and non-pyrogenic," and that they "*may* contain … preservatives…" (i.e., preservatives are optional). AMG1005, ¶[0062]; AMG1002, ¶98. Dr. Balthasar further explains that a POSA would also have generally known that therapeutic antibodies are routinely prepared in sterile, preservative-free solutions. AMG1002, ¶98. In fact, of 22 monoclonal antibodies approved by the FDA before March 15, 2007—and of which the POSA would have been aware—100% of them were formulated in *sterile, preservative-free* solutions. AMG1002, ¶¶98; AMG1056-AMG1076.

**Bell and Hillmen taught a "300mg single-use dosage form"**: As Dr. Balthasar explains, a POSA would have understood that a "unit dosage form" of an antibody as taught in Bell is formulated for use in a single patient and is therefore a "single-use" dosage form as claimed. AMG1002, ¶99; AMG1046, 2989;

AMG1051, 1. For example, a POSA would have generally known that antibody dosage forms should not be shared among patients or returned to storage after opening, to prevent contamination and unnecessary health risks. AMG1002, ¶100; AMG1046, 2989. Alexion agrees, telling the USPTO during prosecution[17] that skilled artisans "would have been well aware … that single-dose vials are intended for a single procedure or injection and should always be discarded at the end of the procedure/injection. They should never be stored for later use or subsequent procedures, even if for the same patient." AMG1026, 208-209 (internal quotation omitted).

Thus, Bell would have motivated a POSA to prepare eculizumab formulations as single-use dosage forms as claimed in claims 1 and 3 using routine formulation preparation techniques that were standard and well-known in the art, particularly for intravenous therapeutic antibody formulations. AMG1002, ¶¶99-100. Indeed, the '880 patent mentions no "newly discovered" advantages of the single-use unit dosage form claim limitation.

Moreover, a POSA would have arrived at the 300 mg single-use dosage form through simple convenience and a logical application of knowledge in the art.

[17] U.S. Appl. No. 13/426,973 is the abandoned parent application of the '880 patent. AMG1001, face.

AMG1002, ¶¶101-104. Both Hillmen and Bell explicitly taught administering eculizumab in doses of 600 mg and 900 mg (AMG1004, 554; AMG1005, ¶[0082]), thus prompting a POSA, as Dr. Balthasar explains, to administer those same doses because they were each shown to successfully treat PNH. AMG1004, 558-559; AMG1005, ¶¶[0089]-[0096]; AMG1002, ¶101.

To accommodate dosages of 600 mg and 900 mg dosages, a 300 mg single-use dosage amount would have been the most obvious and convenient (and thus predictable) means to a POSA. It would have been easier to achieve 600 mg and 900 mg doses with two and three 300 mg dosages, respectively, than to separately manufacture those two strengths. AMG1002, ¶¶102-103. *See KSR Int'l. Co. v. Teleflex Inc.*, 550 US 398, 416 (2007) ("When a work is available in one field, design incentives and other market forces can prompt variations of it … If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability.") Tellingly, Alexion admitted during a European opposition proceeding for a related EP patent[18] that there is nothing critical about the claimed single-usedosage form beyond convenience: "*simple dilution* of product required by the label *conveniently* provides the required 600 or 900 mg administration dosages." AMG1027,

[18] EP Patent No. 2359834 is a European counterpart to the '880 patent.

1104(¶5.3.9).

According to Dr. Balthasar, a POSA at the time of invention would have had a reasonable expectation of successfully preparing a 300 mg single-use dosage form because doing so would have been simple, more efficient, and more convenient than developing, validating, and storing separate dosage forms for each of the 600 mg and 900 mg doses taught in Hillmen and Bell—*i.e.*, a "one size fits all" approach. AMG1002, ¶103-104. Moreover, Bell taught methods for preparing unit dosage forms, and both Hillmen and Bell described successfully preparing and administering 600 mg and 900 mg doses. AMG1004, 553-554; AMG1005, ¶¶[0058]-[0060], [0062], [0082]; AMG1002, ¶104.

**Wang taught a "30 ml of a 10 mg/ml" solution:** Wang taught eculizumab formulations of between *1 and 30 mg/ml*, completely encompassing the claimed 10 mg/ml concentration.[19] AMG1028, Fig. 10, ¶¶[0170]-[0172]; AMG1002, ¶¶105-

[19] Wang's nebulization formulation is equally relevant to intravenous infusion. A POSA would take Wang as confirmation that eculizumab, formulated at a concentration of 1 to 30 mg/mL, would be sufficiently stable and active to be used as a drug. AMG1002, ¶105. And, Wang also shows by SDS-PAGE and HPLC that eculizumab maintains its integrity following formulation and subsequent nebulization. AMG1028, ¶[0173]; AMG1002, ¶105.

108. "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *In re Wertheim*, 541 F.2d 257 (CCPA 1976) (finding when claimed values "overlap or lie inside ranges disclosed by the prior art," a *prima facie* case of obviousness exists.).

Wang's eculizumab concentrations are also consistent with the general knowledge in the art that 10 mg/ml was a common concentration used for formulating therapeutic antibodies. AMG1002, ¶106; AMG1029, Table 1; AMG1030, Table 1. The law is settled: "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Moreover, there is no evidence that the claimed 10 mg/ml concentration is in any way critical to the claimed method.[20] AMG1002, ¶107.

Moreover, given the state of the art as discussed above, a POSA would have prepared the eculizumab formulation in 30 ml based on simple arithmetic. As discussed, 300 mg dosage units would be the easiest way to have one dosage form

[20] Alexion argued in Europe that 10 mg/ml improved stability (AMG1027, 1104(¶5.3.8), but as discussed at Section XV, Alexion's arguments are meritless.

achieve 600 mg and 900 mg dosages. Likewise, 10 mg/mL was the prevailing standard concentration for this class of drug. Therefore, a dose of 300 mg concentrated at 10 mg/ml must be in 30 ml of solution (10 mg/ml x 30 ml = 300 mg). AMG1002, ¶108.

Notably, the '880 patent specification mentions no newly discovered advantage of a 30 ml dosage volume to suggest inventiveness in any way. Alexion even stated that the "low-volume liquid formulation … is *easy for the clinician to store and use*" and that the 30 ml size "*minimises the volume which must be stored* on site at each clinic." AMG1027, 1638(¶3.5), 1104(¶5.3.9). Easier storage for lower volumes compared to larger is common knowledge, not inventive. AMG1002, ¶108.

A POSA would have had a reasonable expectation of success here because formulating the doses into 300 mg single-use formulations of 30 ml of a 10 mg/ml sterile, preservative-free solution required mere conventional wisdom and routine skill. AMG1002, ¶104.

* * *

Accordingly, a POSA would have had motivation to arrive at a "sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml [anti-C5] antibody solution," as claimed, with a reasonable expectation of success based on the teachings in Hillmen, Bell and Wang, rendering claims 1 and 3

obvious.

## XIII. Ground 4: claims 1 and 3 would have been obvious over Hill '05, Bell, and Wang.

As already discussed, Hill '05 disclosed a pharmaceutical composition comprising eculizumab (an anti-C5 antibody) having the claimed sequences either expressly or inherently. *See* §X. AMG1002, ¶¶83-87, 110. Claims 1 and 3 further require that the pharmaceutical composition is "a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody [ or anti-C5 antibody] solution." AMG1001, 39:2-8 and 13-16. Those additional limitations were taught in Bell and Wang, and, a POSA would have had reason to combine Bell and Wang with Hill '05 to arrive at claims 1 and 3, with a reasonable expectation of success for the same reasons as already discussed for Ground 3. AMG1002, ¶¶110-120.

For example, Hill '05 and Bell taught methods of treating a patient suffering from PNH using a pharmaceutical composition comprising eculizumab. AMG1005, ¶¶[0012], [0052], [0081]-[0096]. Wang taught therapeutic antibody formulations, and explicitly taught formulating "*eculizumab* as the antibody therapeutic." AMG1028, ¶[0004]. With all three references explicitly teaching pharmaceutical compositions of eculizumab, a POSA would have had ample reason to combine Hill '05, Bell, and Wang with a reasonable expectation of

success because:

(i) Bell taught that the humanized antibody unit dose formulation "*must be sterile* and non-pyrogenic" and "*may* contain … preservatives…" (i.e., preservatives are not required). AMG1005, ¶[0062]; AMG1002, ¶116. And a POSA would have known that therapeutic antibodies are routinely prepared in sterile, preservative-free solutions. AMG1002, ¶116; AMG1056-AMG1076.

(ii) Wang taught eculizumab formulations of between 1 to 30 mg/ml, encompassing the claimed 10 mg/ml concentration. AMG1028, Fig. 10, ¶[0067]. Wang's disclosure was also consistent with the general knowledge in the art. *See, e.g.,* AMG1029, Table 1; AMG1030, Table 1; AMG1002, ¶118.

(iii) A POSA would have prepared the eculizumab formulation in 30 ml single-use dosage forms using simple mathematics based on a 300 mg dosage unit concentrated at 10 mg/ml. AMG1002, ¶119. Again, there is nothing critical about a 30 ml volume. AMG1027, 1638(¶3.5), 1104(¶5.3.9). Accordingly, a POSA routinely arriving at a 300 mg single-use dose concentrated at 10 mg/ml would also have routinely arrived at a volume of 30 ml. AMG1002, ¶119.

For these reasons, a POSA reading Hill '05, Bell, and Wang would have had

a reasonable expectation of successfully arriving at the claimed pharmaceutical composition recited in claims 1 and 3 for the same reasons discussed above in Ground 3. AMG1002, ¶¶115-120; *see* Section XI.

## XIV. Ground 5: claims 1-3 would have been obvious over Bell, Wang, Bowdish, and Evans.

Discussed below, a POSA would have had a reason to combine Bell, Bowdish, Evans, and Wang with a reasonable expectation of successfully making the pharmaceutical composition of claims 1-3. AMG1002, ¶¶121-154. And no objective indicia weigh in favor of patentability. *See* Section XV.

### A. Bell and Wang taught all the limitations of claims 1-3 except eculizumab's amino acid sequence.

Claims 1-3 are each directed to pharmaceutical compositions "for use in treating a patients afflicted with paroxysmal nocturnal hemoglobinuria (PNH)" (claim 1, or comprising an anti-C5 antibody (claims 2 and 3). Claims 1 and 3 also require that the pharmaceutical composition is "a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody [or anti-C5 antibody] solution." AMG1001, 39:2-8 and 13-16. Bell and Wang taught each of these elements of claims 1-3:

**Bell taught a "[p]harmaceutical composition for use in treating a patients afflicted with paroxysmal nocturnal hemoglobinuria (PNH)"/ "anti-C5 antibody":** Bell taught treating a patient suffering from PNH using a

pharmaceutical composition comprising eculizumab, a known anti-C5 antibody. AMG1005, ¶¶[0012], [0021], [0052], [0081]-[0096]; AMG1002, ¶¶128-132.

**Bell taught "sterile, preservative free":** Bell explains that its eculizumab compositions "*must be sterile* and non-pyrogenic," and that they "*may* contain … preservatives…" (i.e., preservatives are optional). AMG1005, ¶[0062]; AMG1002, ¶133. Dr. Balthasar further explains that a POSA would also have known that therapeutic antibodies are routinely prepared in sterile, preservative-free solutions. AMG1002, ¶133. Indeed, 100% of the 22 monoclonal antibodies approved by the FDA before March 15, 2007 were formulated in *sterile, preservative-free* solutions. AMG1002, ¶133; AMG 1056-AMG1076.

**Bell and Wang taught a "300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution"** : Bell stated that eculizumab can be "administered in a variety of *unit dosage forms*."[21] AMG1005, ¶[0058]. As Dr. Balthasar explains, a POSA would have understood that a "unit dosage form" of an antibody as taught in Bell is formulated for use in a single patient and is therefore a **"single-use" dosage** form as claimed. AMG1002, ¶135; AMG1046, 2989; AMG1051, 1. As already discussed, a POSA would have generally known that antibody dosage forms should not be shared among patients or returned to storage

[21] As did Evans. AMG1007, 17:60-61

after opening, to prevent contamination and unnecessary health risks, and Alexion agrees. AMG1002, ¶135; AMG1046, 2989; AMG1026, 208-209.

Moreover, a POSA would have arrived at the **300 mg** strength through simple convenience and a logical application of knowledge in the art. AMG1002, ¶136. To accommodate Bell's dosages of 600 mg and 900 mg dosages (AMG1005, ¶[0082]), a 300 mg single-use unit dosage amount would have been the most obvious and convenient (and thus predictable) means to a POSA. It would have been easier to achieve 600 mg and 900 mg doses with two and three 300 mg dosages, respectively, than to separately manufacture those two strengths. AMG1002, ¶136. *See KSR*, 550 US at 416. Alexion has already admitted during a European opposition proceeding for a related EP patent that there is nothing critical about the claimed single-use dosage form beyond convenience: "*simple dilution* of product required by the label *conveniently* provides the required 600 or 900 mg administration dosages." AMG1027, 1104(¶5.3.9).

According to Dr. Balthasar, a POSA at the time of invention would have had a reasonable expectation of successfully preparing a 300 mg single-use dosage form because Bell taught methods for preparing unit dosage forms, and described successfully preparing and administering 600 mg and 900 mg doses. AMG1005, ¶¶[0058]-[0060], [0062], [0082]; AMG1002, ¶137.

Lastly, Wang taught liquid eculizumab formulations of between *1 and 30*

*mg/ml*, completely encompassing the claimed **10 mg/ml** concentration, rendering it obvious. AMG1028, Fig. 10, ¶¶[0170]-[0172]; AMG1002, ¶138. *In re Peterson*, 315 F.3d at 1330; *In re Wertheim*, 541 F.2d 257.

Wang's eculizumab concentrations are also consistent with the general knowledge in the art that 10 mg/ml was a common concentration used for formulating therapeutic antibodies. AMG1002, ¶138; AMG1029, Table 1; AMG1030, Table 1. Moreover, there is no evidence that the claimed 10 mg/ml concentration is in any way critical to the claimed method.[22]

Third, given the state of the art as discussed above, a POSA would have prepared the eculizumab formulation in **30 ml** single-use dosage forms based on simple arithmetic: a dose of 300 mg concentrated at 10 mg/ml must be in 30 ml of solution (10 mg/ml x 30 ml = 300 mg). AMG1002, ¶139.

Notably, the '880 patent specification mentions no newly discovered advantage of a 30 ml dosage volume to suggest inventiveness in any way. Alexion even acknowledged that the "low-volume liquid formulation … is *easy for the clinician to store and use*" and that the 30 ml size "*minimises the volume which must be stored* on site at each clinic." AMG1027, 1638(¶3.5), 1104(¶5.3.9). Easier

[22] As discussed at Section XV, Alexion's arguments in Europe that 10 mg/ml improved stability (AMG1027, 1104(¶5.3.8) are meritless.

storage for lower volumes compared to larger is common knowledge, not inventive. AMG1002, ¶139.

A POSA would have had a reasonable expectation of success here because formulating the doses taught in Bell into 300 mg single-use compositions of 30 ml of a 10 mg/ml sterile, preservative-free solution required mere conventional wisdom and routine skill, and eculizumab compositions of 10 mg/ml were already known in the art from Wang. AMG1002, ¶¶137-138.

**B. Bowdish and Evans taught the claimed amino acid sequences.**

Bowdish taught methods of making peptide-antibody chimeric proteins, and described using a humanized anti-C5 antibody as the starter "scaffold" antibody sequence for creating a recombinant TPO-mimetic. Bowdish provided the full antibody amino acid sequence except for the heavy chain CDR3 (HCDR3) sequence, which was replaced with the TPO-mimetic peptide sequence (LPIEGPTLRQWLAARAPV). AMG1006, ¶¶[0191]-[0193], Figs. 13A-13B, and SEQ ID NOs.:67 and 69; AMG1002, ¶¶140-145. As explained in detail below, the missing HCDR3 sequence from Bowdish was taught by Evans. AMG1002, ¶146. Dr. Balthasar's Figure 11 below depicts this combination of art providing the complete eculizumab sequence:

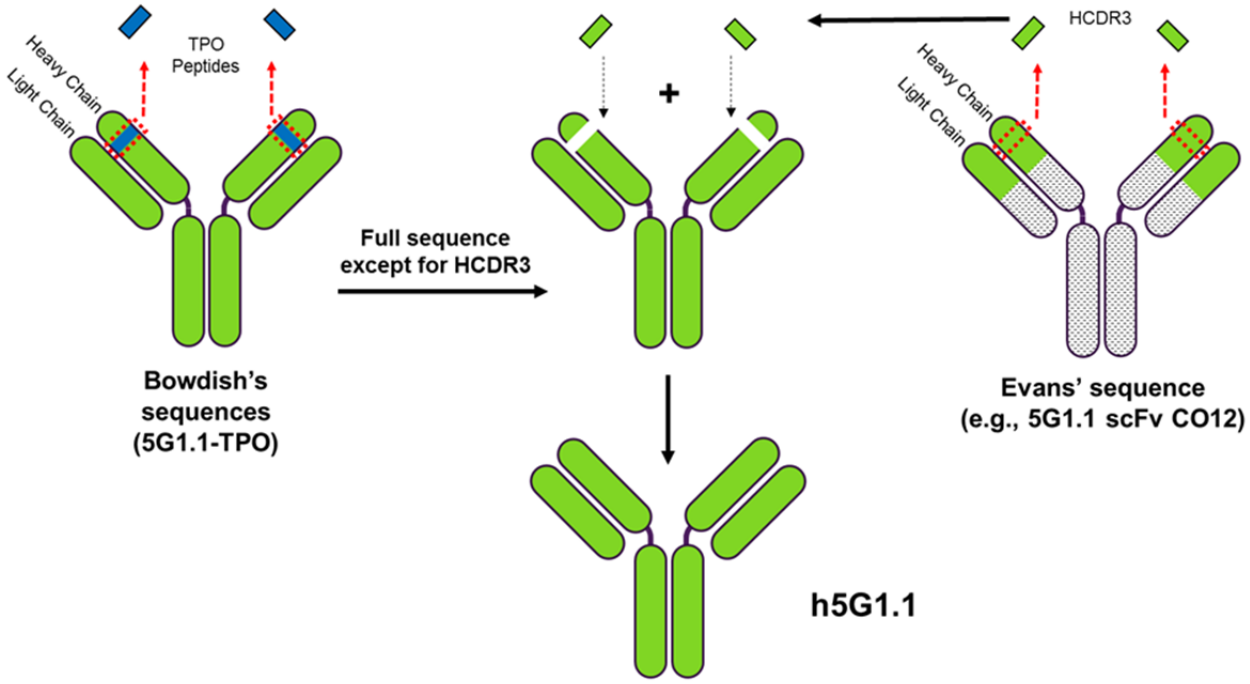


**Figure 11.**

AMG1002, ¶122.

Bowdish provides the complete sequences of the heavy and light chains of a recombinant TPO-mimetic-containing antibody ("5G1.1+TPO") as SEQ ID NO:67 ("5G1.1-TPO Heavy Chain") and SEQ ID NO:69 ("5G1.1 Light Chain") in Figures 13A and 13B, respectively. AMG1006, Figures 13A-13B; AMG1002, ¶143. Dr. Balthasar's Figure 3 below illustrates the structure of Bowdish's 5G1.1+TPO, showing the location of the TPO-mimetic peptide (blue) in the HCDR3 region of the polypeptide of SEQ ID NOs:67 (heavy chain), and the polypeptide of SEQ ID NO:69 (light chain), where green represents sequences 100 % identical to SEQ ID NO:2 and SEQ ID NO:4::

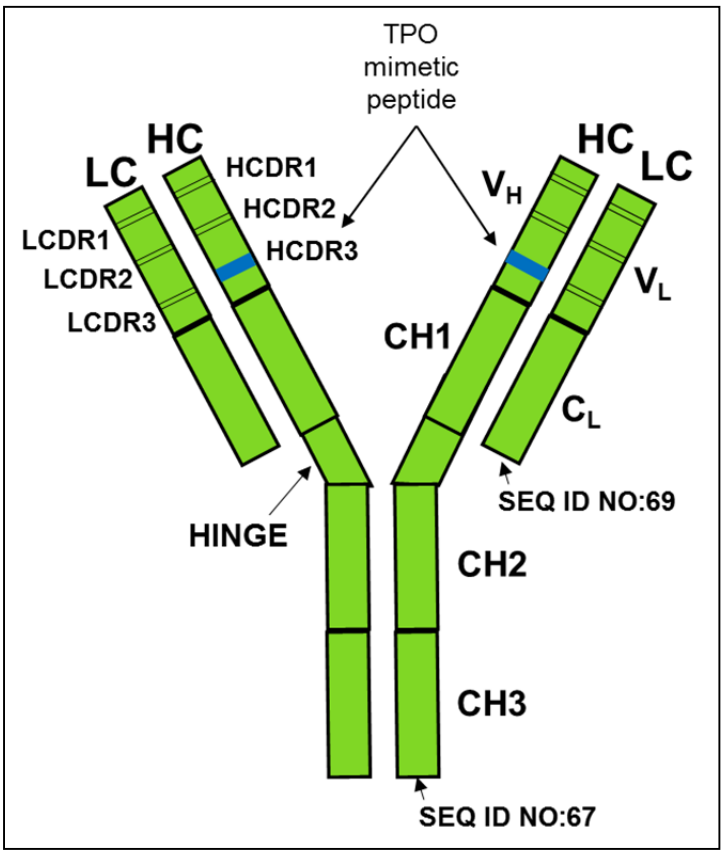


**Figure 3.**

AMG1002, ¶52; AMG1006, Figures 13A-13B.

As Dr. Balthasar explains, the mature portion of Bowdish's SEQ ID NO:69 (i.e., the light chain) is 100% identical to the claimed SEQ ID NO:4; and the mature portion of Bowdish's SEQ ID NO:67 (i.e., the heavy chain) is 100% identical to the claimed SEQ ID NO:2, with the exception of the HCDR3 sequence. AMG1002, ¶148.

Bowdish's sequences in SEQ ID NOs:69 and 67 each contain italicized portions, which Bowdish explicitly denoted as "leader sequence[s]." As Dr.

Balthasar explains, a POSA would have known that any leader sequence would be cleaved from the mature antibody sequence. AMG1002, ¶143. Thus, the POSA would have known that the leader sequences in Bowdish's Figures 13A-13B are not part of the mature antibody sequence[23]. AMG1006, Figures 13A-13B; AMG1002, ¶143; AMG1045, 582.

A POSA wanting to make a humanized anti-C5 antibody would have understood that the only portion of the heavy chain sequence missing from Bowdish is the HCDR3 sequence because Bowdish taught that "[t]he TPO mimetic peptide graft in Fab clone X4b has been *transplanted into the heavy chain CDR3* of another antibody framework, *5G1.1* … The sequence was *cloned into 5G1.1* in such a fashion as to *replace the native CDR3*." AMG1006, ¶[0191]; AMG1002, ¶¶144-145. The missing HCDR3 sequence, however, was taught in Evans, and Bowdish expressly directed a POSA to Evans. AMG1006, ¶[0191].

[23] Alexion is estopped from arguing to the contrary. During prosecution, Alexion amended original SEQ ID NO:4 to *remove* the leader sequence, arguing that "the mature light chain sequence is an *inherent* portion of the precursor sequence … and could have been readily identified at the relevant filing date using well established rules and art-recognized techniques…." AMG1016, 179; *see Vitronics Corp.*, 90 F.3d at 1583; *Tyler Refrigeration*, 777 F.2d at 690.

Evans disclosed preparing humanized C5-binding antibodies, referred to therein as "5G1.1" antibodies. AMG1007, 19:47-49, 37:35-39:30, 40:31-45:4; AMG1002, ¶146. As Dr. Balthasar explains, a POSA would have understood that *each* of the 5G1.1 antibody heavy chain variable regions in Evans contain *the same CDR3 sequence*: YFFGSSPNWYFDV. AMG1007, Fig. 19, 43:13-14, 43:26-27, 43:33-34, 43:60-61, 44:2-3, 44:12-13, 44:21-22, 44:30-31, 44:39-40, 44:49-50, 44:59-60, 45:3-4; AMG1002, ¶146. Thus, regardless of which "version" of Evans' humanized 5G1.1 the POSA selected to combine with Bowdish, that heavy chain would contain the YFFGSSPNWYFDV CDR3 sequence. AMG1002, ¶146. Dr. Balthasar's Figure 11 above shows this, where Evans' HCDR3 sequence is extracted and inserted into Bowdish's construct. AMG1002, ¶122.[24] And a POSA would have expected that inserting Evans' YFFGSSPNWYFDV HCDR3 sequence in place of Bowdish's TPO peptide sequence (LPIEGPTLRQWLAARAPV) in SEQ ID NO:67 would provide a complete heavy chain of a humanized anti-C5 antibody that would bind C5. AMG1002, ¶¶147-148. Dr. Balthasar confirms by sequence alignment that this combination provides a sequence identical to the '880

[24] To be clear, a POSA would have known that this would be achieved by replacing DNA encoding Bowdish's TPO-mimetic (SEQ ID NO:65) with DNA encoding Evan's HCDR3. AMG1002, ¶123.

patent's SEQ ID NO: 2. AMG1002, ¶¶147-148.

### C. A POSA would have had a reason to combine the references with a reasonable expectation of success.

Bell taught that targeting complement protein C5 with an anti-C5 antibody is. AMG1005, ¶¶[0083]-[0096]. Wang taught therapeutic antibody formulations, and explicitly taught formulating "*eculizumab* as the antibody therapeutic." AMG1028, ¶[0004]. Because neither Bell nor Wang expressly provides the amino acid sequence of its anti-c5 antibody, eculizumab, a POSA would have looked to other eculizumab teachings in the art, like Bowdish and Evans. AMG1002, ¶149.

A POSA is "presumed to be aware of all the pertinent prior art." *Standard Oil*, 774 F.2d at 454. A POSA, therefore, would have been well aware that eculizumab was also known in the art as humanized "5G1.1," "h5G1.1," or "h5G1.1-mAb" with a hybrid IgG2/IgG4 constant region. AMG1002, ¶150; AMG1005, ¶[0052]; AMG1034, 1279; *see also*, Section IV.D, *supra*. To possess the amino acid sequence of that antibody, a POSA would have consulted Bowdish because it taught using a humanized 5G1.1 antibody (including the hybrid IgG2/IgG4 heavy chain constant region) as the starter antibody sequence when creating the TPO-mimetic-containing antibody and further provided the amino acid sequence of the chimeric antibody. AMG1002, ¶¶150-151. Knowing that the only change made to the scaffold antibody in Bowdish was replacing its HCDR3 region

with a TPO-mimetic peptide, a POSA would have had a reason to restore the original HCDR3 region to complete the original anti-C5 antibody. AMG1002, ¶151.

The POSA would have looked to Evans for the missing HCDR3 sequence because both Bell and Bowdish explicitly direct the artisan there for information on how the h5G1.1 antibody was originally created. AMG1005, ¶[0052]; AMG1006, ¶[0191]; AMG1002, ¶151. For example, Bell stated: "[m]ethods for the preparation of *h5G1.1-mAb* [eculizumab] … are described in [Evans][25] … incorporated herein in [its] entirety …." AMG1005, ¶[0052]. And Bowdish similarly stated: "[c]onstruction of *5G1.1* is described in [Evans], incorporated herein by reference."[26] AMG1006, ¶[0191].

This combination of prior art would have led a POSA to make a simple substitution of one known element for another—i.e., replace the TPO-mimetic

[25] Bell also cites Thomas. AMG1005, ¶[0052]. A POSA would have known that the humanized "h5G1.1 HuG4" antibody disclosed in Thomas is not eculizumab because Thomas's antibody is an IgG4 isotype—i.e., not a human hybrid IgG2/IgG4 isotype like eculizumab. AMG1002, ¶49; *see also*, Section IV.D, *supra.*

[26] *See* note 5, *supra*.

peptide sequence in Bowdish's antibody with the HCDR3 sequence from Evans—to yield predictable results: a complete humanized anti-C5 antibody. *KSR*, 550 US at 416 ("[A] combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). And, as Dr. Balthasar confirms by sequence alignment, the humanized anti-C5 antibody obtained from this combination of prior art comprises a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4 as claimed. AMG1002, ¶¶147-148, 152.

A POSA would have had a reasonable expectation of successfully arriving at the composition of claim 1 because (i) making a humanized anti-C5 antibody would have required only basic molecular biology techniques to substitute Evans' HCDR3 sequence in place of Bowdish's TPO-mimetic peptide sequence (AMG1002, ¶153); (ii) antibody production methods were well-known in the art (see, e.g., AMG1006, ¶¶[0130]-[0131]; AMG1002, ¶153); (iii) Bell taught that a humanized anti-C5 antibody was a safe and effective treatment for PNH, and it provided methods and guidance on how to administer the treatment (AMG1005, ¶¶[0081]-[0096]); and (iv) Bell and Wang taught methods for preparing single-use dosage forms of humanized anti-C5 antibody compositions, including at 10 mg/ml concentrations. AMG1005, ¶¶[0058]-[0060], [0062]; AMG1028, Fig. 10, ¶¶[0170]-[0172]. This expectation is bolstered by numerous publications of

successful clinical trials involving administering pharmaceutical compositions comprising a humanized anti-C5 antibody for treating PNH. *See, e.g.,* AMG1004; AMG1042; AMG1047; AMG1011; AMG1005; AMG1012; AMG1013; AMG1002, ¶153.

## XV. Ground 6: claims 1-3 would have been obvious over Bell, Wang, Evans, and Meuller.

A POSA would have had a reason to combine Bell, Evans, Mueller, and Wang with a reasonable expectation of successfully making the pharmaceutical composition of claims 1-3. AMG1002, ¶¶155-179. And no objective indicia weigh in favor of patentability. *See* § XV.

### A. Bell and Wang taught all the limitations of claims 1-3 except eculizumab's amino acid sequence.

As shown in § XIII.A., Bell and Wang together taught all of the elements of claims 1-3 except for the claimed antibody sequences. AMG1002, ¶¶155, 159-163.

Bell taught methods of treating a patient suffering from PNH using a pharmaceutical composition comprising eculizumab, a known anti-C5 antibody. AMG1005, ¶¶[0012], [0021], [0052], [0058], [0081]-[0096]. Wang taught therapeutic antibody formulations, and explicitly taught formulating "*eculizumab* as the antibody therapeutic." AMG1028, ¶[0004]. In addition:

(i) Bell taught that the humanized antibody unit dose formulation "*must be sterile* and non-pyrogenic" and "*may* contain … preservatives…"

(i.e., preservatives are not required). AMG1005, ¶[0062]; AMG1002, ¶160. And a POSA would have known that therapeutic antibodies are routinely prepared in sterile, preservative-free solutions. AMG1002, ¶160; AMG1056-AMG1076.

(ii) Wang taught eculizumab formulations of between 1 to 30 mg/ml, encompassing the claimed 10 mg/ml concentration. AMG1028, Fig. 10, ¶[0067]. Wang's disclosure was also consistent with the general knowledge in the art. *See, e.g.,* AMG1029, Table 1; AMG1030, Table 1; AMG1002, ¶162.

(iii) A POSA would have prepared the eculizumab formulation in 30 ml single-use dosage forms using simple mathematics based on a 300 mg dosage unit concentrated at 10 mg/ml. AMG1002, ¶163. Again, there is nothing critical about a 30 ml volume. AMG1027, 1638(¶3.5), 1104(¶5.3.9). Accordingly, a POSA routinely arriving at a 300 mg single-use dose concentrated at 10 mg/ml would also have routinely arrived at a volume of 30 ml. AMG1002, ¶163.

**B. Evans and Mueller taught eculizumab's amino acid sequences.**

As discussed below, Evans disclosed the complete amino acid sequences of the heavy and light chain variable domains of a humanized anti-C5 antibody, . AMG1007, 44:4-13, SEQ ID NO:20; AMG1002, ¶¶170-175. And Mueller

disclosed the amino acid sequence of a light chain constant region and the hybrid IgG2/IgG4 heavy chain constant region. AMG1008, 58-61; AMG1002, ¶¶170-175. Dr. Balthasar's Figure 14 below depicts this combination of art providing the complete eculizumab sequence:

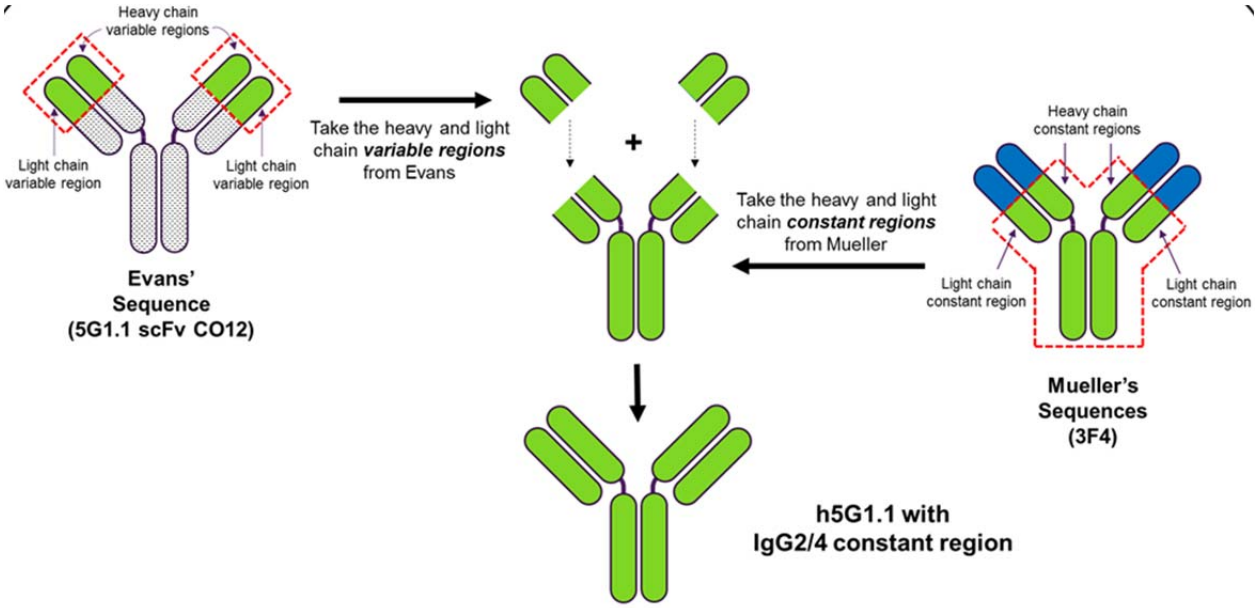


**Figure 14.**

*See* AMG1002, ¶156.

Evans—which Alexion previously said claims Soliris® and provides written description and enablement support for claims directed to eculizumab (AMG1009, 4; AMG1049, 838-839)—discloses making the original mouse 5G1.1 monoclonal antibody. AMG1007, 37:36-39:30 (Example 7); AMG1002, ¶¶164-165. Evans further described constructing a series of humanized 5G1.1 antibody constructs containing the heavy and light chain CDR sequences from the mouse 5G1.1

antibody inserted into a human framework. AMG1007, 42:58-45:4. In particular, Evans described nine different humanized 5G1.1 scFv constructs[27] along with their amino acid sequences. *Id.* (constructs 2 and 11-18); AMG1002, ¶¶165, 171. Evans also described combining the variable regions with constant domains—including hybrid IgG constant domains—to make a complete antibody. AMG1007, 45:24-33.

Knowing that chimeric IgG2/IgG4 constant regions were known not to activate the complement system (AMG1008, 7:28-31, 8:23-26, 12:27-32), a POSA reading Bell and Evans also would have looked to Mueller for "h5G1.1" sequence information. AMG1002, ¶¶166, 173. Mueller taught methods for making "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 … (HuG2/G4 mAb)." AMG1008, 12:27-30; *see also, id.*, 8:23-26. In particular, Mueller described a control antibody "h5G1.1 CO12 HuG2/G4 mAb," which a POSA would have readily identified as a humanized anti-C5 antibody because of the "h5G1.1" nomenclature coupled with the hybrid

[27] A POSA would have known that a scFv comprises light and heavy chain variable domains connected by a linker. *See, e.g.,* AMG1007, 6:39-41 ("single chain antibodies may include one each of only VH and VL domains, in which case they are *referred to as scFv antibodies*"); *see also,* AMG1040, 45-48; AMG1002, ¶165

IgG2/IgG4 constant region ("HuG2/G4"). AMG1008, 12:37, FIG. 15; AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶¶166, 173-174.

As Dr. Balthasar explains, Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant region when Mueller disclosed the sequence of the chimeric anti-VCAM "3F4" antibody. AMG1002, ¶¶169, 173; AMG1008, 58-61. A POSA would have known that a chimeric antibody contains the variable region from a non-human antibody and the constant region from a human antibody, and therefore would have understood that Mueller's chimeric 3F4 HuG2/G4 mAb heavy chain contains the variable regions from murine antibody 3F4 (the blue portions in Dr. Balthasar's Figure 14 above) and the constant regions of human hybrid IgG2/IgG4 (the green portions in Dr. Balthasar's Figure 14). AMG1002, ¶¶156, 173; AMG1040, 29-30.

Mueller separately disclosed the amino acid sequences of the mature 3F4 heavy and light chain variable regions (i.e., the blue portion in Dr. Balthasar's Figure 14). AMG1008, Figure 9; AMG1002, ¶¶156, 173. A POSA aligning the 3F4 heavy and light chain variable region sequences from Figure 9 with the sequences of the 3F4 HuG2/G4 chimeric antibody would have identified the 3F4 variable regions (the regions a POSA would have excluded) as amino acids 20-137 of the 3F4 HuG2/G4 heavy chain and amino acids 20-131 of the 3F4 light chain. AMG1008, Figure 9, 52-53, 58-61; AMG1002, ¶173.

A POSA therefore would have immediately known that the remainder of the 3F4 HuG2/G4 heavy chain (amino acids 138-463) is the hybrid IgG2/IgG4 constant region of that antibody, and that the remainder of the 3F4 light chain (amino acids 132-238) is the light chain constant region of that antibody (i.e., the green portion in Dr. Balthasar's Figure 14). AMG1008, 52-53, 56-57; AMG1002, ¶173. Given that Mueller used this humanized anti-C5 antibody as an isotype control for 3F4 HuG2/G4, a POSA would have reasonably expected the disclosed heavy and light chain constant regions to be the same as those in the 3F4 HuG2/G4 chimeric antibody. AMG1002, ¶¶57, 166.

As Dr. Balthasar explains, overwhelming evidence in the art would have further confirmed a POSA's belief that the amino acid sequences of the heavy and light chain constant regions of Mueller's 3F4 HuG2/G4 antibody are the same as those in eculizumab. AMG1002, ¶¶47, 56, 169, 182. Publications such as Bowdish, Tacken, Mueller II, and Evans all disclosed portions of eculizumab constant regions that either overlapped with or were exact matches to the heavy and light chain constant regions of Mueller's 3F4 HuG2/G4 antibody. AMG1002, ¶¶47, 56, 169, 182; AMG1006, Figs. 13A-13B; AMG1034, 1279; AMG1031, Abstract, 448, Fig. 7; AMG1007, 43:50-55 (SEQ ID NO:15).

With the heavy and light chain constant region sequences obtained from Mueller, a POSA would have looked back to Evans to complete the amino acid

sequence. AMG1002, ¶¶167-168. Knowing that Mueller refers to the control antibody as "h5G1.1 CO12 HuG2/G4 mAb," the POSA would have referred to the series of humanized 5G1.1 scFvs taught in Evans and readily identified construct number 12 (SEQ ID NO:20) as the scFv of interest because Evans used the same "CO12" nomenclature as Mueller by designating it "5G1.1 scFv CO12." AMG1007, 44:4-13; AMG1002, ¶¶167-168. This is shown in Dr. Balthasar's Figure 14 above, where the green portions depict Evans' heavy and light chain variable regions. AMG1002, ¶156; AMG1007, 44:4-13, SEQ ID NO:20.

That Evans taught additional 5G1.1 scFv constructs is irrelevant because, "for an obviousness analysis, even the fact that 'a specific embodiment is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *In re Thomas*, 151 Fed. App'x. 930, 934 (Fed. Cir. 2005) (quoting *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Here, any one of the combinations of Mueller's constant regions with Evans' variable regions would have been obvious, and does not make the combination with any one pair of variable regions any less obvious. *See Merck*, 874 F.2d at 807 ("That the [asserted prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious.")

A POSA would have known that Evans' humanized 5G1.1 scFvs each contains a single polypeptide sequence comprising a humanized heavy chain

variable region of 5G1.1, a linker, and a humanized light chain variable region of 5G1.1. AMG1002, ¶172; AMG1007, 6:39-41; AMG1040, 45-48. As Dr. Balthasar explains, a POSA would have been able to readily identify the heavy and light chain variable regions within SEQ ID NO: 20 of Evans. AMG1002, ¶172.A POSA would have known that the linker in "5G1.1 scFv CO12" (SEQ ID NO:20) is amino acids 112-126 because this 15-amino acid sequence (GGGGSGGGGSGGGGS) was well known in the art as common a linker sequence in scFv antibodies. AMG1007, SEQ ID NO:20 (Certificate of Correction, 42-44); AMG1037, ¶¶[0021], [0097]; AMG1002, ¶172.

Alexion has also argued during prosecution that "the mature light chain sequence … could have been readily identified at the relevant filing date using well established rules and art-recognized techniques" and provided Adderson (AMG1048) as an example showing "the characteristic mature N-terminus (DIQ) of a light V kappa antibody light chain." AMG1014, 513; AMG1048, Fig. 6. Thus, the first two amino acids of Evans' SEQ ID NO:20 (MA) are a leader sequence, based on Alexion's admission that a mature kappa light chain starts with the sequence "DIQ" on its N terminus. AMG1002, ¶172; AMG1048, 734 (Fig. 6). Accordingly, a POSA would have understood that the mature light and heavy chain variable regions in Evans correspond to amino acids 3-111 and 127-248 of SEQ ID NO:20, respectively. AMG1007, 44:4-13; SEQ ID NO:20; AMG1002, ¶172.

Finally, a POSA would have expected that combining Evans' variable region sequences with Mueller's constant region sequences would provide complete heavy and light chain sequences of a humanized anti-C5 antibody.[28] *See* Dr. Balthasar's Figure 14 above; AMG1002, ¶¶156, 174-175.

As Dr. Balthasar shows by sequence alignment, the combination of heavy and light chain variable regions in Evans' SEQ ID NO:20 with Mueller's constant regions would make a humanized anti-C5 antibody having SEQ ID NOs:2 and 4, as claimed. AMG1002, ¶¶174-175.

### C. A POSA would have had a reason to combine the references with a reasonable expectation of success.

Again, a POSA would have generally known that the humanized anti-C5 antibody eculizumab is a humanized 5G1.1 monoclonal antibody with a hybrid IgG2/IgG4 constant region, often referred to as "h5G1.1" in the art. AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶¶44-47. A POSA reading Bell and Wang would have looked to Evans because Bell explicitly cited and incorporated by reference Evans for methods of making a humanized anti-C5 antibody. AMG1005, ¶[0052]; AMG1002, ¶¶164-165, 176-177. A POSA would

[28] To be clear, a POSA would have known that this would be achieved by combining DNA encoding Evans' variable region sequences with that encoding Mueller's constant region. AMG1002, ¶123.

have also looked to Mueller because Mueller disclosed an h5G1.1 antibody named "h5G1.1 CO12 HuG2/G4 mAb" with a hybrid IgG2/IgG4 heavy chain constant region, which a POSA would have readily understood to be the humanized anti-C5 antibody, eculizumab. AMG1002, ¶¶166, 177.

Evans and Mueller taught complementary, familiar elements of eculizumab's amino acid sequences. AMG1002, ¶177. Thus, by combining familiar elements in the art according to known methods, the artisan would have predictably arrived at a humanized anti-C5 antibody comprising a light chain consisting of SEQ ID NO:2 and a heavy chain consisting of SEQ ID NO:4 as claimed. *KSR*, 550 US at 416 ("a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). A POSA would have easily confirmed this prediction by comparing the constructed sequences with another Alexion publication WO 2005/007809, which taught detailed descriptions of expression vectors designed for placing antibody variable regions in frame with chimeric IgG2/IgG4 heavy chain constant regions. AMG1032, 7, 28-32, FIG. 5; AMG1002, ¶177.

With eculizumab in hand, a POSA would have had a reasonable expectation of successfully arriving at the pharmaceutical composition of claims 1-3 because (i) making eculizumab would have required only basic molecular biology techniques to combine Evans' scFv variable regions with Mueller's constant

domains (AMG1002, ¶178); (ii) antibody production methods were well-known in the art (see, e.g., AMG1006, ¶¶[0130]-[0131]; AMG1002, ¶178); (iii) Bell taught that eculizumab was a safe and effective treatment for PNH, and it provided methods and guidance on how to administer the treatment (AMG1005, ¶¶[0081]-[0096]); and (iv) Bell and Wang taught methods for preparing single-use dosage forms of eculizumab compositions, including 10 mg/ml eculizumab. AMG1005, ¶¶[0058]-[0060], [0062]; AMG1028, Fig. 10, ¶¶[0170]-[0172]; AMG1002, ¶178. This expectation is bolstered by numerous publications of successful clinical trials involving administering pharmaceutical compositions comprising a humanized anti-C5 antibody for treating PNH. *See, e.g.,* AMG1004; AMG1042; AMG1047; AMG1011; AMG1005; AMG1012; AMG1013; AMG1002, ¶178.

**XVI. Objective indicia do not support patentability.**

"To be afforded substantial weight, the objective indicia of non-obviousness must be tied to the *novel elements* of the claim at issue." *Univ. Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). Objective evidence that is not "both claimed and *novel in the claim*" lacks nexus to the invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Alexion argued during prosecution of the related '504 patent that "the non-natural, protein-engineered, heavy chain of eculizumab" (i.e., the hybrid IgG2/IgG4 constant domain) provided "surprising and unpredictable" results such

as decreased effector function, reduced immunogenicity and increased half-life. AMG1014, 588, 593(¶8). Eculizumab's hybrid IgG2/IgG4 constant domain was well known in the art (e.g., AMG1034, 1279), however, and cannot be a "novel element." *Marie Curie*, 738 F.3d at 1347; *Kao*, 639 F.3d at 1068. Accordingly, the alleged "surprising and unpredictable" features of eculizumab have no nexus with the challenged claims and do not support non-obviousness. *Id.*

Moreover, Alexion's alleged results would not have been unexpected to a POSA. AMG1002, ¶¶180-182. Mueller II taught in 1997 that antibodies with a hybrid IgG2/IgG4 heavy chain "[do] not contain the antibody sequences necessary for FcR binding," and would not contain "any new epitopes that would likely be immunogenic." AMG1031, 448, 451. It was also well known that a hybrid IgG2/IgG4 heavy chain would "have increased half-life." *See, e.g.,* AMG1032, 5, 19; AMG1002, ¶182. There is nothing unexpected here.

Alexion also argued in Europe that the claimed 10 mg/ml concentration provided "improved stability compared with other concentrations." AMG1027, 1104(¶5.3.8). This argument also carries no weight because a 10 mg/ml concentration of an anti-C5 antibody is not a *novel feature* of the claims. Discussed above, numerous therapeutic antibodies were formulated at this concentration, *including eculizumab*. AMG1002, ¶¶105-106; AMG1028, Fig. 10. Further, data submitted in the opposition proceeding show that 10 mg/ml eculizumab did not

offer any improved stability over other tested concentrations, completely contradicting Alexion's assertion. AMG1027, 19-20, 89-100; AMG1002, ¶¶183-184.

Petitioner is not aware of any other alleged objective indicia, and reserves the right to rebut any evidence asserted by Alexion in this proceeding. *Amneal Pharms., LLC v. Supernus Pharms., Inc*., IPR2013-00368, Paper 8, at 12-13 (Dec. 17, 2013); AMG1002, ¶185.

## XVII. Certification that the Patent May Be Contested via *Inter Partes* Review by the Petitioner and Standing (37 C.F.R. §42.104(a)).

Amgen certifies that the '880 patent is available for IPR and Amgen is not barred or estopped from requesting IPR of any '880 patent claim.

## XVIII. Mandatory Notices (37 C.F.R. §42.8(a)(1).

**Real party-in-interest** 37 C.F.R. §42.8(b)(1): Amgen Inc.

**Related Matters** (37 C.F.R. §42.8(b)(2)): Amgen has concurrently filed petitions for IPR of U.S. Patent Nos. 9,725,504 (IPR2019-00739) and 9,732,149 (IPR2019-00741), which are related to the '880 patent and also owned by Alexion.

**Lead and back-up counsel** (37 C.F.R. §42.8(b)(3)) for Amgen Inc. are

| Lead Counsel | Back-Up Counsel |
|---|---|

| | |
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**Notice of Service Information** (37 C.F.R. §42.8(b)(4)): Please direct all correspondence regarding this Petition to counsel at the above addresses. Amgen consents to service by email at the addresses above.

**Procedural Statements**: This Petition is filed in accordance with 37 C.F.R. §42.106(a). Concurrently filed herewith are a Power of Attorney and Exhibit List under 37 C.F.R. §42.10(b) and §42.63(e), respectively. The required fee is paid through Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 19-0036 (Customer ID No. 45324).

## XIX. Conclusion.

The challenged claims are unpatentable as anticipated or obvious and IPR is warranted.

Respectfully submitted,
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**CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))**

I certify that Amgen Inc.'s Petition for *Inter Partes* Review for U.S. Patent No. 9,718,880 contains 13,703 words as counted by the word-processing program used to generate this response. This total does not include the table of contents, certificate of service, or this certificate of word count.

Respectfully submitted,
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**CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e)), §42.105(a))**

I certify that the above-captioned "Petition for *Inter Partes* Review for U.S. Patent No. 9,718,880" was served in its entirety upon the Patent Owner on February 28, 2019, via FedEx, at the correspondence address of record indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,718,880 B2:

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